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Surgical Metabolism

The Metabolic Care of the Surgical Patient

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This work is dedicated to the memory of ....
Warren B. Davis
and
Paula E. Hyman

Preface

The modern specialist in the treatment of surgical disease must be an expert in more than the traditional skills of cutting and sewing. Our patients are highly complex biochemical systems, with many active metabolic pathways, each with diverse requirements and varied methods of support. In preparing this work, we stepped back from an approach based on explicit diseases or anatomical approaches, and considered the metabolic needs of the patient as primary. We hope to have achieved our goal of creating a textbook that supplements the more traditional approaches and provides the basis in metabolism for an access to surgical knowledge and education.

We must acknowledge the classic text, with a title similar to ours by Dr. Francis Moore, now long out of print. Though we had no direct publishing connection to Dr. Moore's work, it was the inspiration for this book, as well as, of course, the inspiration for much of the modern thinking on the many metabolic aspects of surgical disease. Since that era, surgical science has advanced tremendously, as clinicians have learned about nutrition, then specific metabolic pathways, and mostly recently genetics-based science.

There have been many great contributors to our subject in the two generations since Dr. Moore's era. We would not attempt to be complete in our recognition of all the masters who have made important advances. But we would like to mention our former colleagues and mentors, Dr. Stanley Dudrick and Dr. John Kinney, who both advanced the field and had many intellectual progeny who also contributed.

This volume could not have been produced without the extensive efforts by our many contributors. We would also like to thank our academic chairs at Yale University School of Medicine, Dr. Robert Udelsman of the Department of Surgery and Dr. Roberta Hines of the Department of Anesthesiology. This work could not have been done without the fine efforts of Ms. Elise Paxson from the Springer publishing team.

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Introduction to Metabolism

1

Christy M. Lawson, Chandler A. Long,
Reagan Bollig, and Brian J. Daley

Fasting is a great remedie of fever.

John Withals in "A shorte dictionarie most profitable for yong beginners the second tyme corrected, and augmented, with diuerse phrasys, and other thinges necessarie therevnto added: by Lewys Euans."

Published 1574 by [In Paules churchyarde, at the signe of the Lucreece, by Thomas Purfoote] in Imprinted at London. Ref: www.openlibrary.org

Introduction

Metabolism is defined as "1. The chemical processes occurring within a living cell or organism that are necessary for the maintenance of life. 2. The processing of a specific substance within the living body" [1]. This definition simplifies a process that occurs at the cellular level in every living being and is the driving process of our existence. The consumption of energy is the basis of life; an innate and evolutionarily honed drive to maintain homeostasis and fulfill the needs for energy and cellular function.

Derangements in metabolism are present with every disease process and may even be the cause. The quest to understand the exchange of energy at the cellular level and to develop novel techniques to manipulate, restore, or control this exchange is as old as medicine itself. The goal of this chapter is to review the history of our understanding of metabolic processes, to discuss normal cellular metabolism in a healthy subject, and to identify ways in which metabolism is altered in injury and illness.

History of Metabolism

For centuries, man has struggled to understand the basis of life, often coming up with partially correct or wildly fanciful ways to explain the disease in front of them. Many of the basic explanations the ancients propagated about this concept of metabolism and disease came down to foods that cure or harm. Even today, our fascination with food as a way to manipulate the basis processes of life continues—a simple internet search produces countless reports of foods curing disease, reducing impotence, adding muscle, or losing weight. Yet, to end this never-ending search for the "magic" food source or the fountain of youth, the precisely orchestrated chemical and genetically determined metabolic processes

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at the cellular level must be fully elucidated. Only then can we find specific nutrients or foods that could "cure."

The historical foundation of surgical metabolism over the centuries has constructed our current understanding. Dating back to the beginning of the Common Era, both the Ayurvedic and Greek "Aristotelian" philosophy of health and disease was based on the states of earth, water, fire and air or some combination of such, and was intimately tied to emotions/senses. This so-called humor physiology was pervasive for millenia [2]. Extensive catalogues of medicinal herbs and behaviors were employed to alter the balance between these humors to promote health and abate disease. Avicenna, a Persian philosopher and physician, applied the concept of humors across the spectrum of health and disease, treating excesses of one humor with removal or reduction of its counterpart. Galen is credited with the letting of blood to release the humors, a practice that lasted through the eighteenth century. In 1628, a new philosophy arose. William Harvey published Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus (An Anatomical Study of the Motion of the Heart and of the Blood in Animals), where he first described the cardiovascular system as a unit with the heart at the center pumping blood to the remainder of the body. This significant break with the long held practice of humoralism championed by the likes of Hippocrates and Galen was coupled with Harvey's discovery of circulation and Santorio Sanctorius framework of metabolic balance. Sanctorius' meticulous experiments over years illustrate the difference in weight of ones' total intake compared to the reduced weight of what one excreted. This dissipation of quantity and mass he attributed to a theory called "insensible perspiration" [3]. These concepts were key in creating the understanding of physiologic conservation of energy and the body's transformation of nutrients to functional energy through the bloodstream.

Crucial to the understanding of basic metabolism is the concept of oxygen consumption and cellular respiration. Joseph Priestly is credited with the discovery of oxygen gas. In his paper "*Observations on Respiration and the Use of the Blood*," Priestley was the first to suggest a relationship between blood and air. Lavoisier, widely regarded as the "father of modern chemistry," extrapolated on these findings of combustion and respiration in experiments done in collaboration with Pierre-Simon Laplace [4]. The pair not only devised an ice calorimeter to measure the amount of heat created during combustion or respiration, but calculated the carbon dioxide produced by the guinea pig and compared it to the generative process to create carbon dioxide. This characterized respiration as combustion, and this concept was later published in "*On Heat*." The process of deranged metabolism in response to disease was also a concept that was delineated slowly over time. Louis Pasteur and Fredrich Henle first espoused the germ theory and Lister followed through on the notion of infectious organisms leading to suppuration and sepsis. This basic understanding of the pathogenesis of disease would later become crucial to the understanding of the metabolic response to illness. It would not be until the early twentieth century, however, before metabolism was brought first to the cellular level.

In the twentieth century, the concepts of metabolism and energy exchange in response to stress states were introduced. Sir David Cuthbertson published notable work on the metabolic and nutritional demands of critically ill patients, which still serves as the foundation for current nutritional therapy for the burn, septic, and other critically ill/injured patients [5]. Based on the findings of Lavoisier, indirect calorimetry is a commonly utilized method to estimate energy metabolism through respiratory gas exchange measurements. The carbon dioxide and nitrogen waste from individual's consumption of oxygen is correlated back to the heat energy generation [6]. This technique is noninvasive, and can be applied to investigate numerous aspects of nutrition, thermogenesis, exercise, and the pathogenesis of metabolic diseases.

James Harris and Francis Benedict published *A Biometric Study of Basal Metabolism in Man* in 1919, which provided a method to estimate an individual's basal metabolic rate and daily caloric

requirements without quantitative calorimetric measurements. A regression equation was laboriously constructed. Even today, the Harris-Benedict equation allows healthcare professionals to better estimate and provide the metabolic needs of a patient in a practical and cost effective manner.

Though a significant tragedy, the 1942 Coconut Grove night club fire in Boston germinated a host of medical advances in the treatment of post-burn resuscitation, but more importantly illuminated the connection between fluid resuscitation and metabolic demands. The contributions of this body of literature have helped to recognize the stress response to injury, the importance of restoring hemodynamic stability to cellular metabolism, and began illustrating some of the sequela of resuscitation [7].

In the 1960s, Stanley Dudrick and Douglas Wilmore began investigations on the metabolic effects of intravenous nutrition supplementation and its effects on cellular metabolism, developing what they termed total parental nutrition (TPN). Initially, parenteral nutrition (PN) was designed to provide 100 % of an individual's daily caloric needs, and was designed for those who suffered from short bowel syndrome [8]. The utilization of PN has expanded far past the treatment of short bowel syndrome, and it now has specific indications in any individual unable to tolerate enteral feeds. However, over time it was found that the metabolic derangements found particularly in the liver and gut were often detrimental to the patient, and the indications of PN usage have been narrowed appropriately. There were two major seminal papers in the early 1990s regarding PN. Kudsk's work investigated the importance of the route of nutrition and its relationship with septic complications after trauma. His work demonstrated a lower incidence of septic morbidity in patients fed enterally as compared to with PN, with most of the significant complications occurring in the more severely injured patients [9]. The VA cooperative trial looked at the use of perioperative PN and its relationship with serious complications after major abdominal or thoracic surgical procedures in malnourished patients. That trial concluded that preoperative PN should be limited to only patients that are severely malnourished unless there are other specific indications for its' need [10].

Since the 1970s, significant progress has been made toward the understanding of caloric deficit and protein malnutrition. Malnutrition and metabolic derangements from inadequate caloric provision were identified as common problems within hospitalized patients. The emphasis on caloric deficit gave way to an emphasis on protein energy malnutrition. In 1974, Bistrian and Blackburn published their groundbreaking work entitled *Skeletons in the Closet*. They identified a 50 % incidence of protein energy malnutrition in a modern Boston hospital. From that point forward, we began to better understand malnutrition as a reflection of metabolic derangements associated with stress [11]. Pierre Singer published a body of literature throughout the 1990s and early 2000s on protein catabolism and the turnover of lean body mass in stressed states and the impact this has on wound healing, infection rates, and mortality. Influencing metabolism by provision of goal directed nutritional therapy became the emphasis of many institutional protocols throughout the world.

Throughout the past decade, great strides have been made in the understanding of critical illness and the contributions that adequate, early, and goal directed nutrition can make toward the reduction of morbidity and mortality. In addition to adequate caloric provision, much was published on early goal directed therapy aimed to rapidly resuscitate patients with injury and illness in order to prevent and attenuate metabolic derangements. In 2001, the landmark paper from Rivers et al. entitled *Early Goal Directed Therapy in the Treatment of Severe Sepsis and Septic Shock* was published in the New England Journal of Medicine. Emphasis was placed on adequate fluid resuscitation, vasopressor support, maintenance of central venous pressure, and provision of stress dosed steroids in an attempt to support end organ perfusion and minimize the metabolic impact of critical illness [12]. In addition, recognition of the deleterious effects of stress induced hyperglycemia also was heightened. Through work such as Van den Berghe's

Intensive Insulin Therapy in Critically Ill Patients, published in the New England Journal in 2001, it was demonstrated that elevation of serum blood glucose levels, as well as profound hypoglycemia, were independent predictors of mortality and infectious complications [13]. The maintenance of serum glucose homeostasis helps to prevent this, demonstrating the importance of attenuating the metabolic response to stress.

The basic understanding of cellular metabolism and its effects on the patient is constantly evolving over time. It has far reaching clinical implications for the practitioner; the understanding of the stress response, of nutritional support, of the resuscitation of illness and injury and the manipulation of the gastrointestinal tract to improve disease outcomes all have their basis in cellular metabolism. As our understanding of the complex mechanisms behind these processes has broadened, we have bettered our ability to care for our patients.

Cellular Metabolism

Mitochondrial Metabolism

In order to maintain functional homeostasis in the body as a whole, metabolism must be regulated at the cellular level. Mitochondria are the main source of energy for eukaryotic cells. They divide by fission, which supports the theory that they originated as symbiotic bacteria. They are rod-shaped organelles approximately 0.2–0.5 μm in diameter, with an outer and inner membrane, each with unique characteristics. The outer membrane contains protein channels, or porins, which allow passage of molecules up to 10 kilodaltons (kDa). The inner membrane is composed almost entirely of proteins. Oxidative phosphorylation takes place here, which generates the electrochemical gradient necessary for proton transport and synthesis of adenosine triphosphate (ATP).

Critical metabolic pathways take place in the mitochondria. Oxidative phosphorylation, which generates the electrochemical gradient necessary for proton transport and synthesis of ATP, occurs within the mitochondrial membrane. This process is the culmination of the tricarboxylic acid cycle. This is a highly regulated process with numerous components, and it has been found that mitochondrial dysfunction plays a role as an early cellular event in critical illness. Targeted therapies during these times of metabolic stress have demonstrated improvement in mitochondrial function with regards to the electron transport system, oxidative phosphorylation, ATP production, and reduction of oxidative stress [14]. The clinical impact of these findings is only at the point of basic investigation.

Enzyme Function

Enzymes are the workhorse of metabolic pathways. They are necessary to catalyze the innumerable biochemical processes that are vital for the living cell and organism as a whole. Their proper function is dependent on multiple elements including temperature, pH, availability of substrates, and presence of cofactors. The physiologically stressed patient has derangements in virtually all of these variables that can lead to enzyme dysfunction, such as fever, acidosis or severe malnutrition. Additionally, malabsorption secondary to gastrointestinal (GI) tract dysfunction or disease states amplifies the issue for already nutritionally deficient individual by further decreasing substrates and cofactor availability. Further considerations must be made for the patient with enzyme deficiencies, such as those who are lactose intolerant. This can lead to added substrate and cofactor perturbations as well as enzyme dysfunction.

Metabolism of the Body as a Whole

In the stressed state, the body undergoes various physiologic and metabolic changes. A hypermetabolic state ensues after a stress response, such as surgery, trauma, or sepsis, which leads to insulin resistance and hyperglycemia. There is increased oxidative stress at the cellular level and systemic activation of various inflammatory processes that

lead to complex immunologic changes. There is a poor adaptation to starvation, and accelerated turnover of energy stores [15].

Basics of Whole Body Metabolism

The building blocks of the human body are carbohydrates, proteins and fats. These components are used in various ways and with various levels of efficiency by all aerobic cells. Glucose, the preferred fuel of cellular metabolism, is utilized in the well-fed state. Fat is stored for later oxidation when readily available stores of glucose are depleted. Protein, viewed largely structural in nature rather than used for energy purposes, is used as an endogenous energy source during stressed states and periods of altered metabolism. Glucose is the driving force behind energy production, and maintenance of a readily available source of glucose is of primary importance. Glycogen, the immediately available storage form of glucose, is found primarily in the liver and is available for approximately 12–24 h of fasting. After these stores are depleted, the body will then turn to protein and fat stores to produce glucose through gluconeogenesis. If starvation persists, other metabolic changes occur to provide alternate fuels to sustain cellular metabolism. In the stressed state, energy generation is deranged even further, in conjunction with greatly increased metabolic demand.

Energy Expenditure

Total energy expenditure (TEE) is divided into three components in healthy subjects: resting energy expenditure or metabolic rate (REE), energy required for digestion, and energy expenditure associated with activity. Various other things contribute to TEE, including the ambient temperature, vasoconstriction, shivering or stressed states [16]. To measure energy expenditure, one must have a basic knowledge of what each of these three components contribute to the total.

REE, or the basic metabolic rate in the fasting state at rest, represents anywhere from 60 % to 75 % of TEE. REE can be measured using various methods. In general, this measurement is determined by body size and body composition. Gender, age, and race also affect the basal metabolic rate to varying degrees [17].

Digestion is a thermogenic process that contributes around 5 % to 10 % of the TEE. The magnitude of this contribution is determined by a number of factors, including the size of the meal, the components of the meal, the time of day it is eaten, age, and the amount of caffeine or spice within the meal [18].

Physical activity is the most variable component of TEE and is therefore the most difficult to predict. In hospitalized patients, it is generally considered to compose around 5 % to 10 % of TEE. However, this is incredibly variable and can be affected by the activity of the patient, shivering, "thrashing" behavior, or fever [19].

There are various ways to measure energy expenditure. Because the components of TEE are so variable and unpredictable, predicting this reliably and for an extended period of time remains rather difficult in actuality. There are over 200 predictive equations to estimate energy expenditure, and they are often inaccurate or incomplete, resulting in over or underestimation of energy expenditure, especially in stressed states. Measuring energy expenditure frequently is simply not practical or possible.

Estimating Energy Expenditure

Direct Calorimetry

Direct calorimetry measures the exchange and release of heat from a patient. Heat is the basic byproduct of energy metabolism, and is therefore considered a direct measurement of energy expenditure. Direct calorimeters are complicated and sophisticated machines that measure the change in temperature of air or water that is circulated through the walls of a chamber housing the patient. Although most accurate, this technique is not practical in a clinical setting.

Indirect Calorimetry

Indirect calorimetry (IC) is considered by many to be the clinical "gold standard" of the measurement of energy expenditure. IC is certainly the most accurate for determining resting energy expenditure in the critically ill patient. "Metabolic carts" are available in most institutions, and today are often a component of modern computer driven ventilators. IC is most useful in specific disease states in which predictive equations are demonstrated to be unreliable or inaccurate, such as chronic respiratory distress syndrome, acute respiratory distress syndrome, or obesity. IC is also useful to help understand why patients are failing nutritional therapy when fed by standard predictive equations, as in the case of poor wound healing or delayed ventilator weaning, as it provides directed information on whether appropriate energy is being provided. IC is an effective tool in evaluating whether a patient is being over or underfed by measuring respiratory quotients.

Indirect calorimetry calculates REE and the respiratory quotient (RQ) by measuring whole body oxygen and carbon dioxide gas exchange. The accuracy of IC is dependent on many variables, and these must be manipulated to achieve a steady state (see Table 1.1) [20]. Once obtained, the REE gives a good approximation of the patients energy needs at that time.

The RQ helps direct the amount of energy provided, as well as the component composition of carbohydrate, protein, and lipid that is being provided. An RQ of less than 0.82 implies lipid catabolism, usually from underfeeding, and an increase in caloric delivery is warranted. A RQ of greater than 1 indicates pure carbohydrate oxidation and the potential for lipogenesis, usually from overfeeding. This increases the respiratory demand, and the total caloric and carbohydrate delivery should be reduced. A RQ of 0.85 indicates appropriately mixed substrate delivery, which is a sign of appropriate caloric and component provision. Although useful in clinical settings, care must be exercised when interpreting the RQ, as conditions such as diabetes, ketoacidosis, or hypermetabolism from inflammatory states can alter the value significantly [21, 22].

Table 1.1 Factors decreasing accuracy of indirect calorimetry

• Mechanical ventilation changes during the testing session
• FiO2 of >60
• Positive end expiratory pressure of >12 cm H20
• Leaks in the sampling system
• General anesthesia administered within 6–8 h of the study
• Shivering, thrashing, or excessive skeletal muscle contractions
• Acute pain
• Routine health care activities or nursing care given during testing
• Initiation or slowing of administered enteral nutrition during testing
• Acute changes of ventilatory patterns
• Inability to collect all of expiratory flow
• Supplemental oxygen administered to spontaneously breathing patients
• Hemodialysis, peritoneal dialysis, or continuous renal replacement therapy
• Errors in calibration
• Inadequate length of time for study to be implemented

Adapted from [20]

Predictive Equations

There are many other ways to measure or estimate resting energy expenditure. Body composition measurements can help to estimate this value via water displacement and whole body air displacement plethysmography (ADP) in commercially available machines. These methods are reserved and utilized for outpatient, healthy individuals wishing to gain a better understanding of their metabolic footprint, and has extremely limited usefulness in the inpatient clinical setting.

Numerous equations exist to estimate energy expenditure, and understanding the data needed and the reliability of each formula is important to calculating a sound therapeutic goal. The reverse Fick equation estimates oxygen consumption from the content of oxygen within arterial and mixed venous blood multiplied by cardiac output measurements. However, this requires the placement of a pulmonary artery catheter to obtain data points, and is biased toward underestimation, both contributing to its limited usefulness in the clinical setting [23]. The Harris-Benedict equation predicts

the basal metabolic rate, factoring in variables such as sex and age. This equation is used very commonly; however is limited because it does not take into consideration factors such as body mass index or age and racial diversity of current patient populations. The formulas are as follows [24]:

Men Energy expenditure = 66 + 13.75 (wt in kg) + 5 (ht in cm) − 6.8 (age)

Women Energy expenditure = 655 + 9.6 (wt in kg) + 1.8 (ht in cm) − 4.7 (age)

It is common practice to use "adjusted body weight" parameters within the Harris-Benedict equation:

$$\left[\begin{array}{l}(\text{actual body weight} - \text{ideal body weight}) \\ \times 0.25 + (\text{ideal body weight})\end{array}\right]$$

This practice will underestimate energy expenditure in most obese patients.

To combat this underestimation of the Harris-Benedict equation in the obese, as well as to take into consideration the changes in metabolism that occur in critical illness, many other equations have been put forth. The most commonly used of these are the Penn State and the Ireton–Jones equations. These equations use modifiers for illness severity, inflammatory states, respiratory demands, body weight and height, and include fluid factors like body temperature and minute ventilation. This improves reliability in critical ill patients.

Ireton Jones for spontaneously breathing patients [25]

Energy expenditure = 629 − 11 (age) + 25 (actual body weight) − 609 (BMI > 27 1 = present, 0 = absent)

Ireton Jones for ventilated patients

Energy expenditure = 1784 − 11 (age) + 5 (actual body weight) + 244 (sex, male = 1, female = 0) + 239 (Diagnosis of trauma 1 = present, 0 = absent) + 804 (BMI > 27 1 = present, 0 = absent)

Penn State [26]

REE (kcal/day) = Harris-Benedict equation (0.85) + minute ventilation (33) + Maximum body temperature in 24 h (175) − 6433

To make estimation of energy needs less cumbersome for the bedside practitioner, the American Society of Parenteral and Enteral Nutrition have devised a simple calculation using kcal/kg based on the findings of the various estimation methods. Generally, a range of 20–35 kcal/kg/day is recommended for adults [27]. These requirements can be under or overestimated in patients who are severely critically ill, obese, or failing to respond to energy provided, but are quick and easy to use at the bedside.

Provision of Energy Requirements

Once an accurate estimation of the total energy requirements a patient needs, the next step is to determine what components to provide. A healthy subject generally meets their REE with a carbohydrate: lipid: protein ratio of approximately 50 %: 30 %: 20 %. This ratio changes based on the stress the individual is under and what illnesses or comorbidities they are experiencing [28]. There is also a robust philosophy that protein calories are included in meeting TEE and the limitations on provision of lipids is held at 30 % of TEE and carbohydrates to less than 400 g/day.

Carbohydrates

Carbohydrates are generally the most efficient and readily available form of glucose. The minimal requirement for carbohydrate intake is determined by the brain's need for glucose. A minimum of 50 g of carbohydrates/day is necessary to avoid ketogenesis. The liver produces approximately 50 % of serum glucose via glycogenolysis and 50 % of serum glucose from gluconeogenesis [29, 30]. The main function of glycogenolysis and gluconeogenesis is to maintain plasma glucose homeostasis, usually in the range of 80–120 mg/dL. This level is necessary to supply a constant state of substrate provision to the tissues and organs. The liver plays an integral role in the maintenance of glucose homeostasis during fasting and fed states via production of lipoproteins and glycogen for storage, as well as the breakdown of these storage products to release glucose. Normal blood glucose levels are hormonally regulated through the interplay of cortisol, insulin, and various catecholamines. In illness or injury, peripheral glucose oxidation is slowed. This, coupled with increased circulating levels of stress hor-

mones, causes a stress induced hyperglycemia, contributing to increased protein breakdown from muscles and blunting immune responses [31, 32].

Carbohydrate provision should usually make up no more than 50 % of caloric provision in patients, though this percentage should be altered in specific disease states. Dextrose is the most common carbohydrate form provided in enteral nutrition therapy.

Proteins

While all macronutrients are affected by the metabolic changes associated with the hypermetabolic state, protein catabolism is disproportionately increased [33].

A negative energy balance in critical illness correlates to morbidity [34] and most acutely with loss of lean body mass [33]. Heightened rates of protein catabolism in the stressed state lead to loss of lean body mass. Increased turnover of protein remains unabated after a stress response despite nutritional support that would be considered adequate for a non-stressed individual [33].

There are many factors leading to this increased loss of protein, including mobilization of peripheral stores for gluconeogenesis, production of acute phase reactants, promotion of wound healing via production of cells like fibroblasts, and restoration of acid base balance in the kidney [33]. Support of the immune system via maintenance of gut mucosal integrity is another important source of protein turnover and utilization [35]. Protein turnover is also increased by states such as starvation and prolonged immobilization, both of which are common during critical illness. This heightened and exaggerated catabolism of protein is disproportionate to the overall increase in metabolism as well; we know that provision of nonprotein calories in amounts sufficient to meet energy demands does little to preserve lean body mass and improve nitrogen sparing. In fact, protein requirements can increase to 15–20 % of total calories during times of physiologic stress [36].

Another concept to consider when thinking about protein requirements is the idea of "conditionally essential" amino acids, as mentioned earlier. Certain amino acids which are not considered essential in the non-stressed state become essential during critical illness because of increased requirements for that particular amino acid. For example, high amounts of tryptophan, phenylalanine, and tyrosine are seen in acute phase proteins, and the increased synthesis of these proteins requires proportionately higher need for these amino acids [37]. Similarly, glutamine, which is normally 50 % of the body's intracellular free amino acid pool, serves as fuel for rapidly dividing cells and as a nitrogen shuttle between visceral organs and muscle tissue, rapidly decreases in concentration in certain states and exceeds the body's ability to synthesize it [38, 39]. This alteration in substrate utilization can lead to breakdown of muscle tissue in order to supply these "conditionally essential" amino acids, further enhancing the loss of lean body mass.

Loss of lean body mass and negative nitrogen balance is seen most dramatically in the first 9–12 days following an insult, but even continues to exceed the loss that would be expected based on the increase in resting energy expenditure through the first 21 days [40]. In fact, 16 % of total body protein is lost in that first 21-day period, 67 % of which comes from muscle stores [40]. Loss of lean body mass in critical illness is linked to increased rates of pneumonia, impaired wound healing and prolonged rehabilitation, pressure ulcers, and even mortality [41].

Minimizing the loss of lean body mass and preservation of a positive nitrogen balance is obviously important to reduce the negative impacts of stress catabolism. The question that remains is how do we best achieve this goal? Every patient is different, and different conditions affect this catabolic state differently. For example, minor trauma or surgery has less of an effect on protein turnover than severe sepsis or burns. There are many calculations and methods to assess protein metabolism and nitrogen balance, including assessing nitrogen balance, measuring amino acids directly by sampling directly across tissue beds, measurement of tracers to assess protein degradation, and turnover of individual components, such as urea.

Of these methods, nitrogen balance is the most widely used [33].

Nitrogen balance is best assessed through the quantification of urine urea nitrogen.

$$\text{Nitrogen balance} = \text{Nitrogen intake} - \text{Nitrogen output}$$

Nitrogen output (g/day) = urinary urea nitrogen (mg/100 mL) × urinary volume (L/day)/100 + 20% of urinary urea losses + 2 g [42]

Calculating this equation requires a 24-h urine collection. In addition, this equation must be adjusted to account for losses from renal dysfunction, stool, ostomy, and fistula losses [15]. These losses, plus incomplete urine collections can make this equation somewhat erratic and cumbersome to use at the bedside. However, in general it is a reliable tool to assess the adequacy of protein delivery.

But, there is a paucity of data to suggest there are clinical benefits related to reduction of net N losses through the provision of protein-rich diets. Additionally, since there is some data implying high amounts of protein may in fact be harmful, there is a significant amount of uncertainly about the optimum amount of protein to provide. Current guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN), the European Society for Parental and Enteral Nutrition (ESPEN), and the Society of Critical Care Medicine (SCCM) recommend 1.5–2.0 g protein/kg/day to patients with moderate to severe stress as a result of trauma, sepsis, or surgery [43–45]. Patients with severe sepsis or burns may require up to 2.5–3 g protein/kg/day [46]. Ongoing assessments of adequate protein delivery, such as urine urea nitrogen and documentation of wound healing, should be performed.

While there is much discussion about the potential benefits of protein provision in the stressed state, there is also the question of whether or not protein intake should be limited in certain disease states. There is concern about of the amount of protein to provide patients with chronic liver disease. The concern for hepatic encephalopathy in this patient subset prompts many to restrict dietary protein. This practice can worsen protein calorie malnutrition that is already present in many of these patients and, in turn, worsen outcomes [47]. Most of these patients can tolerate protein without exacerbation of hepatic encephalopathy, and while teleologically sensible, branched chain amino acid diets have not significantly impacted management [47].

Protein provision in renal failure is misunderstood. The restriction of protein in these patients has been the topic of debate for many years. The results of clinical trials are varied, some claiming benefit and others claiming none. The most recent data seems to suggest that a protein-restricted diet could delay the need for hemodialysis and has no harmful effects on nutritional status [48]. Once hemodialysis is started, there is no role for protein restriction.

Fats

Lipids are essential molecules that serve important functions throughout the human body, and are a major form of caloric support, comprising 15–30 % of recommended total energy intake. Depending on the chemical configuration, lipids provide a dense form of calories, at 8.3 kcal/g for medium chain and 9 kcal/g for long chain fatty acids. Similarly, the chemical composition of fatty acids has different effects on inflammation and immune response [49–55]. During times of critical illness or stress, provision of certain formulas can curb the immune response, lower infection, and improve aspects of patient outcomes [56].

Long chain fatty acids (LCFA) are typically composed of 14 or more carbon atoms and are described as saturated or unsaturated based on the degree of hydrogenation and double bonding of the carbon molecules in the chain. Monounsaturated fats have one double bond, where polyunsaturated fatty acids (PUFA) have more than one. As the number of double bonds increase and the number of carbon molecules decrease, the more liquid the fat is at room temperature. Thus, animal fats, which are longer, and tend to be less saturated, are solids at room temperature (i.e., lard) [57]. Location of the double bonds also has a major role in the metabolic end-products putative effects.

Trace Elements/Minerals

Most commercially available formulas provide Daily Recommended Intake (DRI) for vitamins and trace elements (see Table 1.2). Patients with severe malnutrition, high losses as with enteric fistulae, bypass procedures, and/or malabsorption may require additional supplementation. Many vitamins act as cofactors for various metabolic processes, including a vital role in the

Table 1.2 Recommended daily allowance of vitamins and trace minerals

			Females		
Fat-soluble vitamins	M/F	Males	Typical	Pregnant	Lactating
A (mcg)		900	700	770	1,300
D (mcg)	15–20				
E (mg)	15				19
K (mcg)		120	90		
Water-soluble vitamins					
B_1 (mg)		1.2	1.1	1.4	1.4
B_2 (mg)		1.3	1.1	1.4	1.6
B_5 (mg)	5			6	7
B_6 (mg)		1.3–1.7	1.5	1.9	2
B_{12} (mcg)	2.4			2.6	2.8
C (mg)		90	75	85	120
Folate (mcg)	400			600	500
Biotin (mcg)	30				35
Other nutrients					
Choline (mg)		550	425	450	550
Trace elements					
Copper (mcg)	900			1,000	1,300
Chromium (mcg)		30–35	20–25	30	45
Fluoride (mg)		4	3		
Iodine (mcg)	150			220	290
Iron (mcg)		8	18	27	9
Manganese (mg)		2.3	1.8	2	2.6
Molybdenum (mcg)	45			50	50
Selenium (mcg)	55			60	70
Zinc (mg)		11	8	11	12

Adapted from [58]

production of ATP. Deficiencies lead to detrimental physiologic conditions.

Vitamin B6 deficiency is associated with hyperhomocysteinemia and hyperglycemic states in surgical intensive care unit patients [59, 60]. High dose supplementation increased immune response of critically ill patients [61]. While signs and symptoms are nonspecific, vitamin B1 (thiamine) deficiency can go unrecognized in the intensive care unit. Early and appropriate supplementation can prevent negative consequences [62]. Vitamin B2 (riboflavin) is a key factor for flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). A large proportion of critically ill individuals have suboptimal vitamin B2 status, which can be significantly improved with supplementation. However, this improvement is transient, and deteriorates with discontinuation of the intake [63, 64].

Outcome specific data is lacking in regard to certain vitamin deficiencies, however it should be the goal of the physician to provide adequate substrate and cofactors necessary to support the metabolic demands of the stressed patient.

Specific Nutrients and Their Effects on Metabolism

Omega 3 Oils

Omega 3 oils are long chain n-3 PUFA most commonly found in fish and canola oils. They are considered essential fatty acids, as humans cannot synthesize de novo. Two biologically active examples include eicosapentaenoic acid (EPA) (Fig. 1.1), a 20-carbon fatty acid, and docosahexaenoic acid

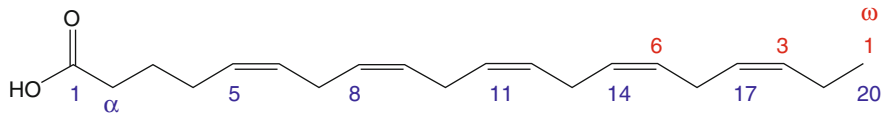

Fig. 1.1 EPA

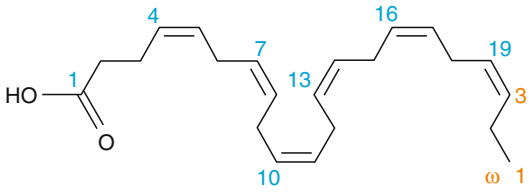

Fig. 1.2 DHA

(DHA) (Fig. 1.2), a 22-carbon molecule. Although found in much smaller amounts, docosapentaenoic acid (DPA) (Fig. 1.3), a 22-carbon fatty acid, also has metabolic importance. These fatty acids (FA) are absorbed from the gastrointestinal tract, transported to the liver, and released into the circulation in lipoproteins and plasma phospholipids. They are incorporated into cell membranes throughout the body. Following initial ingestion of fish oils, there is a nonlinear increase in the concentration of EPA and DHA in membranes within days, and with continued consumption, greatest inclusion around 2 weeks. Upon removal from the diet, elimination from plasma lipids occurs over a few days, while cellular membrane concentrations can remain elevated for up to 2 months [49].

When incorporated into cellular membranes, n-3 PUFAs will increase in proportion to n-6 FAs (such as arachidonic acid). This has clinical importance during stress as metabolism of n-6 FAs leads to proinflammatory and pro-thrombotic eicosanoid derivatives which impair T-cell function, cytokine secretion, leukocyte migration, and reticuloendothelial system function [50]. Conversely, n-3 phospholipid metabolism leads to less active and even anti-inflammatory molecules [51]. Omega-6 fatty acids are predominantly immune-suppressing by means of their products of metabolism, namely through the elongation to arachidonic acid. In large doses, they tend to inhibit the response of the reticuloendothelial system. They alter the function of neutrophils and macrophages [65]. They also affect signal transduction and immune mediation. The entities responsible for these actions are prostaglandins, leukotrienes, and thromboxanes—all eicosanoid mediators of inflammation that are derived from arachidonic acid metabolism [56]. High intake of omega-6 fatty acids has been associated with a prothrombotic and proaggregatory state that can be manifested as increased blood viscosity, decreased bleeding time, vasospasm, and vasoconstriction [66, 67].

Patients both at risk for and those with the diagnosis of acute lung injury are found to have decreased concentrations of n-3 PUFAs of 25 % and as low as 6 % of normal, respectively [51]. While some studies have found a beneficial effect of supplementation with n-3 enriched formulas [52–54], others have failed to show any benefit even with twice day supplementation [55].

In contrast to other omega-6 fatty acids, gamma-linolenic acid acts favorably on the immune system by modifying the cellular lipid composition and altering eicosanoid biosynthesis. The end products of its metabolism are anti-inflammatory and can affect the breakdown of arachidonic acid into its proinflammatory constituents [68, 69]. It has been added to enteral formulas for decades and is found naturally in borage oil [56].

The use of omega-3 fatty acids in inflammatory states has been supported in multiple prospective, randomized studies [68]. Found in oils such as flaxseed, safflower, canola as well as in fatty, cold-water fish (salmon, swordfish), omega-3 fats have been studied for decades secondary to their beneficial effects in critical illness. They have anti-inflammatory and neuroprotective properties from stimulating resolvins, protectins and maresins (lipid mediators), docosatrienes, and neuroprotectins, which are potent

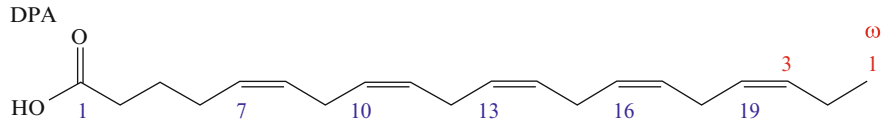

Fig. 1.3 DPA

effectors of the resolution of inflammation [56]. Resolvins function by regulating polymorphonuclear neutrophil transmigration. Neuroprotectin decreases neutrophil infiltration, proinflammatory gene signaling, and nuclear factor-κB binding. Furthermore, EPA and DHA alter cellular level metabolism and response by changing cell membrane phospholipid ratio, affecting gene expression and endothelial expression of intercellular adhesion molecule-1 (ICAM-1), E-selectin and other endothelial receptors that regulate vascular integrity [69, 70]. EPA has also been found to help prevent the loss of diaphragm function in sepsis [71]. It may also enhance resistance to gram-negative pathogens, such as *Pseudomonas*, although this has thus far only been demonstrated in mice [72].

Beginning in 1999, the use of omega-3 fatty acids in acute respiratory distress syndrome (ARDS) and Acute Lung Injury (ALI) showed good results and outcomes [73]. Using EPA, DHA, gamma-linolenic acid (GLA), and antioxidants in ARDS improved ventilation, oxygenation, and intensive care unit (ICU) length of stay. Although with some mixed results, subsequent studies have confirmed the trend toward the beneficial use of these dietary lipids in ARDS and ALI, with modest morbidity and mortality improvement [54, 55, 74]. In many critical care practices it is common to use anti-inflammatory lipid formulas as pharmacologic agents to attenuate inflammatory states, both in passive modulation of the inflammatory response, and the active resolution of inflammation [56].

Despite these encouraging findings, there remain a number of points of concern regarding the widespread use of these agents ubiquitously in the care of the stressed individual. In the early studies, the control formulations used were "proinflammatory" (i.e., *Pulmocare*—a high fat (n-6), low carbohydrate formula). At that time, little was known of the proinflammatory tendency of this feeding. To date, further studies with a more neutral fat composition have not been added as a control to verify the results. It can be interpreted that at least partial benefit was seen secondary to the high omega-6 formula used as control, rather than entirely due to the beneficial effect of the study elements. Additionally, the definition of ARDS and ALI used in some studies was based on prior criteria, rather than contemporary definitions. The benefit seen in these studies may be called into question secondary to selection biases.

Further questions about adding gamma-linolenic acid in ICU setting have been raised. While there are theoretical benefits of supplemental use in the ICU setting [69], isolated benefit has only been shown in animal models [75–77]. Added concerns revolve around the optimal dosage and timing of supplementation, as well as the route of administration. For example, if parenteral nutrition is necessary, formulations with fish oil, olive oils, medium chain triglycerides, or structured lipids are not available in the United States, where soy based preparations are the only option [78]. Finally, many studies showing beneficial in conjunction with omega-3 fatty acids have also been conducted with other favorable agents such as glutamine, arginine, or nucleic acids. It is difficult to delineate the contribution of each agent toward the improved clinical metrics [79].

Valid concerns regarding supplementation with omega 3 FAs also revolve around drug interactions, the bioavailability in diabetics or schizophrenics and fasting hyperglycemia in diabetic patients. Despite a concern for increased risk of bleeding, there are no randomized controlled trials demonstrating this effect. Additional apprehensions center around the "fishy" aroma and the development of gas, bloating, eructation, and diarrhea. Time released preparations can help reduce these effects.

Table 1.3 Support in the literature for the use of immune modulating agents

Author	Journal	Year	Population	*N*	Outcome
Braga M	Arch Surg	99	GI surgery	206	Decreased infection
Senkal	Arch Surg	99	Surgery	154	Decreased infection
Synderman	Laryng	99	H and N Ca	134	Decreased infection
Riso	Clin Nutr	00	Head and N Ca	44	Decreased infection
Tepaske R	Lancet	01	Cardiac	50	Decreased infection
Gianotti L	Gastro	02	GI surgery(N)	354	Decreased infection
Braga M	Arch Surg	02	GI surgery(M)	196	Decreased infection
Giger	Ann Surg Onc	07	GI cancer	46	Decreased infection
Helminen	Scand J Surg	07	GI surgery	50	No change
Klek S	Ann Surg	08	GI surgery/TPN	103	No change
Fukuda T	Dis Esophagus	08	Esophageal Ca	123	Decreased infection
Ryan A	Ann Surg	09	Esophageal Ca	58	No change lean BM
Okamoto	WJS	09	Gastric Ca	60	Decreased SIRS, infection

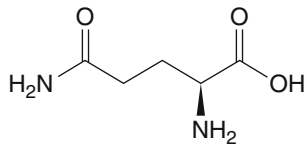

Fig. 1.4 Glutamine

Amino Acids

During times of stress, as in the perioperative period, critical illness or following trauma, specific amino acids and their supplementation deserve consideration. A promising area on the horizon for protein delivery is the idea of specific amino acid delivery and the potential benefits of this practice. Specific amino acids, such as glutamine and arginine are becoming an ever-increasing part of so-called *immunonutrition*. Immunonutrition is the concept that specific therapeutic agents like amino acids, antioxidants, or fish oils can have powerful therapeutic benefits. We know that certain amino acids exert pharmacologic activity when given during critical illness, and that these actions can have wide and varied clinical results.

The amino acids that are the most promising as therapeutic targets are those that are conditionally essential. There is an overwhelming amount of data to support the claim that these immune modulating formulas impact outcomes (see Table 1.3). It is difficult, however, to know which portion of the formula is causing the clinical effect. Specialty formulas designed to enhance the immune system are costly, and many practitioners express concern that in the absence of hard data to support their use we cannot rationalize the expense. However, ASPEN and SCCM both recommend the use of immune modulating formulas containing arginine, glutamine, nucleic acids, omega-3 fatty acids, and antioxidants are recommended for patients undergoing major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation. This is not a panacea however with caution being exercised in those with severe sepsis [45].

Glutamine

Glutamine (Fig. 1.4) is the most abundant free amino acid in the human body, making up more than 50 % of the intracellular free amino acid pool. It has been studied in great detail over the past 15 years, and its effects and uses are wide and varied. Glutamine is an important fuel source for rapidly dividing cells, such as fibroblasts and reticuloendothelial cells, as well as the gut mucosa of the small bowel [33]. In addition, it carries two nitrogen moieties per molecule, and serves as a shuttle for nitrogen between muscle tissue and visceral organs [15]. Glutamine obviously plays an important role in cell homeostasis and organ metabolism. Because of these functions, glutamine stores rapidly deplete and decreased circulating concentrations are seen in exercise, sepsis, and trauma [80]. When the circulating concentration of glutamine exceeds the

body's ability to synthesize de novo glutamine, atrophy of intestinal mucosa, impairment of immune function, and decreased protein synthesis are seen [81]. Decreased levels of plasma glutamine have also correlate with increased mortality [82].

Glutamine exhibits a direct antioxidant effect and reduces oxidative stress on cells by attenuating the iNOS pathway in sepsis. It also acts directly on the tissue by preserving mitochondrial function and acting as a substrate for ATP synthesis. In addition, it attenuates cytokine expression [81]. But perhaps the most important manner in which glutamine exerts its actions on the immune system is by the upregulation of heat shock proteins. Heat shock proteins function to refold misfolded proteins coming off the endoplasmic reticulum, help eliminate irreversibly damaged proteins by marking them for apoptosis, stimulate the innate immune system, and attenuate proinflammatory cytokines [83]. Heat shock proteins are induced by a stress response, and this is enhanced by glutamine administration, heightening the response [84, 85]. The proposed mechanism is attenuation of the inflammatory response by binding and inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thus limiting interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), which occurs as a proinflammatory response to injury/sepsis [86].

Glutamine supplementation in critical illness has been shown to decrease mortality, length of stay, and infectious morbidity. Interestingly, there data that suggest there is no effect from glutamine supplementation. These studies are very heterogeneous with respect to patient population, route of glutamine administration, and amount of glutamine administration [86]. It seems that high doses given via a parenteral route demonstrate greater effect than low doses given by the enteral route. It is recommended to give high dose oral glutamine at levels greater than 0.2–0.3 g/kg/day (or, roughly, 20–40 g/day). There is more data for intravenous (IV) than oral (PO) glutamine; however PO in high doses seems to be efficacious [85].

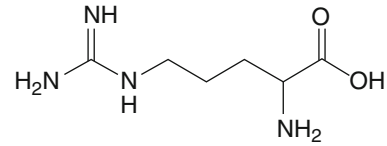

Fig. 1.5 Arginine

Arginine

Arginine (Fig. 1.5) is considered a nonessential amino acid under normal physiologic conditions. l-Arginine is available to the host from endogenous synthesis via citrulline conversion in kidney, from endogenous protein breakdown, and from dietary protein sources [87]. Arginine plays an active role in cell growth and proliferation, wound healing, immune function and regulation, and waste ammonia disposal through the urea cycle [33]. Arginine also helps regulate vascular endothelial vasodilatation through the nitrogen oxygen synthase (NOS) pathway and the generation of nitric oxide (NO) [88]. NO is also a potent intracellular signaling molecule influencing virtually every mammalian cell type and is involved in the cytotoxicity of activated macrophages [87]. De novo synthesis, as well as dietary supplementation of arginine is diminished in critical illness, making it a conditionally essential amino acid.

In critical illness, the cellular demand for arginine is increased due to the up regulation of arginase-1 in trauma and surgery [89]. In addition, plasma arginine levels diminish rapidly in trauma, critical illness, and sepsis [90]. When arginase pathways are upregulated, there is a resultant decrease in substrate availability for the opposing NOS pathway, thereby downregulating NO synthesis [87]. This inhibition of the NOS pathway is secondary to increased circulating levels of asymmetric dimethylarginine (ADMA), which may have a direct inhibitory effect on the NOS pathway [91, 92]. ADMA is then converted to citrulline, which is then use to synthesize arginine [19]. The question is whether this downregulation of the NOS pathway and resultant decrease in the levels of circulating NO is the source of the vasoconstriction and end organ malperfusion seen in sepsis, or if this downregulation

is an adaptive strategy the body undergoes to prevent hypotension after critical illness [93].

This is the source of much controversy in the topic of arginine supplementation. Is the increased activity of arginase-1 involved in the increased levels of ADMA purely a mechanism by which to increase de novo synthesis of arginine in times of need? Does supplementation of arginine fuel the NOS pathway in preference to the arginase-1 pathway? In hemodynamically unstable critically ill patients, there was concern that vasodilatation related to increased nitric oxide could worsen systemic hypotension [94]. As arginine is a common constituent of many immune-enhancing formulas utilized in the critically ill patient, this concept led to growing concern about immunonutrition use in septic patients.

Making generalized statements about amino acid metabolism in critical care is extremely difficult because the "critically ill" population is not a homogeneous group. Making any generalized statements about the toxicity or benefits of any dietary supplement, let alone an amino acid with the metabolic complexity of arginine is not advisable as no study of these individual supplements can effectively be done in a clinical setting. Although theoretical concern is understood, both animal and human data are available to support arguments for and against the use of arginine [95, 96]. In light of this conflicting data, currently ASPEN recommends against the use of arginine containing formulas in the hemodynamically unstable patient regardless of the nature of the insult [45]. Further research as to the safety and efficacy of arginine in sepsis is needed.

In hemodynamically stable patients, the optimal dose of arginine to be delivered has yet to be determined. It seems that the 15–30 g of enteral supplemental arginine is safe and appears to meet the needs of the patient [97]. This is the amount that is commonly received at goal rates with immune modulating formulas.

Amino Acids on the Horizon

There are many other promising amino acid targets that are the fuel for ongoing research. Citrulline (Fig. 1.6) is one such amino acid. Citrulline is utilized in the de novo synthesis of arginine and is produced through conversion of ADMA, as previously discussed [92]. Studies demonstrate that citrulline availability is closely linked with arginine availability [95, 97]. Provision of citrulline may provide for de novo synthesis of arginine, thereby reducing the amounts of circulating ADMA and its deleterious effects.

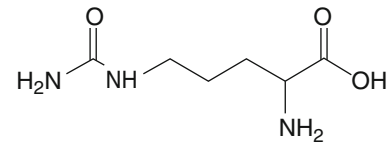

Fig. 1.6 Citrulline

Choline is another essential amino acid that is necessary for cell membrane structure. Choline is not a part of many parenteral nutritional formulations, and patients on long-term PN have impaired choline synthesis [33]. There is some evidence to support that this choline deficiency plays a role in the hepatic impairment seen in patients on long-term PN, and enteral repletion of choline to prevent or treat PN-induced hepatic failure is currently under research and shows promise [98].

States of Altered Metabolism

Metabolism in the Stressed State

One of the key ways in which metabolism impacts the surgical patient is catabolism. Surgical stress, trauma, burn injury, and critical illness all impact basic cellular metabolism, essentially creating a metabolic pathway leading to energy consumption and tissue breakdown. The inflammatory response is propagated by the release of inflammatory mediators, such as the numerous interleukins and tumor necrosis factor alpha [99]. The metabolic response to stress may be further altered by the presence of bacterial products, such as endotoxin. Even pain and anxiety can indirectly trigger a catabolic response through activation of the neuroendocrine system [100]. This catabolic response is directly proportional to the degree of stress that the host experiences, and can persist for weeks to months following the injury or illness [101].

The so-called "ebb phase" of the metabolic response to injury occurs immediately following the insult and lasts for several hours after the injury. It is characterized by elevated blood glucose levels with normal glucose production, elevated free fatty acid levels, low insulin levels, high levels of circulating catecholamines and glucagon, elevated serum lactate level, decreased oxygen consumption, and increased cardiac output [102]. The "flow phase" of metabolic response occurs next and can last weeks following injury, and is characterized by glucose intolerance, inflammation, and muscle wasting [102].

One of the most objective ways to measure the degree of response to stress in the host is to measure the alterations in resting energy expenditure (REE), via indirect calorimetry [103]. In minor trauma, such as long bone fracture, REE can increase from 10 % to 30 % over baseline. In sepsis, REE increases from 20 % to 25 % over baseline, while in severely stressed states, such as burn injury, REE can increase from 40 % to 100 % [104]. This increased need for substrates is due to the need for wound healing, synthesis of cellular and humoral immune components and acute phase reactants [33]. Amino acids are the major substrate for cellular metabolism during periods of catabolic stress, and lean body mass turnover is rapidly accelerated [33]. The body turns over muscle mass to provide alanine and glutamine as substrates to meet the increased energy needs [35, 36]. If exhausted or not appropriately supplemented, failure of gluconeogenesis in the liver, severe hypoglycemia, and amino acid deficiencies will result and, if left uncontrolled long enough, will lead to death.

The hypermetabolic state of the stressed host is attenuated by providing energy substrates. After an insult however, a compensatory anti-inflammatory response syndrome (CARS) has been described following periods of metabolic stress [105]. If CARS persists following injury or illness, the patient is metabolically deranged, immunocompromised, and susceptible to infectious complications. This is a major contributor to late deaths after trauma and injury and puts patients who have survived the acute illness at high risk for other or repeated infections.

Metabolic Response in Obesity

There are divergent outcomes about the effects of obesity in critical illness and injury. There are a number of studies that suggest that obesity confers a survival advantage to patients, or at minimum has no increased risk of mortality. However, there is also a growing body of literature demonstrating obesity is an independent predictor of mortality and significantly increases the risk of morbidity in this patient population. Studies that demonstrate obesity does not increase morbidity or mortality surmise the higher levels of anti-inflammatory adipokines such as IL-10 and leptin positively modulate surgical stress [106]. These studies have demonstrated that there is a decreased incidence of ARDS in the severely obese, a trend toward reduced length of stay, and despite a higher incidence of organ failure, no difference in mortality [107–110].

These results must be considered with the knowledge that extremely obese patients have a higher number of comorbid conditions, and that those conditions contribute to ICU-related mortality and morbidity [111, 112]. Studies dealing directly with the severely obese or those with centripetal obesity (the so-called "metabolic syndrome"), demonstrate increased risk of mortality, pneumonia, organ failure, and other complications [113–116]. These studies argue that the circulating levels of adipokines that are anti-inflammatory, such as IL-10, are actually decreased in the morbidly obese patient compared to their lean counterparts. In addition, circulating levels of proinflammatory adipokines, such as resistin and visfatin, are significantly increased in obesity, contributing to increased complications and death [117]. As the number of patients with obesity continues to grow worldwide, the mechanisms behind these findings are increasingly important to understand.

Metabolism in Malnutrition/ Starvation

Starvation has a linear and temporally progressive negative impact on the patient. In early starvation, blood glucose concentrations decrease

and serum insulin levels decrease in response to this change. Glycogen stores within the liver are depleted within 12–24 h. Soon after glycogen stores are depleted, the body induces a catabolic response, turning over protein stores for gluconeogenesis by the liver. Lipolysis increases as well, providing substrate for hepatic ketogenesis that peaks after 2–3 days of starvation [118].

After the early starvation phase peaks and wanes, the body enters an adapted starvation response. This host metabolism is designed to minimize protein breakdown by reducing energy expenditure. Keto-acids become the primary metabolic fuel for the brain and erythrocytes, replacing glucose. Ever decreasing circulating insulin levels allow for increased lipolysis. After all lipid stores are depleted, protein is the only source available for cellular metabolism. While the relationship of decay is linear and the resultant complications pattern or weakness, bedridden, skin breakdown, pneumonia follows, most deaths ensue from cardiac arrhythmias or arrest due to electrolyte abnormalities [119].

Areas of Future Research

Genomic Considerations

After injury or illness ensues, the inflammatory response is regulated by a release of cytokines, often termed a "cytokine storm." These cytokines and the subsequent inflammatory cascade are implicated in the pathophysiology of organ failure after injury or illness [120]. Completely obliterating this inflammatory cascade has detrimental effects, often contributing to significant morbidity and early mortality. Conversely, a brisk and pronounced inflammatory response early after an insult has also been demonstrated to be disadvantageous [121].

It follows from the patient unique cytokine response to injury and illness that varies in time from insult and in degree to type of insult, that genetic encoding is responsible for the metabolic response to stress. The systemic inflammatory response syndrome (SIRS) is associated with activation of innate immunity. With severe SIRS, increased levels of TNF-α and toll-like receptor 4 (TLR4) circulate, and decreased circulating levels of IL-10 and transforming growth factor β1 (TGFβ1) are present [122–124]. A balance between pro and anti-inflammatory cytokines is crucial to prevention of SIRS-related complications and survival [125]. To date we have not been able to achieve this likely because the triggers for synthesis is unique to the DNA. Altered responses to stress such as trauma survival and ARDS frequency seem to be sex linked.

As we further elucidate the role of genetic encoding and its role in the development of the metabolic response to stress, potential targets for inflammatory modulation could be identified. If these targets could be manipulated early enough in the stress response and cytokine storm cascade, perhaps survival rates could be impacted dramatically.

References

1. "metabolism." Merriam-Webster.com. 2011. http://www.merriam-webster.com (8 May 2011).
2. Dunn PM. Aristotle (384–322 bc): philosopher and scientist of ancient Greece. Arch Dis Child Fetal Neonatal Ed. 2006;91(1):F75–7.
3. Eknoyan G. Santorio Sanctorius (1561-1636) - founding father of metabolic balance studies. Am J Nephrol. 1999;19(2):226–33.
4. Karamanou M, Androutsos G. Antoine-Laurent de Lavoisier (1743-1794) and the birth of respiratory physiology. Thorax. 2013. doi:10.1136/thoraxjnl-2013-203840.
5. Fleck A. Obituary Notice: Sir David P. Cuthbertson. Br J Nutr. 1990;63:1–4.
6. Ferrannini E. The theoretical bases of indirect calorimetry: a review. Metabolism. 1988;37(3):287–301.
7. Saffle JR. The 1942 fire at Boston's Cocoanut Grove nightclub. Am J Surg. 1993;166(6):581–91.
8. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Nutr Hosp. 2001;16(6):287–92.
9. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, Kuhl MR, Brown RO. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg. 1992;215(5):503–11. discussion 511–3.
10. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total

parenteral nutrition in surgical patients. N Eng J Med. 1991;325(8):525–32.
11. Bistrian B, Blackburn J, Vitale J, Cochran D, Naylor J. Prevalence of malnutrition in general medical patients. JAMA. 1976;235:1567–70.
12. Rivers E, Nguyen B, Ressler J, Muzzin A, Knoblich B, Peterson E, et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. NEJM. 2001;345:1368–77.
13. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz E, et al. Intensive insulin in critically ill patients. NEJM. 2001;345:1359–67.
14. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNMC, Delarue J, Merger MM. Negative impact of hypocaloric feeding and energy balance on critical outcome in ICU patients. Clin Nutr. 2005; 24:502–9.
15. Lin E, Calvano SE, Lowry SF. Systemic response to injury and metabolic support. In: Brunicardi FC, Anderson DK, et al., editors. Schwartz's principles of surgery. New York: McGraw-Hill; 2005. p. 3–41.
16. Van Ooijen AM, Lichtenbelt VM, van Steenhoven AA, Westerterp KR. Seasonal changes in metabolic responses to cold in humans. Physiol Behav. 2004;82:545–53.
17. Compher CW, Frankenfield DC, Roth-Yousey L, Evidence Analysis Working Group. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc. 2006;106:881–903.
18. James WPT. From SDA to DIT to TEF. In: Kinney MM, Tucker HN, editors. Energy metabolism tissue determinants and cellular corollaries. New York, NY: Raven; 1992. p. 163–86.
19. Weissman C, Kemper M, Elwyn DH, Askanazi J, Hyman AI, Kinney JM. The energy patient: an analysis. Chest. 1986;89:254–9.
20. Wooley JA, Sax HC. Indirect calorimetry: applications to practice. Nutr Clin Pract. 2003;18:434–9.
21. Brandi LS, Bertonlini R, Calafà M. Indirect calorimetry in critically ill patients: clinical applications and practical advice. Nutrition. 1997;13:349–58.
22. Frankenfield DC, Sarson GY, Blosser SA, Cooney RN, Smith JS. Validation of a 5-minute steady state indirect calorimetry protocol for resting energy expenditure in critically ill patients. J Am Coll Nutr. 1996;15:397–402.
23. Ogawa AM, Shikora SA, Burke LM, Heetderks-Cox JE, Bergren CT, Muskat PC. The thermodilution technique for measuring resting energy expenditure does not agree with indirect calorimetry for the critically ill patient. JPEN J Parenter Enteral Nutr. 1998;22:347–51.
24. Frankenfield DC, Muth E, Rowe WA. The Harris-Benedict studies of human basal metabolism: history and limitations. J Am Diet Assoc. 1998;98:439–45.
25. Ireton-Jones CS, Jones JD. Why use predictive equations for energy expenditure assessment? Am Diet Assoc. 1997;97:A-44.
26. Frankenfield DC, Smith JS, Cooney RN. Validation of two approaches to predicting resting metabolic rate in critically ill patients. JPEN J Parenter Enteral Nutr. 2004;28:259–64.
27. Cerra FB, Benitez, Blackburn GL, Irwin RS, Jeejeebhoy K, Katz DP, et al. Applied nutrition in ICU patients: a concensus statement of the American College of Chest Physicians. Chest. 1997;111: 769–78.
28. Wilmore DW. Metabolic response to severe surgical illness: overview. World J Surg. 2000;24:705–11.
29. Chandramouli V, Ekberg K, Schumann WC, Kalhan SC, Wahren J, Landau BR. Quantifying gluconeogenesis during fasting. Am J Phsiol. 1997;273: E1209–15.
30. Landau BR, Wahren J, Chandramouli V, Schumann WC, Ekberg K, Kalhan SC. Contributions of gluconeogenesis to glucose production in the fasted state. J Clin Invest. 1996;53(suppl):S101–6.
31. McCowen KC, Malhotra A, Bistrian B. Stress-induced hyperglycemia. Crit Care Clin. 2001;17: 107–24.
32. Montori VM, Bistrian BR, McMahon MM. Hyperglycemia in acutely ill patients. JAMA. 2002;288:2167–9.
33. Young LS, Kearns LR, Schoepfel SL. Protein in the chamber. In: Gottschlich MM, editor. The A.S.P.E.N. Nutrition Support Curriculum. Cincinatti: A.S.P.E.N., 2007; p. 71–87.
34. Jabbar A, Wei-Kuo C, McClave SA, Dryden GW, McClave SA. Gut immunology and the differential response to feeding and starvation. Nutr Clin Pract. 2003;18:461–82.
35. Shaw JH, Wildborne M, Wolfe RR. Whole body protein kinetics in severely septic patients. The response to glucose infusion and total parenteral nutrition. Ann Surg. 1987;205:288–94.
36. Reeds PJ. Dispensible and indispensible amino acids for humans. J Nutr. 2000;130:1835S–40.
37. Griffiths RD, Allen KD, Andrews FJ, Allen KD, Andrews FJ, Jones C. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. Nutrition. 2002;18:546–52.
38. Alpers DH. Glutamine: do the data support the cause for glutamine supplementation in humans? Gastroenterology. 2006;130:S106–16.
39. Monk D, Plank LD, Franch-Arcas G, Finn PJ, Streat SJ, Hill GL. Sequential changes in the metabolic response in critically injured patients during the first 25 days after blunt trauma. Ann Surg. 2001;234(2): 245–55.
40. Martindale RG, Zhou M. Nutrition and metabolism. In: O'Leary JP, Tabuenca A, editors. Physiologic basis of surgery. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 112–49.
41. Wilmore DW. Metabolic management of the critically ill. New York: Plenum; 1977, p. 193.
42. Stroud M. Protein and the critically ill; do we know what to give? Proc Nutr Soc. 2007;66:378–83.
43. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, et al. ESPEN (European Society for Parenteral and Enteral

Nutrition): ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25:210–33.
44. Jacobs DG, Jacobs DO, Kudsk KA, Moore FA, Oswanski MF, Poole GV, et al. Practice management guidelines for nutritional support of the trauma patient. J Trauma. 2004;57:660–79.
45. McClave SA, Martindale RG, Vanek VW, et al. A.S.P.E.N. Board of Directors; American College of Critical Care Medicine; Society of Critical Care Medicine: Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). JPEN J Parenter Enteral Nutr. 2009; 33:277–316.
46. Chadalavada R, Sappati BRS, Maxwell J, Sappati Biyyani RS, Maxwell J, Mullen K. Nutrition in hepatic encephalopathy. Nutr Clin Pract. 2010; 25(3):257–64.
47. Schulz GJ, Campos AC, Coelho JC. The role of nutrition in hepatic encephalopathy. Curr Opin Clin Nutr Metab Care. 2008;11(3):275–80.
48. Garneata L, Mircescu G. Nutritional intervention in uremia – myth or reality? J Ren Nutr. 2010;20 (5 Suppl):S31–4.
49. Masson S, Latini R, Tacconi M, Bernasconi R. Incorporation and washout of n-3 polyunsaturated fatty acids after diet supplementation in clinical studies. J Cardiovasc Med (Hagerstown) 2007;8 Suppl 1:S4.
50. Kudsk KA. Immunonutrition in surgery and critical care. Annu Rev Nutr. 2006;26:463–79.
51. Calder PC. n-3 fatty acids, inflammation, and immunity – relevance to postsurgical and critically ill patients. Lipids. 2004;39(12):1147–61.
52. Kumar KV, Rao SM, Gayani R, Mohan IK, Naudu MU. Oxidant stress and essential fatty acids in patients with risk and established ARDS. Clin Chim Acta. 2000;298(1–2):111–20.
53. Gadek JE, et al. Enteral nutrition in ARDS study group. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Crit Care Med. 1999;27(8):1409–20.
54. Singer P, DeMichele SJ, Karlstad MD, Pacht ER, et al. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med. 2006;34(4):1033–8.
55. Pontes-Arruda A, Aragão AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med. 2006;34(9): 2325–33.
56. Munroe C, Frantz D, Martindale RG, McClave SA. The optimal lipid formulation in enteral feeding in critical illness: clinical update and review of the literature. Curr Gastroenterol Rep. 2011;13:368–75.
57. Calder PC, Dangour AD, Diekman C, Eilander A, Koletzko B, Meijer GW, et al. Essential fats for future health. Proceedings of the 9th Unilever nutrition symposium, 26–27 May 2010. Eur J Clin Nutr. 2010;64 Suppl 4:S1–13.
58. Vanek VW, Borum P, Buchman A, et al. A.S.P.E.N. Position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. Nutr Clin Pract. 2012;27(4):440–91.
59. Hou CT, Wu YH, Huang PN, Cheng CH, Huang YC. Higher plasma pyridoxal 5′-phosphate is associated with better blood glucose responses in critically ill surgical patients with inadequate vitamin B-6 status. Clin Nutr. 2011;30(4):478–83.
60. Hou CT, Wu YH, Cheng C, Huang PN, Huang YC. Higher plasma homocysteine is associated with lower vitamin B6 status in critically ill surgical patients. Nutr Clin Pract. 2012;27(5):695–700.
61. Cheng CH, Chang SJ, Lee BJ, Chang SJ, Lee BJ, Lin KL, Huang YC. Vitamin B6 supplementation increases immune responses in critically ill patients. Eur J Clin Nutr. 2006;60(10):1207–13.
62. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. Curr Opin Clin Nutr Metab Care. 2011;14(6):610–7.
63. Vasilaki AT, McMillan DC, Kinsella J, Duncan A, O'Reilly DS, Talwar D. Relation between riboflavin, flavin mononucleotide and flavin adenine dinucleotide concentrations in plasma and red cells in patients with critical illness. Clin Chim Acta. 2010; 411(21–22):1750–5.
64. Gariballa S, Forster S, Powers H. Riboflavin status in acutely ill patients and response to dietary supplements. JPEN J Parenter Enteral Nutr. 2009;33(6): 656–61.
65. Roy CC, Bouthillier L, Seidman E, Levy E. New lipids in enteral feeding. Curr Opin Clin Nutr Metab Care. 2004;7(2):117–22.
66. Calder PC, Deckelbaum RJ. Harmful, harmless or helpful? The n-6 fatty acid debate goes on. Curr Opin Clin Nutr Metab Care. 2011;14(2):113–4.
67. Simopoulos AP. Essential fatty acids in health and chronic disease. Am J Clin Nutr. 1999;70(3Suppl): 560S–9S.
68. Calder PC. The 2008 ESPEN Sir David Cuthbertson Lecture: Fatty acids and inflammation – from the membrane to the nucleus and from the laboratory bench to the clinic. Clin Nutr. 2010;29(1):5–12.
69. Fan YY, Chapkin RS. Importance of dietary gamma-linolenic acid in human health and nutrition. J Nutr. 1998;128(9):1411–4.
70. Singer P, Shapiro H, Theilla M, Anbar R, Singer J, Cohen J. Anti-inflammatory properties of omega-3 fatty acids in critical illness: novel mechanisms and an integrative perspective. Intensive Care Med. 2008;34(9):1580–92.
71. Supinski GS, Vanags J, Callahan LA. Eicosapentaenoic acid preserves diaphragm force generation following endotoxin administration. Crit Care. 2010;14(2):R35.
72. Tiesset H, Pierre M, Desseyn JL, Guéry B, Beermann C, Galabert C, Gottrand F, Husson MO. Dietary

(n-3) polyunsaturated fatty acids affect the kinetics of pro- and anti-inflammatory responses in mice with Pseudomonas aeruginosa lung infection. J Nutr. 2009;139(1):82–9.
73. Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, et al. Effect of enteral feeding with Eicosapentaenoic acid, gamma-linolenic acid and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. Crit Care Med. 1999;27(8): 1409–20.
74. Pacht ER, DeMichele SJ, Nelson JL, Hart J, Wennberg AK, Gadek JE. Enteral nutrition with Eicosapentaenoic acid, gamma-linolenic acid, and antioxidants reduces alveolar inflammatory mediators and protein influx in patients with acute respiratory distress syndrome. Crit Care Med. 2003;31(2): 491–500.
75. Chang CS, Sun HL, Lii CK, Chen HW, Chen PY, Liu KL. Gamma-linolenic acid inhibits inflammatory responses by regulating NF-kappaB and AP-1 activation in lipopolysaccharide-induced RAW 264.7 macrophages. Inflammation. 2010;33(1):46–57.
76. Mancuso P, Whelan J, DeMichele SJ, Snider CC, Guszcza JA, Karlstad MD. Dietary fish oil and fish and borage oil suppress intrapulmonary proinflammatory eicosanoid biosynthesis and attenuate pulmonary neutrophil accumulation in endotoxic rats. Crit Care Med. 1997;25(7):1198–206.
77. Murray MJ, Kumar M, Gregory TJ, Banks PL, Tazelaar HD, DeMichele SJ. Select dietary fatty acids attenuate cardiopulmonary dysfunction during acute lung injury in pigs. Am J Physiol. 1995;269(6 Pt 2):H2090–9.
78. Calder PC. Satellite symposium: throw another fish on the fire: the role of n-3 in inflammation. Rationale and use of n-3 fatty acids in artificial nutrition. Proc Nutr Soc. 2010;36(2):289–95.
79. Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. Crit Care Med. 2009;37(5):1757–61.
80. Oudemans-van Straaten HM, Bosman RJ, Treskes M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive Care Med. 2001;27:84–90.
81. Wischmeyer P. Glutamine: role in gut protection in critical illness. Curr Opin Clin Nutr. 2006;9: 607–12.
82. Novak F, Heyland DK, Avenell A, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med. 2002;30:2022–9.
83. Macario AJL, Conway de Macario E. Sick chaperones, cellular stress and disease. NEJM. 2005;353: 1489–1501.
84. Oliveira GP, Dias CM, Rocco PR. Understanding the mechanisms of glutamine action in critically ill patients. Ann Acad Bras Cienc. 2010;82(2):417–30.
85. Kelly D, Wischmeyer PE. Role of L-glutamine in critical illness: new insights. Curr Opin Clin Nutr Metab Care. 2003;6(2):217–22.
86. Singleton KD, Beckey VE, Wischmeyer PE. Glutamine prevents activation of nfkappab and stress kinase pathways, attenuates inflammatory cytokine release, and prevents acute respiratory distress syndrome (ARDS) following sepsis. Shock. 2005;24(6):583–9.
87. Zhou M, Martindale RG. Arginine in the critical care setting. J Nutr. 2007;137:1687S–92.
88. Albina JE, Mills CD, Henry Jr WL, Caldwell MD. Regulation of macrophage physiology by L-arginine: role of the oxidative L-arginine deaminase pathway. J Immunol. 1989;143:3641–6.
89. Morris SM. Recent advances in arginine metabolism. Curr Opin Clin Nutr Metab Care. 2004;7: 45–51.
90. Chiarla C, Giovannini I, Siegel JH. Plasma arginine correlations in trauma and sepsis. Amino Acids. 2006;30:81–6.
91. Arrigoni F, Ahmetaj B, Leiper J. The biology and therapeutic potential of the DDAH/AMDA pathway. Curr Pharm Des. 2010;16(37):4089–102.
92. Pope AJ, Karrupiah K, Xia Y, Karrupiah K, Kearns PN, Xia Y, Cardounel AJ. Role of dimethylarginine dimethylaminohydrolases in the regulation of nitric oxide production. J Biol Chem. 2009;284(51): 36338–47.
93. Fortin CF, McDonald PP, Fülöp T, Lesur O. Sepsis, leukocytosis, and nitric oxide (NO): an intricate affair. Shock. 2010;33(4):344–52.
94. Suchner U, Heyland DK, Peter K. Immune-modulatory actions of arginine in the critically ill. Br J Nutr. 2002;87 Suppl 1:S121–32.
95. Kao CC, Bandi V, Guntupalli KK, Wu M, Castillo L, Jahoor F. Arginine, citrulline and nitric oxide metabolism in sepsis. Clin Sci (Lond). 2009;117(1): 23–30.
96. Luiking YC, Poeze M, Ramsay G, Deutz NE. Reduced citrulline production in sepsis is related to diminished de novo arginine and nitric oxide production. Am J Clin Nutr. 2009;89(1): 142–52.
97. Pan M, Choudry HA, Epler MJ, Meng Q, Karinch A, Lin C, Souba W. Arginine transport in catabolic disease states. J Nutr. 2004;134:2826S–9S; discussion 2853S.
98. Piton G, Belon F, Cypriani B, Regnard J, Puyraveau M, Manzon C, et al. Enterocyte damage in critically ill patients is associated with shock condition and 28-day mortality. Crit Care Med. 2013;41:2169–76.
99. Seigel JH, Cerra FB, Coleman B, Giovannini I, Shetye M, Border JR, McMenamy RH. Physiological and metabolic correlations in human sepsis. Surgery. 1979;86:163–93.

100. Cuthbertson DP. Surgical metabolism: historical and evolutionary aspects. In: Wilkinson AW, Cuthbertson DP, editors. Metabolism and the response to injury. Chicago: Year Book Medical Publishers; 1977. p. 1.
101. Wilmore DW, Goodwin CW, Aulick LH, Powanda MC, Mason Jr AD, Pruitt Jr BA. Effect of injury and infection on visceral metabolism and circulation. Ann Surg. 1980;192:491.
102. Wilmore DW. Metabolic management of the critically ill. New York: Plenum; 1980.
103. Hwang TL, Huang SL, Chen MF. The use of indirect calorimetry in critically ill patients-the relationship of measured energy expenditure to Injury Severity Score, Septic Severity Score, and APACHE II Score. J Trauma. 1993;34(2):247–51.
104. Lawrence PF. Essentials of general surgery. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 1997.
105. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
106. Wu B, Fukuo K, Suzuki K, Yoshino G, Kazumi T. Relationships of systemic oxidative stress to body fat distribution, adipokines, and inflammatory markers in healthy middle-aged women. Endocr J. 2009;56(6):773–82.
107. Dossett LA, Heffernan D, Lightfoot M, Collier B, Diaz JJ, Sawyer RG, May AK. Obesity and pulmonary complications in critically injured adults. Chest. 2008;134(5):974–80.
108. Winfield RD, Delano MJ, Dixon DJ, Schierding WS, Cendan JC, Lottenberg L, et al. Differences in outcome between obese and nonobese patients following severe blunt trauma are not consistent with an early inflammatory genomic response. Crit Care Med. 2010;38(1):51–8.
109. Alban RF, Lyass S, Bargulies DR, Shabot MM. Obesity does not affect mortality after trauma. Ann Surg. 2006;72(10):966–9.
110. Dossett LA, Dageforde LA, Swenson BR, Metzger R, Bonatti H, Sawyer RG, May AK. Obesity and site specific nosocomial infection risk in the intensive care unit. Surg Infect. 2009;10(2):137–48.
111. Khaodhiar L, McCowen KC, Blackburn GL. Obesity and its comorbid conditions. Clin Cornerstone. 1999;2(3):17–31.
112. Muñoz E, Rosner F, Friedman R, Sterman H, Goldstein J, Wise L. Financial risk, hospital cost, and complications and comorbidities in medical non-complications and comorbidity-stratified diagnosis-related groups. Am J Med. 1988;84(5):933–9.
113. Neville AL, Brown CV, Weng J, Demetriades D, Velmahos GC. Obesity is an independent risk factor of mortality in severely injured blunt trauma patients. Arch Surg. 2004;139(9):983–7.
114. Brown CV, Neville AL, Rhee P, Salim A, Velmahos GC, Demetriades D. The impact of obesity on the outcomes of 1,153 critically injured blunt trauma patients. J Trauma. 2005;59(5):1048–51.
115. Choban PS, Weireter Jr LJ, Maynes C. Obesity and increased mortality in blunt trauma. J Trauma. 1991;31(9):1253–57.
116. Bochicchio GV, Joshi M, Bochicchio K, Nehman S, Tracy JK, Scalea TM. Impact of obesity in the critically ill trauma patient: a prospective study. J Am Coll Surg. 2006;203(4):533–8.
117. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. Am J Physiol Heart Circ Physiol. 2005;288(5):H2031–41.
118. Berg JM, Tymoczko JL, Starvation SL. Biochemistry. 5th ed. New York: W. H. Freeman; 2002.
119. Felig P, Marliss EB, Cahill Jr GF. Metabolic response to human growth hormone during prolonged starvation. J Clin Invest. 1971;50(2):411–21.
120. Dietch EA. Multiple organ failure. Pathophysiology and potential future therapy. Ann Surg. 1992;216(2):117–34.
121. Rivers EP, McIntyre L, Rivers KK. Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity. CMAJ. 2005;173(9):1054–65.
122. Song Z, Song Y, Yin J, Shen Y, Yao C, Sun Z, et al. Genetic variation in the TNF gene is associated with susceptibility to severe sepsis, but not with mortality. PLoS One. 2012;7(9):e46113.
123. Song Z, Yin J, Yao C, Sun Z, Shao M, Zhang Y, et al. Variants in the Toll interacting protein gene are associated with susceptibility to sepsis. Crit Care. 2011;15(1):R12.
124. Song Z, Yao C, Yin J, Tong C, Zhu D, Sun Z, Jiang J, et al. Genetic variation in the TNF receptor associated factor 6 gene is associated with susceptibility to sepsis induced acute lung injury. J Transl Med. 2012;10:166.
125. Reid CL, Perrey C, Pravica V, Hutchinson IV, Campbell IT. Genetic variation in proinflammatory and anti-inflammatory cytokine production in multiple organ dysfunction syndrome. Crit Care Med. 2002;30(10):2216–21.

Fluid and Electrolytes

2

Bishwajit Bhattacharya and Linda L. Maerz

Introduction

Fluid and electrolyte physiology is central to the clinical management of surgical patients. The composition and regulation of body fluids has been studied for centuries, and the concept of intravenous infusion of fluids was established over a century ago [1]. David Sabiston, one of the premier surgeons of the twentieth century, reviewed Alfred Blalock's landmark work on the pathogenesis of shock, which demonstrated that fluid losses related to injury could be treated with intravascular volume repletion. This work provided the foundation for intravenous therapy in the management of hypovolemia [2]. Subsequently, the body of knowledge encompassing the complex interactions between body fluid compartments and the relationship to electrolyte physiology has increased significantly. This chapter reviews the physiologic principles underpinning fluid therapy, as well as the application of these principles to clinical fluid management. The relationship between disorders of water balance and sodium metabolism is delineated, as are the physiology and management of disorders of sodium, potassium, calcium, magnesium, and phosphorus metabolism.

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Total Body Water and the Fluid Compartments

Total body water (TBW) is defined as the total volume of water within the body. TBW is a percentage of body weight and is dependent on both the fat content and the chronological age of the individual. TBW as a percentage of body weight decreases with increasing body fat and with increasing age [3]. As a general rule, TBW is 60 % of body weight in men and 50 % of body weight in women [4].

TBW is comprised of the intracellular and the extracellular compartments. Intracellular fluid (ICF) makes up two thirds of TBW, and extracellular fluid (ECF) accounts for the remaining one third. ECF is subdivided into the intravascular and interstitial spaces. The intravascular space accounts for 25 % of the ECF and 8 % of the TBW; this space contains the plasma volume. The interstitial space comprises the remaining 75 % of the ECF and 25 % of the TBW; this space contains a free phase of fully exchangeable water and a bound phase of minimally exchangeable water. The transcellular compartment is an additional ECF designation; this compartment contains cerebrospinal fluid, synovial fluid, the water in cartilage and bone, eye fluids and lubricants of the serous membranes. This type of fluid

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is poorly exchangeable and comprises approximately 4 % of the TBW. The exchangeable components of the compartments comprising TBW are in dynamic equilibrium [5].

Effective circulating volume is the portion of the ECF that perfuses the organs. Under normal physiologic conditions, this corresponds to the intravascular volume. This relationship is altered in some disease states. For example, in congestive heart failure and in patients who have arteriovenous fistulae, the intravascular volume as well as total body salt and water are high, but effective circulating volume is low. A different type of alteration of the physiologic state occurs in bowel obstruction, pancreatitis, and the sepsis syndrome. Under these circumstances, the total ECF remains constant or increases initially, but intravascular volume is significantly decreased due to external losses or vasodysregulation. These conditions result in "third-space loss." This concept was initially recognized over 50 years ago, when experimental models of early hemorrhagic shock and elective operative tissue trauma were used to investigate changes in the body fluid compartments [6]. It was observed that ECF decreased more than the measured loss of plasma volume in these experiments. Shock and operative trauma were hypothesized to cause extracellular fluid to be sequestered in an "unexchangeable" compartment as a result of capillary leak [6, 7]. This heretofore undefined ECF compartment became known as the "loss to the third space," "deficit in functional extracellular volume," or the "nonanatomic third-space loss" [6, 8, 9]. In the ensuing decades, this concept was accepted as convention, some would argue resulting in unnecessarily aggressive resuscitation and perioperative fluid management strategies in an effort to compensate for fluid lost to the third space. The existing "third space" literature was reviewed by Brandstrup and colleagues during the past decade. They determined that the evidence in the early literature supporting the concept of the third space was based on flawed methodology [10, 11]. However, it is clear that disease processes such as bowel obstruction, pancreatitis, severe sepsis, and septic shock warrant aggressive fluid management strategies because the intravascular volume is markedly diminished in these clinical scenarios. Hypoperfusion is the end result in these cases and is best managed with restoration of circulating volume and treatment of vasodysregulation with vasoactive pressor agents.

Even though the intravascular volume is only a small percentage of the TBW, significant decreases in intravascular volume are poorly tolerated when decreased mean arterial pressure occurs. This is illustrated in the clinical consequences of the classes of hemorrhagic shock: class I (loss of <15 % blood volume), class II (loss of 15–30 % blood volume), class III (loss of 30–40 % blood volume), and class IV (loss of >40 % blood volume). Hypotension occurs in class III shock and is a relatively late manifestation of acute blood loss. Cardiac arrest ensues when >50 % of total blood volume is lost. On the other hand, the interstitial space is extremely compliant and buffers loss or excess of the intravascular space. Therefore, the volume of the interstitial space is highly variable. This relationship between the intravascular space and the interstitial space is possible because of the membranes that separate the body fluid compartments [12].

The ionic composition of the ECF and the ICF is highly defended in the normal physiologic state. The predominant cation in the ECF is sodium. Therefore, the ECF contains most of the sodium content of the body (60 mEq/kg). The ECF also contains small quantities of other cations, including potassium, calcium, and magnesium. The cations are electrochemically balanced principally by chloride and lactate anions. Bicarbonate, phosphate, sulfate, albumin, and other extracellular proteins also provide negative charge in the ECF. The predominant cation in the ICF is potassium. The ICF contains most of the potassium content of the body (42 mEq/kg). The ICF also contains smaller quantities of other cations, including magnesium and sodium. Phosphates and intracellular proteins are the primary anions of the ICF, and chloride and bicarbonate are present in lower concentrations [5].

The principles of osmosis dictate the movement of water between fluid compartments. Osmotic

equilibrium occurs when two solutions separated by a semipermeable membrane equalize the concentration of osmotically active particles on either side of that membrane as water moves along a concentration gradient. Osmolarity is measured in milliosmoles per liter, mOsm/L. Osmolality is measured in milliosmoles per kilogram H_2O, mOsm/kg H_2O. Both define the osmotic activity of particles in solution and are considered equivalent if the concentration of solutes is very low [5].

Plasma osmolality (Posm) indicates total body osmolality. Sodium [Na^+] is the predominant extracellular cation, and glucose and blood urea nitrogen (BUN) concentrations are significant in certain disease states. Therefore, the following formula is used for determination of Posm:

$$\text{Posm}\left(\text{mOsm}/\text{kg}\,\text{H}_2\text{O}\right) = 2\times\text{serum}\left[\text{Na}^+\right] + \text{glucose}/18 + \text{BUN}/2.8$$

The principles of osmosis as they relate to hypothetical semipermeable membranes are generalizations. The physiologic membranes that separate the body fluid compartments are much more complex. The capillary endothelium serves as the membrane that separates the intravascular and interstitial compartments. The endothelium exhibits different characteristics in different organs and is more permeable in the lung and liver than in the periphery [13]. The capillary endothelium is very permeable, allowing for rapid equilibration between the intravascular and interstitial spaces. Therefore, the interstitial space can serve as a buffer for the more highly defended intravascular space. Of particular clinical significance, leakage of albumin depends on the endothelial characteristics of tissue. Albumin leakage is high in lung and liver [14] and low in the peripheral tissues [15]. The cell surface membrane is impermeable to protein, but permeable to water, bicarbonate, and chloride. The sodium–potassium pump (Na^+, K^+-ATPase) actively transports sodium out of cells and potassium into cells, an energy-dependent process. This enzyme-dependent cell membrane integrity is disrupted in severe shock states as a result of impaired oxygen delivery and utilization. Passive sodium entry then leads to intracellular water migration, cellular swelling, and ultimately cell death [12].

Volume Control Mechanisms

Under normal physiologic circumstances, plasma osmolality is tightly controlled, averaging 289 mOsm/kg H_2O. Thirst and antidiuretic hormone (ADH) are the two primary regulators of water balance. Osmoreceptor cells in the paraventricular and supraoptic nuclei of the hypothalamus detect small changes in cell volume and activate the neuronal centers that control thirst and ADH secretion. Therefore, osmoreceptors control the fine-tuning of volume relationships [16]. Stimulants of ADH secretion include nicotine, ether, morphine, barbiturates, and tissue injury (including operative tissue dissection and manipulation). Ethanol inhibits ADH secretion and its water resorption activity in the renal collecting ducts.

The relationship of aquaporins to ADH physiology has been the subject of significant investigation over the course of the past two decades. Peter Agre, MD, an American medical doctor and molecular biologist, won the 2003 Nobel Prize in Chemistry for the discovery of aquaporins [17, 18]. Aquaporins are integral membrane pore proteins that regulate the flow of water. These water channels are ubiquitous in nature, including in the human body. Aquaporin proteins are comprised of six transmembrane alpha-helices arranged in a right-handed bundle, with the amino and the carboxyl termini located on the cytoplasmic surface of the membrane. The specific types of aquaporins differ in their peptide sequences [19, 20].

The principal cells lining the renal collecting ducts control the fine-tuning of body water homeostasis by regulating water resorption through aquaporin-2 (AQP_2) aquaporin-3 (AQP_3) and aquaporin-4 (AQP_4). AQP_3 and AQP_4 are embedded in the basolateral plasma membrane. ADH binds to the vasopressin-2 (V_2) receptor on the basal membrane of the renal collecting duct. This triggers redistribution of AQP_2 from intracellular vesicles into the apical plasma membrane. Water enters into the cells via AQP_2 and exits through AQP_3 and AQP_4 [21].

The mechanism of action of ADH with respect to the water permeability of the renal collecting

duct has therapeutic implications. A number of nonpeptide V_2 antagonists (vaptans) are in development. The mixed V_2/V_{1a} antagonist conivaptan has been approved by the US Food and Drug Administration (FDA) for intravenous use in the treatment of euvolemic and hypervolemic hyponatremia. Conivaptan produces aquaresis (solute-free water excretion), resulting in increased serum sodium levels, free water clearance, urine flow, and plasma osmolality [22, 23].

Baroreceptors control volume via sympathetic and parasympathetic connections in a less precise manner than do osmoreceptors. Stretch receptors detect changes in pressure and changes in volume that are manifested by changes in pressure. Volume receptors are located in the intra-thoracic capacitance vessels (vena cava) and the atria. Depending on volume status, these receptors either increase or decrease sympathetic tone to the kidney, which affects renal blood flow and tubular sodium resorption. Pressure receptors of the aortic arch and carotid arteries are important in extreme changes in arterial pressure (such as occurs with hemorrhage). Intra-renal baroreceptors of the afferent arteriole cause variability in release of renin depending on pressure. Hepatic volume receptors and cerebrospinal volume receptors have also been characterized [5].

Endocrine and hormonal factors also play a role in volume control mechanisms. The renin–angiotensin–aldosterone system is the primary hormonal mediator of volume control. The natriuretic peptide system is an endocrine mechanism that regulates blood volume and electrolyte balance. There are three members of the mammalian natriuretic peptide family: atrial natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [24, 25].

Renal prostaglandins (PGE_2 and PGI_2) may play a role in volume control, especially in conditions such as sepsis and jaundice. Normally, inhibition of prostaglandin production has little effect on renal function. However, nonsteroidal anti-inflammatory agents (inhibitors of cyclooxygenase) can precipitate renal failure in patients with renal dysfunction due to loss of the protective effects of renal prostaglandins [26].

Endothelins are peptide vasoconstrictors involved in volume and pressure regulation [27]. Nitric oxide (NO) is a free radical produced by nitric oxide synthases and is involved in many biologic functions, including volume and pressure regulation [28]. There is interaction between the endothelin and NO systems. In general, NO and endothelin actions oppose one another.

Baseline Water and Electrolyte Requirements

Sensible water losses can be measured and include urine (800–1,500 mL/24 h), stool (0–250 mL/24 h) and sweat (minimal). Sweat is a hypotonic mixture of electrolytes and water and does not contribute significantly to daily water loss except in very arid and hot climates. Insensible water losses are unmeasurable and include loss from the skin and lungs. This accounts for 600–900 mL/24 h (8–12 mL/kg/day). Insensible water loss increases 10 % for each degree of body temperature >37.2 °C. Therefore, fever is a significant contributor to insensible water loss. The normal daily sodium requirement is 1–2 mEq/kg/24 h; the potassium requirement is 0.25–0.50 mEq/kg/24 h [5].

Parenteral Solutions

Intravenous fluids are used for maintenance and resuscitation of surgical patients. The two broad categories of parenteral solutions are crystalloids and colloids. The appropriate choice of crystalloid or colloid solution depends on maintenance fluid requirements, fluid deficits, and ongoing fluid losses.

Lactated Ringer's (LR) solution is a commercially available crystalloid and has a composition similar to plasma. It is usually utilized as a resuscitative fluid to replace loss of fluid with a similar composition to plasma and is ideal when the patient's serum electrolyte concentrations are normal. LR has a relatively low sodium content (130 mEq/L), which makes this solution slightly hypotonic. Hyponatremia may result with exces-

sive or prolonged use or in patients who have impaired renal function and diminished ability to excrete free water. This may become problematic in patients who have traumatic brain injuries and other conditions that mandate a higher Posm. The lactate in LR occurs as sodium-lactate, which dissociates at physiologic pH. The lactate anions are metabolized to bicarbonate and, therefore, do not contribute to acidosis under normal conditions [29].

Normal saline solution (NSS) is another resuscitative crystalloid fluid and contains 154 mEq of both sodium and chloride. NSS is useful for treatment of hyponatremic hypochloremic metabolic alkalosis. However, the excessive and equal quantities of sodium and chloride can lead to significant electrolyte and acid–base disturbances, such as hyperchloremic metabolic acidosis (HCMA), which can aggravate any preexisting acidosis.

If a true isotonic fluid is required, but clinical circumstances mandate limitation of chloride, half-NSS (1/2 NSS) mixed with 75 mEq $NaHCO_3$/L can be utilized (1/2NSS +75 mEq $NaHCO_3$). The sodium content is essentially equivalent to NSS, but the chloride load is halved.

Hypertonic saline (HTS) solutions are utilized to replace sodium deficits in symptomatic hyponatremia. Most commonly used are 3 % NaCl and 1.5 % NaCl. The former should be administered via central venous access; the latter may be administered via peripheral veins. HTS has also been suggested for early resuscitation of hypovolemia in trauma and burn patients. Intravascular volume is increased more quickly and the total resuscitation volume may be decreased compared to standard crystalloid resuscitation. However, caution should be used because of the potential for induction of significant acid–base and electrolyte abnormalities [30].

Naturally occurring plasma volume expanders include albumin preparations (4, 5, 20, and 25 %) and fresh frozen plasma. Only 5 and 25 % albumin are available in the United States. Albumin preparations are usually prepared in NSS; therefore, large volume administration can result in HCMA. Additionally, the albumin molecule is of such a molecular weight that it readily passes through capillary pores that open in conditions that create a capillary leak [14, 15]. The SAFE trial demonstrated that albumin administration is as "safe as saline" and that hypoalbuminemia is associated with not only decreased colloid oncotic pressure but also perturbed pharmacologic agent carriage, detoxification, and immune responsivity [31].

Synthetic colloids may be utilized as resuscitative fluids, especially in surgical patients. Hydroxyethyl starch (HES) preparations are the most common. They are categorized by their average molecular weight, degree of substitution (DS) (molar substitution: # hydroxyethyl groups per 100 glucose groups) and concentration. Starches include hetastarch (DS = 0.7), pentastarch (DS = 0.5), and tetrastarch (DS = 0.4). Six percent solutions are the most commonly used in the United States. The vehicles for the starches differ. Hespan is a 6 % solution of hetastarch in a NSS vehicle, while Hextend is the identical starch in a solution with a composition similar to LR. Some interventional trials have noted an association with acute kidney injury or acute renal failure with the use of starch preparations [32]. Resuscitation with starch solutions alone provides little to no free water. Therefore, starch administration must occur in conjunction with maintenance fluid administration to mitigate against hyperoncotic renal injury [33].

Maintenance Fluid Therapy

Maintenance fluid therapy replaces fluids normally lost during the course of a day. Conversely, resuscitative fluid therapy replaces preexisting deficits or additional ongoing losses. Maintenance and resuscitative fluid therapy may occur simultaneously, but two different solutions are used to achieve differing goals.

Weight-based formulas are used to calculate maintenance water requirements, accounting for both sensible and insensible losses. One of the most commonly used is the "4–2–1 Rule":
First 10 kg body weight: 4 cc/kg/h
Second 10 kg body weight: 2 cc/kg/h
Each additional 10 kg body weight: 1 cc/kg/h

Using this formula, the hourly volume requirement for a 70 kg patient is 110 cc/h.

In patients who have clinically severe obesity, adjusted body weight (ABW) should be used when calculating a maintenance fluid rate:

$$\text{ABW} = \text{ideal body weight}\left(\text{IBW}\right) + 1/3\left(\text{actual} - \text{IBW}\right)$$

Maintenance fluid is hypotonic and contains 5 % dextrose as an aid in gluconeogenesis. The prototypical fluid is $D_5$1/2NSS + 20 mEq KCl/L in the adult. This provides the appropriate quantity of sodium and potassium based on the daily requirements outlined earlier. However, patients with renal impairment or anuria should not have potassium included in their maintenance fluid.

Resuscitative Fluid Therapy

The goal of resuscitative fluid therapy is to replace preexisting deficits and ongoing fluid losses. Crystalloid is the most common broad category of resuscitative fluid. An isotonic (or nearly isotonic) salt solution without added dextrose is utilized. LR is the most common resuscitative fluid used in surgical patients [34, 35].

The capillary endothelium is permeable to the components of an isotonic salt solution. Therefore, crystalloid distributes between the intravascular and interstitial spaces in proportion to the starting volumes of these spaces. Since the intravascular space comprises 25 % of the ECF and the interstitial space comprises 75 % of the ECF, the resultant ratio is 1:3. For each liter of crystalloid infused intravenously, 250 cc remains in the intravascular space and 750 cc diffuses into the interstitial space [12]. Additionally, crystalloid has pro-inflammatory effects [36, 37]. Strategies to limit these inflammatory effects have been investigated [38]. Limited intravascular volume expansion and the pro-inflammatory effects of crystalloid are the cornerstone of the crystalloid versus colloid debate from a historical perspective.

Leakage of albumin into the interstitial space is proportional to the net leakage of albumin in the body. This is variable, averaging a 25–35 % leakage rate under normal physiologic conditions [15]. This would be true of other iso-oncotic solutions as well. For each liter of 5 % albumin infused intravenously, approximately 750 cc remains in the intravascular space and 250 cc diffuses into the interstitial space. This proportion is opposite that of infusion of crystalloid isotonic salt solutions. The ratio of intravascular filling between colloid and crystalloid solutions is, therefore, 3:1 [12]. However, this model is overly simplified. Even under physiologic conditions, there is a high degree of variability in the leakage rate of albumin, depending on the unique characteristics of various capillary beds. Abnormalities in microvascular permeability are the norm in the surgical patient, particularly in the critically ill. Under pathologic conditions, up to half of exogenously administered albumin may diffuse into the interstitial space [5].

The use of exogenously administered albumin in critically ill patients was analyzed in a Cochrane report published in 1998. In the three categories of patients studied (those with hypovolemia, burns or hypoalbuminemia), the risk of death in the albumin-treated groups was higher than in the comparison groups [39, 40]. This review was criticized for various reasons, including the inclusion characteristics and small volume effects limitations. Subsequently, the SAFE (*S*aline versus *A*lbumin *F*luid *E*valuation) trial indicated no difference between albumin and saline in a double-blind randomized study of approximately 7,000 critically ill patients. These patients did not require massive plasma volume administration. Albumin was noted to be as safe as saline in this population [31]. Albumin appears safe in most groups but may not provide a survival advantage. In patients with traumatic brain injury, there may be a durable increased risk of death with exogenous albumin [39, 40].

The synthetic plasma expanders are alternatives to albumin. These include the broad category of HES, delineated above. A paradigm shift in the use of these solutions is again occurring. In 2012, several papers were published comparing the use of HES to crystalloid in subsets of the critically ill population. Perner et al. demonstrated that patients with severe sepsis receiving HES 130/0.42

had an increased risk of death at day 90 and were more likely to require renal replacement therapy, compared to patients receiving Ringer's acetate [41]. Myburgh et al. demonstrated that there was no significant difference in 90-day mortality between randomly selected critically ill patients resuscitated with 6 % HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal replacement therapy [42]. In patients with severe sepsis, Bayer et al. demonstrated that shock reversal was achieved equally fast with synthetic colloids or crystalloids. Use of colloids resulted in only marginally lower required volumes of resuscitation fluid. In addition, they found that both low molecular weight HES and gelatin may impair renal function [43].

Another Cochrane review of colloids versus crystalloids for fluid resuscitation in critically ill patients was published in 2013. From assessment of randomized controlled trials, the authors con - cluded that there is no evidence to indicate that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns, or following surgery. The use of HES might increase mortality. Since colloids are not associated with improved survival and are more expensive than crystalloids, continued use in clinical practice may not be justified [44]. When extrapolating these studies to clinical practice, each clinical scenario must be considered carefully, keeping in mind the patient populations assessed in the reviewed literature, the specific types of fluids studied and the limitations of the studies.

The Relationship Between Disorders of Water Balance and Sodium Balance

Sodium is the primary extracellular cation and principal determinant of plasma osmolality. The concentration of sodium and TBW shares an inverse relationship. As TBW increases, the serum sodium concentration decreases and vice versa. The sodium level thereby is a marker of TBW. Abnormal sodium concentration reflects abnormal TBW content [45].

Disorders of sodium levels are a common occurrence in clinical practice. Such disturbances are usually secondary to changes in water balance and not sodium levels. Sodium concentration is a reflection of body fluid tonicity and not a reflection of total body sodium content [46]. Often clinicians misinterpret changes in sodium levels as changes in total body sodium content. There are scenarios in which sodium content is abnormal, but this occurs less often than instances in which TBW is abnormal.

Disorders of Sodium Metabolism

Sodium abnormalities are a common occurrence in the surgical patient. Sodium abnormalities occur due to a host of reasons, some iatrogenic and some physiological.

Hyponatremia is defined as a sodium level of less than 135 mEq/L. It is the most common electrolyte abnormality in the hospitalized patient, occurring in as many as 20–25 % of hospitalized patients and in 30 % of patients in the intensive care unit (ICU). Approximately 4.4 % of surgical ward patients develop the abnormality within one week of surgery [47]. Hyponatremia is a risk factor for mortality, with 10–15 % mortality in chronic hyponatremia and 50 % in acute circumstances. Hyponatremia has been demonstrated to be a predictor of inpatient mortality in several patient populations [48–50]. Mortality likely represents the severity of the underlying disease and not accrual mortality from the electrolyte abnormality itself [51]. Hyponatremia in critically ill patients is more likely secondary to elevated secretion of ADH without an osmotic stimulus [52–54]. Critically ill patients are also more likely to have multi-organ failure that is associated with impaired water handling [55]. The inflammatory cascade via interleukin-6 may also play a role in ADH secretion and hyponatremia [56].

Hyponatremia is usually asymptomatic. In severe cases, cerebral edema may occur as fluid tonicity falls, thereby causing inflow of water into cells. Severe hyponatremia may present clinically as nausea, vomiting, lethargy, confusion, seizures, cerebral herniation, coma, and death [57].

Table 2.1 Causes of hyponatremia

– Hypovolemic hyponatremia
Gastrointestinal losses
Cerebral salt wasting
Diuretics
Third space loss
Gastrointestinal losses
– Euvolemic hyponatremia
SIADH
Malignancy related
Psychiatric polydipsia
Glucocorticoid deficiency
Hypothyroidism
– Hypervolemic hyponatremia
Congestive heart failure
Liver failure
Nephrotic syndrome
Renal failure

Hyponatremia can be classified according to volume status as hypovolemic hyponatremia, euvolemic hyponatremia, and hypervolemic hyponatremia (Table 2.1). Treatment strategies should be guided based upon etiology of the hyponatremia and volume status [46].

Hypovolemic hyponatremia results from a deficit of total body sodium and water with the sodium deficit greater than the water deficit. The decrease in ECF increases ADH secretion to help preserve ECF volume. In hypervolemic hyponatremia, there is an excess of total body sodium and water, though the water gain is greater than the sodium gain. The hyponatremia is a result of the volume overload. It is possible for total body sodium stores to be depleted, resulting in hyponatremia. In such circumstances, the sodium and chloride levels are both low.

The decision to treat depends on the presence or absence of symptoms and the rapidity of onset of the hyponatremia. Acute hyponatremia develops within a 48-h time frame, whereas chronic hyponatremia develops over greater than 48 h. Symptomatic hyponatremia should be treated. The sodium deficit can be calculated by the following formula:

$$\text{Sodium deficit} = 0.5 \times \text{lean body weight} \times \left(120 - \text{measured}\left[\text{Na}^{+}\right]\right)$$

Hyponatremia corrected at too rapid a rate may result in osmotic pontine demyelination (also known as central pontine demyelination or central demyelination syndrome). The development of this syndrome is a risk when there are sudden changes in concentration (12–15 mEq/L per 24h) or a rapid rate of change (>1–2 mEq/L/h). Clinically, the syndrome presents as generalized encephalopathy followed by behavioral changes, cranial nerve palsies, and quadriplegia 2–3 days after the sodium level is corrected. High risk patient populations include those with chronic hyponatremia that is rapidly corrected, such as alcoholics, the malnourished, geriatric patients, and those with thermal injury [57–67].

Sodium can be administered as 3 % NaCl. The hyponatremia should be corrected at a rate similar to the rate of developing the imbalance. Acute hyponatremia should be corrected more quickly than chronic hyponatremia. Dilutional hyponatremia is more common than total body sodium deficit. Therefore, administration of 3 % NaCl can be combined with forced diuresis and volume restriction to remove the excess water load. Recently, vasopressin receptor antagonists (vaptans) have been developed in the treatment of hypervolemic and euvolemic hyponatremia. Vaptans are not approved for the treatment of hypovolemic hyponatremia [68].

Most hyponatremic patients are not symptomatic and do not require treatment with hypertonic saline. Most hyponatremic patients are euvolemic, and the most common diagnosis is syndrome of inappropriate antidiuretic hormone (SIADH). SIADH is a diagnosis of exclusion with specific criteria, including a plasma osmolality <270 mOsm/kg H_2O; urine osmolality >100 mOsm/kg H_2O; euvolemia; elevated urine sodium concentration; absence of adrenal, thyroid, pituitary or renal insufficiency and absence of diuretic use [46].

Hypernatremia is a state of serum sodium greater than 145 mEq/L. It occurs in approximately 2 % of hospitalized patients and 15 % of patients in the intensive care unit. Mortality rates approach 70 % [51]. Hypernatremia results from either free water deficit or excess total body sodium and can occur in the setting of hypovolemia, euvolemia, or hypervolemia. Therapy can

be correctly guided by assessing volume status and urine sodium to determine the etiology of hypernatremia.

Hypernatremia increases extracellular tonicity and thereby results in cellular dehydration. Symptoms are referable to the central nervous system and include confusion, weakness and lethargy progressing to seizures, coma and death. Hypernatremia must be corrected carefully to avoid cerebral edema. In general, just as is the case with hyponatremia, hypernatremia should be corrected as quickly as the onset. The mainstay treatment for hypernatremia is the replacement of the free water deficit. The deficit is calculated as follows:

$$\text{Free water deficit} = \left[0.6 \times \text{total body weight}\right] \times \left[\left(\text{measured}\left[\text{Na}^{+}\right]/140\right) - 1\right]$$

Half the calculated deficit should be replaced in the first 12–24 h so as not to correct at a rate faster than 2 mEq/L/h. The remaining deficit should be replaced over the next 48 h.

Disorders of Potassium Metabolism

The normal extracellular concentration of potassium range is 3.5–5.0 mEq/L. It is the principal cation in the intracellular fluid, ranging from 140 to 160 mEq/L. This difference in concentration is essential in providing a transmembrane potential required to maintain the excitability of nerve and muscle tissues. Potassium deficiency in dietary intake has been implicated in the development of hypertension, cardiovascular disease, and glucose intolerance [69].

Hypokalemia refers to a serum potassium level of less than 3.6mEq/L. Causes of hypokalemia include losses through the gastrointestinal (GI) tract via diarrhea, vomiting or high nasogastric tube (NGT) output through intentional decompression. Hypokalemia may result from intracellular shifting of potassium in a variety of conditions (Table 2.2). Pseudohypokalemia may occur in specimens collected from leukemia patients with profound leukocytosis. Under these circumstances, white blood cells absorb potassium in vitro [70]. Common iatrogenic etiologies include losses via renal excretion caused by potassium wasting diuretic use.

Table 2.2 Causes of hypokalemia

– Insufficient intake
– Increased losses
GI losses
Diarrhea
Vomiting
NGT decompression
Ileostomy
Laxatives
Renal losses
– Drug induced losses
Mannitol
Diuretics
Aminoglycosides
Amphotericin
– Hyperaldosteronism
– Skin losses
Sweat
Burns
– Transcellular shifts
Overfeeding syndrome
Drug induced
Insulin administration
Beta adrenergic agonists
– Miscellaneous
Hypomagnesemia
Mountain sickness

Mild hypokalemia is usually asymptomatic. In severe cases, it may present as muscle cramps and weakness and in extreme cases progresses to muscle breakdown and necrosis. An ascending muscle paralysis may result in respiratory failure and arrest [71]. Cardiac signs include EKG changes appearing as ST depression, flattened T waves, U waves and QT interval prolongation and ventricular arrhythmias [72]. Disturbances in cardiac conduction resulting in death can be seen in patients with underlying cardiac disease and digitalis use [73].

Severe hypokalemia should be repleted intravenously or orally depending on the clinical scenario. In cases of hypokalemia due to transcellular shifts, treating the underlying condition is necessary, versus replacement in the case of true depletion. Sustained hypokalemia results

from true depletion compared to transient hypokalemia from transcellular shifts. Serum potassium falls approximately 0.3 mEq/L for every 100 mEq/L decrease in total body potassium [74]. A serum potassium level below 3.0 mEq/L should be corrected using intravenous replacement in a monitored setting due to the risk of arrhythmias. If hypomagnesemia is present, it should be corrected first, as such a state promotes excretion of potassium. Hypokalemia accompanies hypomagnesemia about 60 % of the time due to reduced Na^+, K-ATPase activity, in which magnesium acts as a dependent enzyme [75, 76]. When serum potassium is below 3.0 mEq/L, an additional 8–10 g of magnesium may also be required. Once the serum potassium level falls below 3.0 mEq/L, the amount of replacement required increases in a nonlinear fashion, and a minimum of 100 mEq is required to restore normal levels.

Hyperkalemia refers to a serum potassium level greater than 5.0 mEq/L. Pseudohyperkalemia results from marked leukocytosis, thrombocytosis or hemolysis of collected specimens, resulting in release of intracellular potassium. Pseudohyperkalemia can also be seen in blood samples of patients who have hereditary spherocytosis and hereditary stomatocytosis. A temperature dependent breakdown and leakage of potassium from these abnormal cells occurs. There are many possible causes of true hyperkalemia (Table 2.3).

Mild hyperkalemia is usually asymptomatic, but predominantly affects the muscular and cardiac systems. Muscular symptoms include parasthesias, extremity weakness, and flaccidity. Ascending muscle weakness may involve the trunk and respiratory muscles. Hyperkalemia can lead to cardiac conduction abnormalities. EKG findings include peaked T waves, widening of the QRS complex, AV conduction abnormalities, ventricular fibrillation, and eventual asystole [72].

Hyperkalemia results from: (1) an inability to secrete potassium due to renal dysfunction, (2) a shift of potassium out of cells, and (3) excessive administration of potassium. Renal failure is the most common cause of inability to excrete potassium. Traditional teaching has held that there is an inverse relationship between serum potassium levels and pH [77]. However, this has been disproven, and the relationship is complex and not completely understood.

Table 2.3 Causes of hyperkalemia

–	Excessive intake (rare with normal renal function)
–	Pseudohyperkalemia
	Hemolysis
	Leukocytosis
	Thrombocytosis
–	Impaired excretion
	Renal failure
–	Outward shift of potassium from cells
	Cell destruction
	Tumor lysis
	Intravascular hemolysis
	Tissue destruction
	Rhabdomyolysis
	Burns
–	Drugs
	Succinylcholine
	Digoxin

Symptomatic hyperkalemia as demonstrated by EKG changes or asymptomatic patients with a serum potassium level greater than 6.5 mEq/L should be treated emergently. Strategies include [71]:

1. Cardiac stabilization with calcium chloride.
2. Shifting potassium intracellularly with administration of insulin.
3. Increasing potassium excretion by volume expansion followed by the administration of potassium wasting diuretics.
4. Increasing excretion through the GI tract with sodium polystyrene sulfonate.
5. Extra-corpeal removal via dialysis.

In most cases, dialysis is reserved for patients who have renal failure. In rare circumstances, patients with healthy kidneys will have their excretory capacity overwhelmed and require temporary emergent dialysis as a life-saving intervention.

Disorders of Calcium Metabolism

Calcium is a divalent cation that plays an important role in several biological processes. Extracellularly, it is the main substrate for the skeletal system and is bound to phosphate as

hydroxyapatite. The average adult has 1–2 kg of total body calcium localized in bone as hydroxyapatite. In its intracellular form, calcium plays an important role as a signaling molecule for several pathways, including cardiac, skeletal and smooth muscle contraction, and neurotransmitter release. The concentration of extracellular and intracellular calcium is tightly regulated. The extracellular concentration of calcium is 10,000 times greater than intracellular concentrations. Release of calcium from its vast stores in the skeletal system is regulated by parathyroid hormone (PTH).

Serum calcium levels normally range from 9.4 to 10 mg/dL. The incidence of hypocalcemia ranges from 70 to 90 % when total serum calcium is measured versus 15–50 % when ionized calcium is measured [78]. This is due to the high incidence of hypoalbuminemia in critically ill and postoperative patients. Calcium is bound to albumin in serum, though the ionized form is the biologically active form.

Hypocalcemia refers to a serum calcium level of less than 8.5 mg/dL or an ionized level of less than 1.0 mmol/L. There are many reasons for hypocalcemia in the postoperative and critically ill patient population. The etiology is usually multifactorial. Ionized hypocalcemia is common in patients with sepsis, pancreatitis, severe trauma or postoperatively after plasma volume expansion with hypocalcemic solutions and is associated with increased mortality [78, 79]. Cytokine levels in critically ill patients, especially tumor necrosis factor, interleukin-6 and prolactin, serve as a measure of systemic inflammation and correlate with the degree of hypocalcemia [80, 81].

Mild hypocalcemia is usually asymptomatic. However, severe derangements result in significant physiological consequences. Diminished cardiac contractility can result in refractory hypotension. Arrhythmias include ventricular tachycardia. Prolonged QT interval and marked QRS and ST segment changes may mimic acute myocardial infarction and heart block. Calcium plays an important role in the coagulation process, including the conversion of fibrin to fibrinogen and enhancement of other coagulation factors. Maintaining an ionized calcium level above 0.9 mmol/L has a beneficial cardiovascular and coagulation effect in the resuscitation of patients in massive hemorrhage [82]. Citrate components present in blood products may also exacerbate the hypocalcemia by precipitation. Therefore, calcium levels should be monitored during massive transfusion.

Neurologically, hypocalcemia may present as parasthesias and seizures. Neuromuscular symptoms include spasms and tetany. An acute decline in the serum calcium level can result in laryngospasm and death. Chronic hypocalcemia may present with less pronounced symptoms that include neuromuscular irritability. At the bedside, hypocalcemia can be detected by testing for Chvostek's sign or Trousseau's sign. Chvostek's sign is facial nerve irritability that is elicited by gently tapping the facial nerve. Chvostek's sign is present in approximately 10–25 % of normal adults and may be absent in chronic hypocalcemia. Trousseau's sign is carpopedal spasm that is elicited by decreasing blood flow to the hand with a blood pressure cuff inflated to 20 mm Hg for 3 min. It is absent in one third of hypocalcemic patients. Psychiatric symptoms of hypocalcemia include dementia, psychosis, and depression [83, 84].

Symptomatic hypocalcemia and severe hypocalcemia (0.8 mmol/L) should be treated with intravenous calcium administration [85–87]. Intravenous calcium can be administered as calcium gluconate or calcium chloride. Calcium chloride has the advantage of being immediately available in equal amounts of calcium and chloride. Calcium gluconate must undergo hepatic degluconation to be available in the ionized form. Calcium chloride contains more calcium in terms of milliequivalents than calcium gluconate. Calcium infusions can also be used in the therapy of cardiac drug toxicity involving beta blockers and calcium channel blockers [86, 87].

Hypercalcemia is rare in the ICU setting and occurs in less than 15 % of hospitalized patients [78]. Hypercalcemia refers to a serum calcium level greater than 10.4 mg/dL. In the critically ill patient, increased bone reabsorption resulting from paraneoplastic syndromes and prolonged immobilization are common etiologies. Hyperparathyroidism and malignancy causing excessive PTHrP

are the most common causes of hypercalcemia in hospitalized patients, occurring in more than 50 % of cases [88]. Conversely, among outpatients referred to endocrinologists for hypercalcemia, more than 90 % are found to have primary hyperparathyroidism [89]. Other causes include renal failure, thyrotoxicosis, adrenal insufficiency, and drugs. In particular, thiazides may increase proximal tubule reabsorption of calcium [83, 84, 88].

Calcium levels greater than 12 mg/dL result in symptoms that particularly impact the neurologic and digestive systems and include fatigue, lethargy, confusion, coma, anorexia, abdominal pain, and constipation. Cardiac arrhythmias may also occur, including bradyarrhythmias or heart block. ST segment elevation responsive to treatment of the hypercalcemia may also occur.

Calcium levels greater than 14 mg/dL and symptomatic patients should be treated. Hypercalcemia can be treated by volume expansion with fluids followed by diuresis. In cases of excessive calcium reabsorption from bone due to underlying malignancy, a bisphosphonate or plicamycin may be used to suppress calcium reabsorption. Treatment of the underlying cause is necessary. Rarely in the acute care setting is dialysis with a low or zero calcium dialysate or parathyroidectomy necessary for the treatment of hypercalcemia refractory to medical management.

Disorders of Magnesium Metabolism

Magnesium is a divalent cation that plays an important role in the metabolism of other cations including sodium, potassium, and calcium. Magnesium is also an important cofactor in ATP energy metabolism. It is the second most common intracellular cation and fourth most common extracellular cation [89]. Normal serum concentration ranges from 1.5 to 2.3 mg/dL. The body stores magnesium mainly in the bones, muscles, and soft tissues. Total body magnesium can be low in low albumin states without affecting ionized magnesium levels. Sixty seven percent of serum magnesium is in the ionized form. Ionized magnesium is the biologically active form that can be measured using ion selective electrodes, but this technique has limitations with respect to accuracy [90, 91]. There are no known hormonal pathways in the regulation of magnesium. Magnesium homeostasis is achieved through absorption via the kidneys, digestive tract, and bone mobilization. Disorders of magnesium metabolism are seen in 15–60 % of patients in the critical care setting [92].

A serum magnesium level less than 1.5 mg/dL defines hypomagnesemia. There are several etiologies of hypomagnesemia (Table 2.4). In surgical and critically ill patients, common causes are plasma volume expansion, diuretic use, and severe sepsis. Other etiologies are excess GI losses from diarrhea, laxative use, and enteric decompression. It is often seen in association with hypocalcemia, hypokalemia, and hypophosphatemia. Hypokalemia and hypocalcemia are refractory to correction unless magnesium is replaced first [93, 94].

Hypomagnesemia is usually asymptomatic. When symptoms do occur, they are often similar to those associated with hypocalcemia, hypokalemia,

Table 2.4 Causes of hypomagnesemia

– Inadequate intake
– GI losses
Diarrhea
Vomiting
Fistula loss
Nasogastric decompression
Bowel preparation
– Renal losses
Genetic magnesium wasting syndromes
ATN
Ethanol
Drug induced
Digoxin
Diuretics (loop, thiazide, osmotic)
Cis-platinum
Cyclosporine
Tacrolimus
Cetuximab
– Intracellular shift of magnesium
Refeeding syndrome
Catecholamines
Correction of respiratory acidosis
Correction of diabetic ketoacidosis
– Blood transfusions
– Extensive burns
– Excessive sweating

and hypophosphatemia due to the close metabolic relationship of the cations. Symptoms include muscle weakness, cramps, seizures and arrhythmias, namely torsades de pointes. The treatment for torsades de pointes and symptomatic hypomagnesemia is intravenous replacement of magnesium, 1–2 g over 5 min.

Magnesium also has therapeutic properties in certain clinical scenarios. Magnesium competitively binds to *N*-methyl-D-aspartate receptors to depress the seizure threshold and is therefore used in the treatment of preeclampsia and eclampsia [93–96]. Magnesium also has smooth muscle relaxant properties that make it useful for treating bronchospasm in asthmatics [95, 96].

Hypermagnesemia is usually seen in the setting of renal failure, because normal kidneys can excrete large quantities of magnesium, up to 500 mEq/day [89]. Other etiologies are extensive soft tissue ischemia or necrosis in patients with trauma, sepsis, cardiopulmonary arrest, burns, or shock. Symptoms of hypermagnesemia occur at levels above 4 mg/dL and involve the muscular, neurologic, and cardiac systems. Muscular symptoms range from depressed deep tendon reflexes to muscle paralysis, including respiratory depression at levels above 8–10mg/dL. Neurologic symptoms include somnolence and lethargy. Cardiovascular symptoms include bradycardia and hypotension unresponsive to volume expansion and vasopressors. Complete heart block resulting in cardiac arrest is seen at levels approaching 20 mg/dL [89, 97]. Hypermagnesemia related hypotension can be treated with administration of calcium. Excess levels can be removed with hydration and forced diuresis with furosemide. Extreme cases of magnesium toxicity may require dialysis. Hypermagnesemia is a rare phenomenon in the ICU setting, excluding patients undergoing tocolysis with large doses of magnesium.

Disorders of Phosphorous Metabolism

The majority of the body's total reserve of phosphorous is stored in the bones as hydroxyapatite along with calcium [89]. The metabolic pathways of the two ions are closely intertwined. Phosphate plays an important role as a constituent of nucleic acids, phospholipids, complex carbohydrates, glycolytic intermediates, enzymatic phosphoproteins, and nucleotide cofactors for enzymes. Phosphate is also important for energy metabolism as a constituent of ATP. Phosphate levels are regulated by PTH, mainly via three routes: (1) bone reserves, (2) intestine, and (3) kidneys.

A serum phosphate level less than 3.0 mg/dL defines hypophosphatemia, which is classified according to degree of deficiency. Mild hypophosphatemia ranges 2.5–3.0 mg/dL, moderate 1.0–2.5 mg/dL, and severe less than 1 mg/dL. Phosphate depletion refers to low stores of total body phosphate. There are numerous causes of phosphate depletion (Table 2.5). Among hospitalized patients, the overall prevalence of severe

Table 2.5 Causes of hypophosphatemia

–	Shifts of extracellular phosphate into cells or bone
	Insulin administration
	Refeeding syndrome (initiation of carbohydrate causes an insulin spike, which increases cellular phosphate uptake)
	Respiratory alkalosis
	Catecholamines (epinephrine, albuterol, dopamine)
	Net bone formation
	Post-parathyroidectomy
	Osteoblastic metastases
–	Impaired intestinal phosphate absorption
	Malnutrition
	Aluminum containing antacids
	Chronic diarrhea
	NGT suction
	Malabsorption
–	Extreme catabolic states
	Burns
	Trauma
	Sepsis
–	Renal losses
	Excess PTH or PTHrP
	Diuretics
	Intrinsic renal disease
	Fanconi Syndrome
–	Hyperthermia/rewarming
–	Heavy metal poisoning
–	Amyloidosis

hypophosphatemia is less than 1 %, whereas mild or moderate hypophosphatemia occurs in 2–5 % of these patients [98].

Hypophosphatemia results in several clinical manifestations. Neuromuscular symptoms vary depending on the degree of phosphate depletion, ranging from progressive lethargy, muscle weakness and paresthesias to paralysis, coma, and death. Confusion, profound weakness, paralysis, seizures, and other major sequelae are usually limited to those patients who have serum phosphate concentrations lower than 0.8–1.0 mg/dL [99]. Rhabdomyolysis is observed within 2 days in more than one third of patients whose serum phosphate concentrations fall to less than 2 mg/dL [100]. Respiratory muscle weakness may prevent successful weaning from mechanical ventilation [101, 102]. Cardiac symptoms resulting from profound hypophosphatemia include left ventricular dysfunction, heart failure, and ventricular arrhythmias but may not be significant if the serum phosphate concentration is greater than 1.5 mg/dL [103]. Hematologic derangements include acute hemolytic anemia and leukocyte dysfunction. Depletion requires electrolyte replacements via enteric or intravenous routes. Severe depletion warrants intravenous replacement. Replacements should be carried out with caution in patients with renal failure and hypercalcemia due to the risk of metastatic calcifications.

Hyperphosphatemia refers to a serum phosphate level greater than 4.5 mg/dL. Elevated phosphate levels result most often from acute or chronic renal dysfunction in which the renal tubules are unable to clear the daily phosphate load despite maximal inhibition of phosphate reabsorption in the remaining functional nephrons. Cellular damage from rhabdomyolysis, tumor lysis syndrome, hemolysis, and thyrotoxicosis may also result in increased phosphate levels [104]. Iatrogenic causes include excess electrolyte correction, laxative use, and bisphosphonate therapy.

Hyperphosphatemia results in hypocalcemia through three mechanisms: (1) precipitation of calcium, (2) interfering with PTH levels, and (3) decreasing vitamin D levels [105]. Hyperphosphatemia, therefore, clinically presents as hypocalcemia. Tetany, muscle cramps, paresthesias, and seizures may occur. Calcium phosphate precipitation into soft tissues may cause organ dysfunction, particularly renal failure.

Excess phosphate may be removed by increasing urinary excretion with hydration and diuresis, acetazolamide being the most effective [106]. Dialysis may be necessary in acute cases. Patients with chronic renal failure may require oral phosphate binders to prevent hyperphosphatemia. Enteral nutrition should also be modified to decrease the phosphate load when feasible. In the acute care setting, increased dietary protein requirements may prevent phosphate load reduction.

References

1. Cosnett JE. The origins of intravenous fluid therapy. Lancet. 1989;1(8641):768–71.
2. Sabiston DC. The fundamental contributions of Alfred Blalock to the pathogenesis of shock. Arch Surg. 1995;130(7):736–7.
3. Ritz P, Vol S, Berrut G, Tack I, Arnaud MJ, Tichet J. Influence of gender and body composition on hydration and body water spaces. Clin Nutr. 2008;27:740–6.
4. Edelman IS, Leibman J. Anatomy of body water and electrolytes. Am J Med. 1959;27:256–77.
5. Wait RB, Alouidor R. Fluids, electrolytes, and acid–base balance. In: Mulholland MW, Lillemoe KD, Doherty GM, Maier RV, Simeone DM, Upchurch GR, editors. Greenfield's surgery: scientific principles and practice. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 189–213.
6. Shires T, Williams J, Brown F. Acute changes in extracellular fluids associated with major surgical procedures. Ann Surg. 1961;154:803–10.
7. Shires GT. Shock and metabolism. Surg Gynecol Obstet. 1967;124:803–10.
8. Kaye AD, Riopelle JM. Intravascular fluid and electrolyte physiology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's anesthesia. Philadelphia: Churchill Livingstone Elsevier; 2010. p. 1705–38.
9. Chan STF, Kapadia CR, Johnson AW, Radcliffe AG, Dudley HAF. Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. Br J Surg. 1983;70:36–9.
10. Brandstrup B, Svensen C, Engquist A. Hemorrhage and operation cause a contraction of the extracellular space needing replacement–evidence and implications? A systematic review. Surgery. 2006;139:419–32.
11. Brandstrup B. Fluid therapy for the surgical patient. Best Pract Res Clin Anaesthesiol. 2006;20:265–83.
12. Kasiewicz J, Puyana JC. Resuscitation of hypovolemic shock. In: Vincent JL, Abraham E, Moore FA,

Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Saunders; 2011. p. 1395–8.
13. Baldwin AL, Thurston G. Mechanics of endothelial cell architecture and vascular permeability. Crit Rev Biomed Eng. 2001;29(2):247–78.
14. Emerson TE. Unique features of albumin: a brief review. Crit Care Med. 1989;17(7):690–4.
15. Bent-Hansen L. Whole body capillary exchange of albumin. Acta Physiol Scand Suppl. 1991;603:5–10.
16. Rose BD, Post TW. Regulation of plasma osmolality. In: Rose BD, Post TW, editors. Clinical physiology of acid–base and electrolyte disorders. New York: McGraw-Hill; 2001. p. 285–98.
17. Agre P. The aquaporin water channels. Proc Am Thorac Soc. 2006;3(1):5–13.
18. Carbrey JM, Agre P. Discovery of the aquaporins and development of the field. Handb Exp Pharmacol. 2009;90:3–28.
19. Gonen T, Walz T.The structure of aquaporins. Q Rev Biophys. 2006;39(4):361–96.
20. Fu D, Lu M. The structural basis of water perme - ation and proton exclusion in aquaporins. Mol Membr Biol. 2007;24(5–6):366–74.
21. Fenton RA, Moeller HB. Recent discoveries in vasopressin-regulated aquaporin-2 trafficking. Prog Brain Res. 2008;170:571–9.
22. Moen MD, Keating GM. Intravenous conivaptan. Am J Cardiovasc Drugs. 2008;8(5):341–8.
23. Metzger BL, DeVita MV, Michelis MFObservations regarding the use of the aquaretic agent conivaptan for treatment of hyponatremia. Int Urol Nephrol. 2008;40:725–30.
24. Lee CY, Burnett JC. Natriuretic peptides and thera - peutic implications. Heart Fail Rev. 2007;12:131–42.
25. McGrath MF, de Bold ML, de Bold AJ. The endocrine function of the heart. Trends Endocrinol Metab. 2005;16:469–77.
26. Wait RB, Kahng KU. Renal failure complicating obstructive jaundice. Am J Surg. 1989;157:256–63.
27. Remuzzi G, Benigni A. Endothelins in the control of cardiovascular and renal function. Lancet. 1993;342: 589–93.
28. Bachmann S, Mundel P. Nitric oxide and the kidney: synthesis, localization, and function. Am J Kidney Dis. 1994;24(1):112–29.
29. Kaplan LJ, Frangos S. Clinical Review: Acid–base abnormalities in the intensive care unit. Critical Care. 2005;9(2):198–203.
30. Kramer GC. Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care. J Trauma. 2003;54(5 Suppl):S89–99.
31. Finfer S, Bollomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(2):2247–56.
32. Vincent JL, Sakr Y, Reinhart K. Is albumin administration in the acutely ill associated with increased mortality? Results of the SOAP study. Crit Care. 2005;96(6):R745–54.
33. Schortgen F, Girou E, Deye N, Brochard L. The risk associated with hyperoncotoic colloids in patients with shock. Intensive Care Med. 2008;34(12):2157–68.
34. Hartmann AF, Senn MJ. Studies in the metabolism of sodium r-lactate. III. Response of human subjects with liver damage, disturbed water and mineral balance, and renal insufficiency to the intravenous injection of sodium r-lactate. J Clin Invest. 1932;11: 345–55.
35. Cordell AR. Milestones in the development of cardioplegia. Ann Thorac Surg. 1995;60:793–6.
36. Rhee P, Burris D, Kaufmann C, Pikoulis M, Austin B, Ling G, et al. Lactated Ringer's solution resuscitation causes neutrophil activation after hemorrhagic shock. J Trauma. 1998;44(2):313–9.
37. Deb S, Martin B, Sun L, Ruff P, Burris D, Rich N, et al. Resuscitation with lactated Ringer's solution in rats with hemorrhagic shock induces immediate apoptosis. J Trauma. 1999;46(4):582–8.
38. Cai B, Chen F, Lin X, Miller E, Szabo C, Deithch EA, et al. Anti-inflammatory adjuvant in resuscitation fluids improves survival in hemorrhage. Crit Care Med. 2009;37(3):860–8.
39. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomized controlled trials. BMJ. 1998;317(7153):235–40.
40. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2004;4:CD001208.
41. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34.
42. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901–11.
43. Bayer O, Reinhart K, Kohl M, Kabisch B, Marshall J, Sakr Y, et al. Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: a prospective sequential analysis. Crit Care Med. 2012;40:2543–51.
44. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013;2, CD000567.
45. Wait RB, Kahng KU, Mustafa IA. Fluid, electrolytes, and acid–base balance. In: Greenfield LJ, Mulhholland MW, Oldham KT, Zelenock GB, Lillemoe KD, editors. Surgery: scientific principles and practice. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 244–69.
46. Todd SR. Disorders of water balance. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Saunders; 2011. p. 841–9.
47. Upadhyay A, Jabber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119 (7 Suppl 1):S30–5.

48. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290:2581–7.
49. Londono MC, Guevera M, Rimola A, Navasa M, Tauara P, Mas A, et al. Hyponatremia impairs early post transplantation outcome in patients with cirrhosis undergoing liver transplantation. Gastroenterology. 2006;130:1135–43.
50. Zilberberg MD, Exuzides A, Spalding J, Foreman A, Jones AG, Colby C, et al. Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study. BMC Pulm Med. 2008;8:16. PubMed PMID: 18710521.
51. McIwaine JK, Corwin HL. Hypernatremia and hyponatremia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Saunders; 2011. p. 53–5.
52. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342(21):1581–9.
53. Schrier RW. Pathogenesis of sodium and water retention in high output and low output cardiac failure, nephritic syndrome, cirrhosis, and pregnancy (2). N Eng J Med. 1988;319(17):1127–34.
54. Schrier RW. Pathogenesis of sodium and water retention in high output and low output cardiac failure, nephritic syndrome, cirrhosis, and pregnancy (1). N Eng J Med. 1988;319(16):1065–72.
55. Sedlaceck M, Schoolwerth AC, Remillard BD. Electrolyte disturbances in the intensive care unit. Semin Dial. 2006;19(6):496–501.
56. Swart RM, Hoorn EJ, Betjes MG, Zieste R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol. 2011;118:45–51.
57. Fraser CL, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. Am J Med. 1997;102:67–77.
58. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA. 1999;81:2299–304.
59. Stems RH. Severe hyponatremia: the case for conservative management. Crit Care Med. 1992;20:534–9.
60. Cohen BJ, Jordan MH, Chapin SD, Cape B, Laureno R. Pontine myelinolysis after correction of hyponatremia during burn resuscitation. J Burn Care Rehabil. 1991;12:153–6.
61. Laurene R. Central pontine myelinolysis following rapid correction of hyponatremia. Ann Neurol. 1983;13:232–42.
62. Laurene R, Karp BI. Myelinolysis after correction of hyponatremia. Ann Intern Med. 1997;126:57–62.
63. Laureno R, Karp BI. Pontine and extrapontine myelinolysis following rapid correction of hyponatraemia. Lancet. 1988;1:1439–41.
64. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. Medicine. 1993;72:359–73.
65. Stems RH. Neurological deterioration following treatment for hyponatremia. Am J Kidney Dis. 1989;13:434–7.
66. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. J Am Soc Nephrol. 1994;4:1522–30.
67. Stems RH, Riggs JE, Schochet Jr SS. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med. 1986;14:1535–42.
68. Lehrich RW, Greenberg A. Hyponatremia and the use of vasopressin receptor antagonists in critically ill patients. J Intensive Care Med. 2012;27(4):207–18.
69. Adrogué HJ, Madias NE. Mechanisms of disease: sodium and potassium in the pathogenesis of hypertension. N Engl J Med. 2007;356:1966–78.
70. Naparstek Y, Gutman A. Case Report: Spurious hypokalemia in myeloproliferative disorders. Am J Med Sci. 1984;288:175–7.
71. Zanotti-Cavazzoni S, Dellinger RP. Hyperkalemia and hypokalemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Saunders; 2011. p. 56–9.
72. Slovis C, Jenkins R. ABC of clinical electrocardiography: conditions not primarily affecting the heart. BMJ. 2002;324:1320–3.
73. Schulman M, Narins RG. Hypokalemia and cardiovascular disease. Am J Cardiol. 1990;65:4E–9.
74. Gennari FJ. Hypokalemia. N Engl J Med. 1998;339:451–8.
75. Whang R, Welt LA. Observations in experimental magnesium depletion. J Clin Invest. 1963;42:305–13.
76. Wong NLM, Sutton RA, Navichak V, Quame GA, Dirks JH. Enhanced distal absorption of potassium by magnesium-deficient rats. Clin Sci. 1985;69:626–39.
77. Burnell JM, Scribner BH, Uyeno BT, Villamil MF. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. J Clin Invest. 1956;35:935–9.
78. Hassan M, Cooney RN. Hypocalcemia and hypercalcemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Saunders; 2011. p. 65–7.
79. Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia. A pervasive metabolic abnormality in the critically ill. Am J Kidney Dis. 2001;37:689–98.
80. Zaloga GP. Ionized hypocalcemia during sepsis. Crit Care Med. 2000;28:266–8.
81. Müller B, Becker KL, Kränzlin M, Schächinger H, Huber PR, Nylèn ES, et al. Disordered calcium homeostasis of sepsis: association with calcitonin precursors. Eur J Clin Invest. 2000;30:823–31.
82. Lier H, Krep H, Schroeder S, Stuber FPreconditions of hemostasis in trauma: a review. The influence of

acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. J Trauma. 2008;65(4):951–60.
83. Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med. 1992;20:251–61.
84. Aguilera IM, Vaughan RS. Calcium and the anaesthetist. Anaesthesia. 2000;55:779–90.
85. Carlstedt F, Lind L. Hypocalcemic syndromes. Crit Care Clin. 2001;17:139–53.
86. Strubelt O, Diederich KW. Experimental investigations of the antidotal treatment of nifedipine overdosage. J Toxicol Clin Toxicol. 1986;24(2):135–49.
87. Tai YT, Lo CW, Chow WH, Cheng CH. Successful resuscitation and survival following massive overdose of metoprolol. Br J Clin Pract. 1990;44:746–7.
88. Forster J, Querusio L, Burchard KW, Gann DS. Hypercalcemia in critically ill surgical patients. Ann Surg. 1985;202:512–8.
89. Bringhurst FR, Demay MB, Kronenberg HM. Hormones and disorders of mineral metabolism. In: Melmed S, Polonsky K, Larsen PR, Kronenberg H, editors. Williams textbook of endocrinology. Philadelphia: W.B. Saunders; 2011. p. 1237–304.
90. Johansson M. Weak relationship between ionized and total magnesium in serum of patients requiring magnesium status. Biol Trace Elem Res. 2007; 115(1):13–21.
91. Ben Rayana MC, Burnett RW, Covington AK, D'Orazio P, Fogh-Andersen N, Jacobs E, etal. IFCC guideline for sampling, measuring and reporting ionized magnesium in plasma. Clin Chem Lab Med. 2008;46(1):21–6.
92. Hassan M, Cooney RN. Hypomagnesemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care medicine. Philadelphia: Elsevier Saunders; 2011. p. 63–4.
93. Norhona JL, Matuschak GM. Magnesium in critical illness: metabolism, assessment, and treatment. Intensive Care Med. 2002;28:667–79.
94. Topf JM, Murray PT. Hypomagnesemia and hypermagnesemia. Rev Endocrin Metab Disord. 2003;4:195–206.
95. Dacey MJ. Hypomagnesemic disorders. Crit Care Clin. 2001;17:155–73.
96. Fox C, Ramsoomair D, Carter C. Magnesium: its proven and potential clinical significance. South Med J. 2001;94:1195–201.
97. Zalman AS. Hypomagnesemia. J Am Soc Nephrol. 1999;10(7):1616–22.
98. Daily WH, Tonnesen AS, Allen SJ. Hypophosphatemia: incidence, etiology and prevention in the trauma patient. Crit Care Med. 1990;18: 1210–4.
99. Vanneste J, Hage J. Acute severe hypophosphatemia mimicking Wernicke's encephalopathy. Lancet. 1986;1(8471):44.
100. Singhal PC, Kumar A, Desroches L, Gibbons N, Mattana J. Prevalence and predictors of rhabdomyolysis in patients with hypophosphatemia. Am J Med. 1992;92:458–64.
101. Aubier M, Murciano D, Lecocguic Y, Viires N, Jacquens Y, Squara P, Pariente R. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Eng J Med. 1985;313:420–4.
102. Newman JH, Neff TA, Ziporin P. Acute respiratory failure associated with hypophosphatemia. N Engl J Med. 1977;296(19):1101–3.
103. Bollaert PE, Levy B, Nace L, Laterre PF, Larcan A. Hemodynamic and metabolic effects of rapid correction of hypophosphatemia in patients with septic shock. Chest. 1995;107(6):1698–701.
104. Vachvanichsanong P, Maipang M, Dissaneewate P, Wongchanchailert M, Laosombat V. Severe hyperphosphatemia following acute tumor lysis syndrome. Med Pediatr Oncol. 1995;24:63–6.
105. Sutlers M, Gaboury CL, Bennett WM. Severe hyperphosphatemia and hypocalcemia: a dilemma in patient management. J Am Soc Nephrol. 1996; 7(10):2056–61.
106. Bauer C, Dhillon A. Hypophosphatemia and hyperphosphatemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Saunders; 2011. p. 60–2.

Acid–Base Physiology

3

Suresh Agarwal and Amy E. Liepert

General Principles

Physiologic Basis for Acid–Base Disorders and Their Compensation

Normal blood pH is maintained in a very narrow range, between 7.37 and 7.43. Changes seen in pH are a reflection of an inverse change in hydrogen ion (H^+) concentration. By formula, pH is a negative logarithm of H^+:

$$\mathrm{pH} = -\log_{10}\left[\mathrm{H}^+\right]$$

As such, at a blood pH of 7.40, there are 40 nEq/L of H^+. Factors that increase H^+ concentration, and reduce pH, or decrease H^+ concentration, and increase pH, are called acidosis and alkalosis respectively. An increase in H^+ and decrease in pH is called acidemia whereas a decrease in H^+ and increase in pH is called alkalemia.

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Calculation of pH is performed by using the Henderson–Hasselbach Formula, which uses measurable quantities of CO_2 and HCO_3^-: $\mathrm{pH} = \mathrm{p}K_a + \log$ (base/acid) or $\mathrm{pH} = \mathrm{p}K_a + \log [HCO_3^-]/[H_2CO_2]$. As H_2CO_2 is not measured, the proportionality constant between P_{CO_2} and $[H_2CO_2]$, 0.03, is utilized to give us:

$$\mathrm{pH} = \mathrm{p}K_a + \log\left[\mathrm{HCO}_3^-\right] / \left[0.03 \times \mathrm{P}_{co_2}\right]$$

$\mathrm{p}K_a$, the value describing the ratio of concentrations between buffer acids and buffer bases, for the HCO_2^-/CO_2 buffer system is 6.1. As this is the most important buffering system in the human body, it is the one that is characteristically used.

Nonlogarithmically, this can be expressed as the formula: $[H+] = 24 \times P_{CO_2} / [HCO_3^-]$.

Chemical Buffering Systems

The body is able to maintain an arterial pH in a very narrow range due to intracellular and extracellular mechanisms that are able to correct for large physiologic perturbations (Fig. 3.1). The most common mechanisms for compensation of pH abnormalities is through the respiratory and renal systems which alter carbon dioxide (CO_2) and bicarbonate (HCO_3^-) resorption and excretion. Carbon dioxide, a volatile acid, is a byproduct of cellular aerobic respiration that combines with water to form carbonic acid (H_2CO_3) which can be catalyzed by carbonic anhydrase to produce protons (H^+) and bicarbonate (HCO_3^-).

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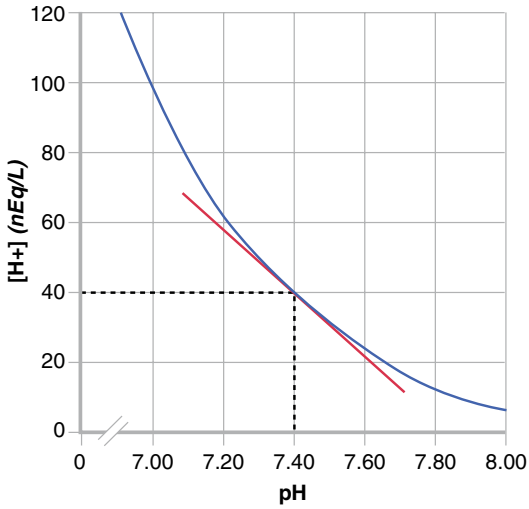

Fig. 3.1 The relation between the plasma hydrogen ion concentration ($[H^+]$) and the pH of the blood ($pH = -\log_{10}[H^+]$) (Modified from [136])

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Nonvolatile acids can be produced from protein catabolism as seen with sulfuric acid (H_2SO_4), phospholipid breakdown as seen with phosphoric acid (H_3PO_4), as a byproduct of anaerobic respiration as is the case with lactic acid, or as a result of a disease process such as that seen with ketoacid production in patients with diabetes.

Buffering solutions, weak acids or bases and their conjugate bases and acids, respectively, are the first line of defense against significant changes in the pH. These can be found, both in extracellular fluid, or within cells themselves. Most common extracellular buffers include the bicarbonate and carbon dioxide system described above. Other buffering systems, such as Phosphates, Intracellular Proteins, and Hemoglobin, also exist but have a less profound impact upon the maintenance of pH.

Physiologic Determinants of Acid–Base Maintenance

Both the respiratory and renal systems control the concentrations of bicarbonate and carbon dioxide in the body to maintain a stable pH; the lungs acting largely acutely and the kidneys in a more chronic manner (Fig. 3.2).

Renal System

Plasma flows to the kidneys at a rate of approximately 600 mL/min. The glomeruli filter the plasma, producing filtrate at a rate of 120 mL/min. The filtrate, in turn, is processed by reabsorption and secretion mechanisms in the tubular cells along which it passes on its way to the ureters. Normally, more than 99 % of the filtrate is reabsorbed and returned to the plasma. Thus, the kidney can excrete only a very small amount of strong ions into the urine each minute, which means that several minutes to hours are required to make a significant impact on the total body acid–base status.

The handling of strong ions by the kidney is extremely important because every chloride ion that is filtered but not reabsorbed increases the plasma strong ion difference (SID). The human diet typically contains similar ratios of strong cations to strong anions. The body's multiple buffering systems act to preserve overall acid–base neutrality due to the effects of diet. Ultimately the primary regulating mechanism is chloride exchange via the renal system to eliminate any excess ingested non-metabolizable acid. However, the contribution of acid or alkali that the diet provides is a mere fraction of the overall acid–base capacity processed each day in the human body. Given that renal Na^+ and K^+ handling is influenced by other priorities (e.g., intravascular volume and plasma K^+ homeostasis), it is logical that the kidney regulates excess acid through management of Cl^- balance.

Renal Reabsorption of Bicarbonate and Excretion of Acid

The kidneys play a large role in the chronic maintenance of blood pH through the regulation of bicarbonate concentration and acid removal. Maintenance of a bicarbonate level of 25 mEq/L requires reabsorption of the majority of the filtered bicarbonate, most of which occurs in the proximal tubule through active and passive mechanisms (Fig. 3.3).

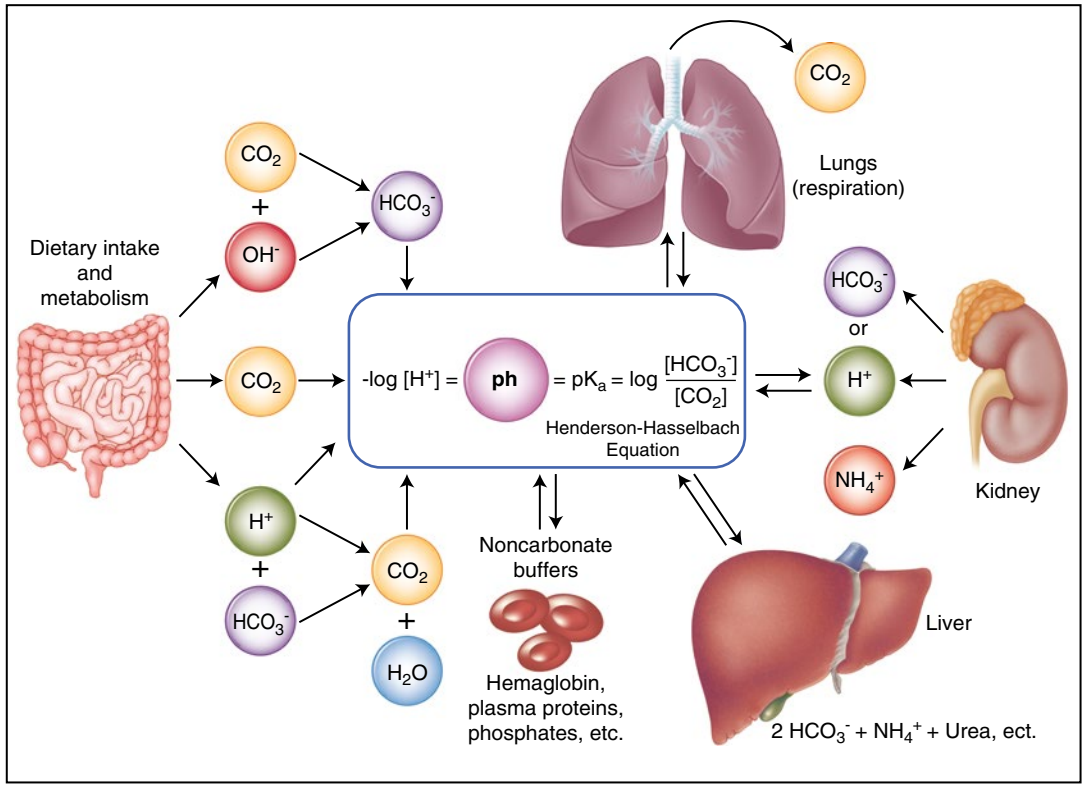

Fig. 3.2 Systematic contributions to acid–base balance (Modified from [136])

Acid excretion from the kidneys occurs in the proximal and distal collecting tubules through an active mechanism. This process may be inhibited by urine pH of less than 4.5, but this mechanism may be voided by the presence of urinary buffers (Figs. 3.4 and 3.5). Ammonia is the most prevalent of these buffers. In conditions such as renal insufficiency where ammonia is deficient, metabolic acidosis may result. Ammonia production, which occurs in the proximal tubule and collecting tubule, is stimulated by acidemia and hypokalemia and inhibited by alkalemia and hyperkalemia (Fig. 3.6). Traditional approaches to the question of renal acid handling have focused on H^+ excretion, emphasizing the importance of ammonia (NH_3) and its add-on cation, ammonium (NH_4^+). However, H^+ excretion actually is irrelevant as water provides an essentially infinite source of free H^+. Indeed, the kidney does not excrete H^+ to any greater degree in the form of NH_4^+ than in the form of H_2O. The purpose of renal ammoniagenesis is to allow the excretion of Cl^- without Na^+ or K^+. This purpose is achieved by supplying a weak cation (NH_4^+) that is excreted along with Cl^-. The mechanisms of RTA are currently being reinterpreted by some authors in the light of a growing body of evidence showing that abnormal chloride conductance, rather than H^+ or HCO_3^- handling, is responsible for these disorders [1].

Kidney–Liver Interaction

The importance of NH_4^+ to systemic acid–base balance, rests not on its carriage of H^+ or its direct action in the plasma (normal plasma NH_4^+ concentration < 0.01 mEq/L) but on its excretion with Cl^-. Of course, production of NH_4^+ is not restricted to the kidney. Hepatic ammoniagenesis (as well as glutaminogenesis) is also important for systemic acid–base balance and is also tightly

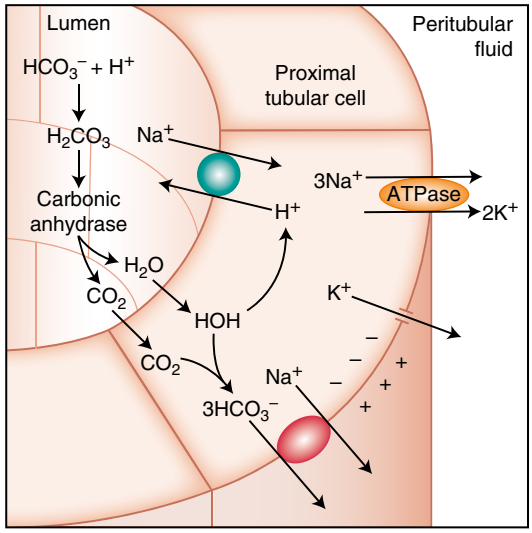

Fig. 3.3 Proximal tubular bicarbonate reabsorption is activated by the Na+, K^+-ATPase pump in the peritubular cell membrane. Exchanging peritubular K^+ for intracellular Na^+ keeps the intracellular [Na^+] low, allowing Na^+ to move down its concentration gradient from the tubular lumen through the Na^+–H^+ antiporter to the cell interior. HCO_3^- filtered across the glomerular capillaries combines with secreted H^+ to form H_2CO_3. Rapid dissociation of H_2CO_3 to CO_2 and H_2O in the presence of luminal carbonic anhydrase permits movement into the cell, where redissociation occurs. Ultimately, the reabsorbed H^+ is resecreted in exchange for Na^+, and HCO_3^- moves down an electrical gradient from the cell interior to the peritubular space, where it is reabsorbed into the systemic circulation (Modified from [136])

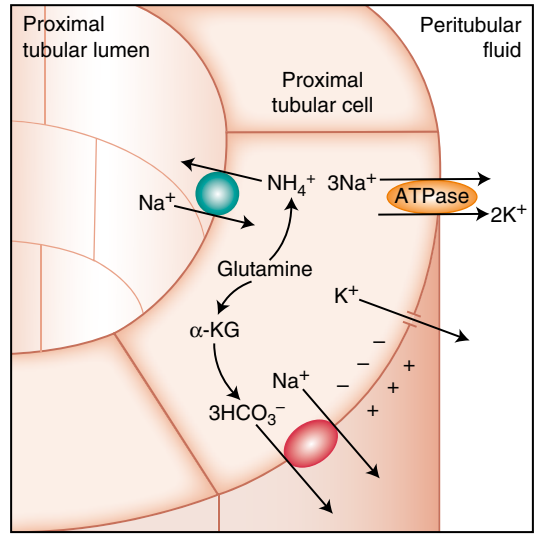

Fig. 3.4 All of the ammonia used to buffer urinary H^+ in the collecting tubule is synthesized in the proximal convoluted tubule, and glutamine is assumed to be the main source of this ammonia. As glutamine is metabolized, α-ketoglutarate (α-KG) is formed, which ultimately breaks down to bicarbonate, which is then secreted into the peritubular fluid by an NA^+–HCO_2^- cotransporter (Modified from [136])

controlled by mechanisms sensitive to plasma pH [2]. This reinterpretation of the role of NH_4^+ in acid–base balance is supported by the evidence that hepatic glutaminogenesis is stimulated by acidosis [3]. Metabolism of nitrogen by the liver can yield urea, glutamine, or NH_4^+. Normally, the liver releases only a very small amount of NH_4^+, incorporating most of its nitrogen into either urea or glutamine. Hepatocytes have enzymes to enable them to produce either of these end products, and both allow regulation of plasma NH_4^+ at suitably low levels. At the level of the kidneys, however, the production of urea or glutamine has significantly different effects in that the kidneys use glutamine to generate NH_4^+ and facilitate the excretion of Cl^-. Thus, production of glutamine by the liver can be seen as having an alkalinizing effect on plasma pH because the kidneys use this substance to excrete Cl^-.

Further support for this scenario comes from the discovery that hepatocytes are anatomically organized according to their enzymatic content [4]. Hepatocytes with a propensity to produce urea are positioned closer to the portal venule; those with a propensity to produce glutamine are positioned farther downstream. The upstream (urea-producing) hepatocytes have the first chance at the NH_4^+ delivered. However, acidosis inhibits ureagenesis, thereby leaving more NH_4^+ available for the downstream (glutamine-producing) hepatocytes. The leftover NH_4^+ is thus, in a sense, packaged as glutamine for export to the kidney, where it is used to facilitate Cl^- excretion.

Gastrointestinal Tract

The GI tract is often not given the attention it deserves as a component of acid–base balance. It does however handle strong ions very differently along its length. In the stomach, Cl^- is pumped out of the plasma and into the lumen, thereby reducing

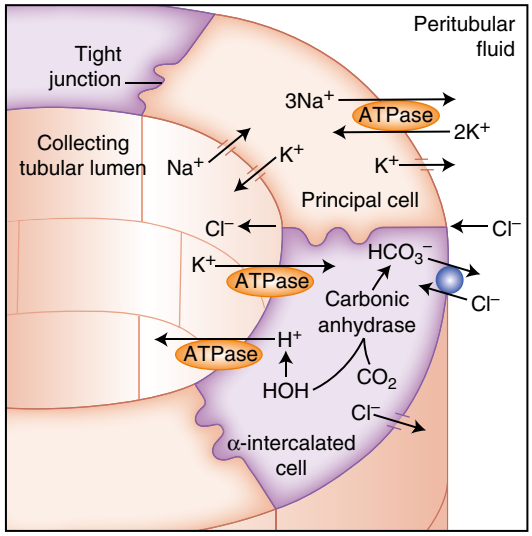

Fig. 3.5 Secretion of H^+ from the cortical collecting tubule is indirectly linked to Na^+ reabsorption. Intracellular potassium is exchanged for sodium in the principal cells, whereas H^+ is actively transported by an adenosine triphosphate (ATPase) pump from the α-intercalated cells. Aldosterone stimulates H^+ secretion by entering the principal cell, where it opens NA^+ channels in the luminal membrane and increases NA^+, K^+-ATPase activity. The movement of cationic Na^+ into the principal cells then creates a negative charge within the tubular lumen. K^+ moves from the principal cells and H^+ from the α-intercalated cells down this electrochemical gradient and into the lumen. (When K^+ is depleted, principal cell K^+ secretion is reduced, and K^+ reabsorption via an ATPase pump in the α-intercalated cell is stimulated.) Aldosterone apparently also stimulates the H^+-ATPase directly in the intercalated cell, further enhancing H^+ secretion. HCO_3 is returned to the blood across the peritubular membrane in exchange for Cl^-, thus maintaining electroneutrality (Modified from [136])

the SID and the pH. Simultaneously, as the Cl^- ion is pumped into the lumen, HCO_3^- is pumped in the opposite direction into the plasma via an exchanger. The SID is increased by the loss of Cl^- and the pH rises, producing the so-called alkaline tide that occurs at the beginning of a meal, when gastric acid secretion is maximal [5].

In the duodenum, Cl^- is reabsorbed and the plasma pH is restored. Normally, only slight changes in plasma pH are evident because Cl^- is returned to the circulation almost as soon as it is removed. If, however, gastric secretions are removed from the patient, whether by catheter suctioning or vomiting, Cl^- will be progressively lost and the SID will steadily increase and acidosis ensues. It is important to remember that it is the loss of Cl^-, not of H^+, that determines the plasma pH. Although H^+ is lost as HCl, it is also lost with every molecule of water removed from the body. When Cl^-, a strong anion, is lost without the corresponding loss of a strong cation, the SID is increased, and, therefore, the plasma H^+ concentration is decreased. When H^+ is lost as water rather than as HCl, the SID does not change; thus, the plasma H^+ concentration does not change either.

The pancreas secretes fluid into the small intestine that possesses an SID much higher than the plasma SID and is very low in Cl^-. Thus, the plasma perfusing the pancreas has its SID decreased, a phenomenon that peaks about 1 h after a meal and helps counteract the alkaline tide. If large amounts of pancreatic fluid are lost (e.g., as a consequence of surgical drainage), the resulting decrease in the plasma SID will lead to acidosis.

In the large intestine, the intraluminal fluid also has a high SID because most of the Cl^- was removed in the small intestine and the remaining electrolytes consist mostly of Na^+ and K^+. Normally, the body reabsorbs much of the water and electrolytes from this fluid, but when severe diarrhea occurs, large amounts of cations may be lost. If this cation loss persists, the plasma SID will decrease and acidosis will result.

In addition to the acid–base effects of abnormal loss of strong ions from the GI lumen, the small intestine, may contribute strong ions to the plasma. This contribution is most apparent when mesenteric blood flow is compromised and lactate is produced, sometimes in large quantities. Although global hypoperfusion may compromise the mesentery, the intestine does not appear to be a source of lactic acid in patients resuscitated from a septic state [6]. Moreover, whether the GI tract is capable of regulating strong ion uptake in a compensatory fashion has not been well studied. There is some evidence that the gut may modulate systemic acidosis in experimental endotoxemia by removing anions from the plasma [7]; however, the full capacity of the gut to affect acid–base balance remains to be determined.

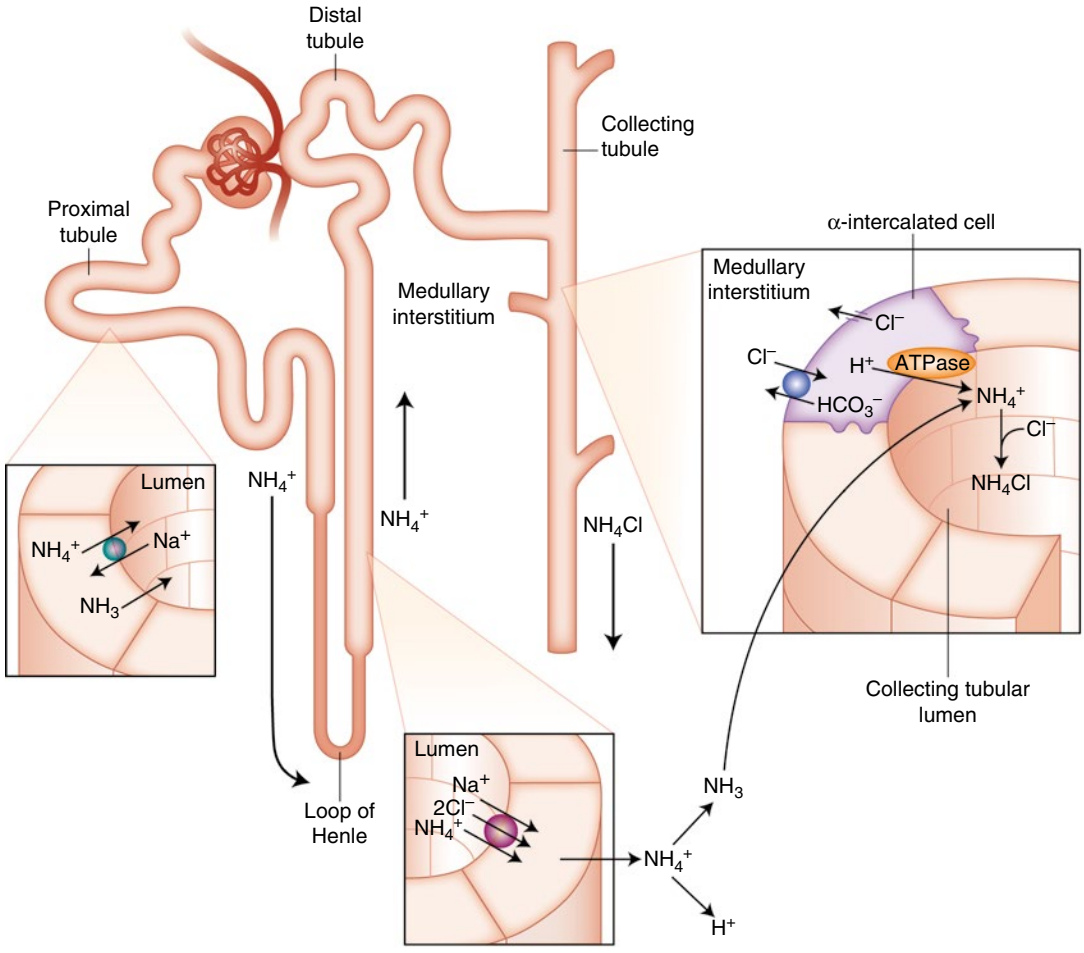

Fig. 3.6 The ammonia used to buffer urinary hydrogen ions is synthesized in the proximal convoluted tubule. It then diffuses into the proximal tubular lumen or can become acidified within the cell, forming ammonium, which can enter the tubular lumen by substituting for hydrogen ions on the Na^+–H^+ antiporter. Ammonium flows through the thick ascending limb of the loop of Henle, where it is transported from the tubule into the medullary interstitium by replacing potassium on an Na^+–K^+–2Cl transporter. In the interstitium, ammonium dissociates to ammonia, which diffuses down its concentration gradient into the lumen of the collecting tubule. Here ammonia combines with secreted H^+ to form ammonium; NH_4^+ is then excreted as NH_4Cl to maintain electroneutrality. A bicarbonate molecule is regenerated for each H^+ eliminated in the urine. *ATPase* Adenine triphosphatase (Modified from [136])

Respiratory Regulation of Carbon Dioxide

Alveolar ventilation changes due to subtle changes in pH through signals from respiratory chemoreceptors in the midbrain. For example, when arterial pH decreases (acidemia), the acute response is to increase alveolar ventilation (minute ventilation is a product of respiratory rate and tidal volume) to return the pH towards its set-point (Fig. 3.7).

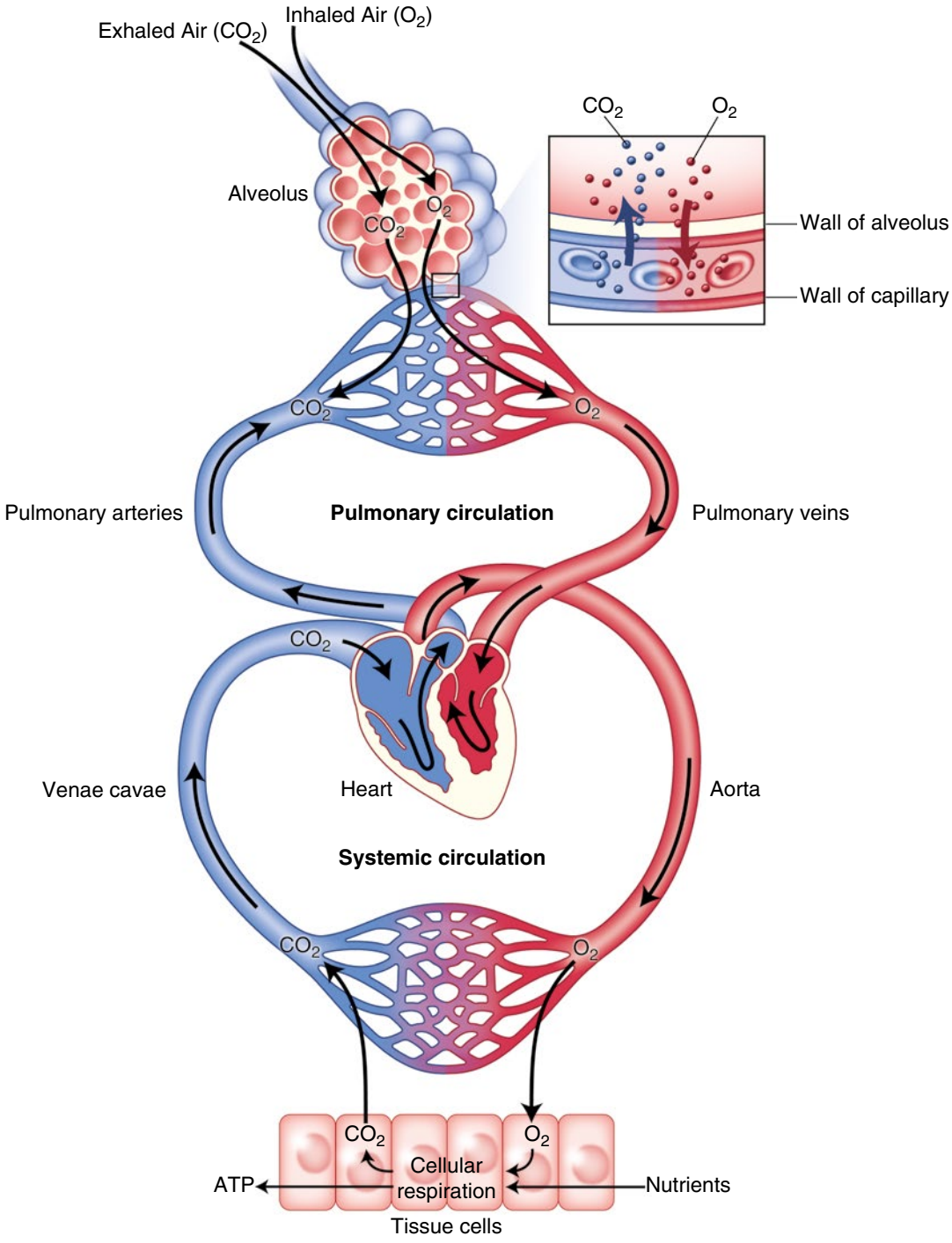

Fig. 3.7 Oxygen and carbon dioxide exchange between respiratory and circulatory systems. *ATPase* Adenine triphosphate (Modified from [136])

Description and Classification of Acid–Base Disorders

There are three widely accepted methods of describing and classifying acid–base abnormalities. Essentially, they differ from one another only with the assessment of the metabolic component of the abnormality. All three treat P_{CO_2} as an independent variable. The first method quantifies the metabolic component by using the bicarbonate ion (HCO_3^-) concentration (in the context of P_{CO_2}); the second, by using the standard base excess (SBE); and the third, by using the strong ion difference (SID). In practice, these three methods yield virtually identical results when used to quantify the acid–base status of a given blood sample [1, 7–12]. Thus, the only significant distinctions between the methods are conceptual; related to how each one approaches the understanding of the mechanism of the disorder [11–15]. In this chapter, we emphasize the physicochemical determinants of pH in the blood and the tissues utilizing the approach of the SID; however, it is a simple matter to convert from one approach to the other if desired [10]. Traditional techniques of assessing acid–base status, relied largely in the difference in anion gap. This usually results in a similar assessment of acid–base derangement, but may place an overemphasis on the anion gap as they do not consider non-bicarbonate buffers. This can lead to error in clinical practice as the other components, such as weak anion and cation, derangements may be missed.

There are three mathematically independent determinants of blood pH: (1) the SID, defined as the difference in concentration between strong cations (e.g., sodium [Na^+] and potassium [K^+]) and strong anions (e.g., chloride [Cl^-] and lactate); (2) the (Atot), defined as the total concentration of weak acids mainly consisting of albumin and phosphate; and (3) P_{CO_2}. These three variables, and only these three, can independently affect plasma pH. The H^+ and HCO_3^- concentrations are dependent variables whose values in plasma are determined by the SID, Atot, and P_{CO_2}. Changes in the plasma H^+ concentration occur as a result of changes in the dissociation of water and Atot, brought about by the electrochemical forces generated by changes in the SID and P_{CO_2}. The SBE is mathematically equivalent to the difference between the current SID and the SID required restoring the pH to 7.4, given a P_{CO_2} of 40 mm Hg and the prevailing Atot. Thus, an SBE of −10 mEq/L means that the SID is 10 mEq less than the value required to achieve a pH of 7.4.

The essential element of this physicochemical approach is the emphasis on independent and dependent variables. Only changes in the independent variables can bring about changes in the dependent variables. That is, movement of H^+ or HCO_3^- cannot affect plasma H^+ or HCO_3^- concentrations unless changes in the SID, Atot, or P_{CO_2} also occur. Several reviews of this approach are available in the literature [1, 9–20]. In what follows, we discuss the clinical application of this approach to the diagnosis and treatment of individual acid–base disorders.

Assessment of Acid–Base Balance

Acid–base homeostasis is defined by the plasma pH and by the conditions of the acid–base pairs that determine it. Normally, arterial plasma pH is maintained between 7.35 and 7.45. Because blood plasma is an aqueous solution containing volatile acids (e.g., CO_2) and fixed acids, its pH is determined by the net effects of all these components on the dissociation of water. The determinants of blood pH can be grouped into two broad categories, respiratory and metabolic. Respiratory acid–base disorders are disorders of P_{CO_2}; metabolic acid–base disorders comprise all other conditions affecting pH, including disorders of both weak acids and strong acids (organic and inorganic) and bases. Any of the following indicators serves to identify an acid–base disorder:

Table 3.1 Acid–base disorder subtypes

	Physicochemical parameter		
Disorder	HCO_3^- concentration (mEq/L)	P_{CO_2} (mm Hg)	SBE (mEq/L)
Metabolic acidosis	<22	$=(1.5\times HCO_3^-)+8$ $=40+SBE$	<−5
Metabolic alkalosis	>26	$=(0.7\times HCO_3^-)+21$ $=40+(0.6\times SBE)$	>+5
Acute respiratory acidosis	$=\left[\left(P_{CO_2}-40\right)/10\right]+24$	> 45	= 0
Chronic respiratory acidosis	$=\left[\left(P_{CO_2}-40\right)\right]/3+24$	>45	$=0.4\times\left(P_{CO_2}-40\right)$
Acute respiratory alkalosis	$=24-\left[\left(40-P_{CO_2}\right)/5\right]$	<35	= 0
Chronic respiratory alkalosis	$=24-\left[\left(40-P_{CO_2}\right)/2\right]$	<35	$=0.4\times\left(P_{CO_2}-40\right)$

1. An abnormal arterial blood pH (pH<7.35 signifies acidemia; pH>7.45 signifies alkalemia)
2. An arterial carbon dioxide tension (P_{CO_2}) that is outside the normal range (35–45 mm Hg)
3. A plasma HCO_3^- concentration that is outside the normal range (22–26 mEq/L).
4. An arterial SBE that is either abnormally high (g3 mEq/L) or abnormally low (f-3 mEq/L)

Once identified, an acid–base disorder can be classified according to a simple set of rules (Table 3.1). A disorder that does not fit well into the broad categories established by these rules can be considered a mixed (or complex) disorder. Some of the basic categories can be further divided into various subcategories (see below), but before the issue of classification is addressed in detail, three general caveats must be considered.

First, interpretation of arterial blood gas values and blood chemistries depends on the reliability of the data. Advances in clinical chemistry have improved the sensitivity of instruments used to measure electrolyte concentrations (e.g., ion-specific electrodes) and have greatly enhanced the speed and ease of analysis. Inevitably, however, prolonged exposure to the atmosphere results in a lowering of the P_{CO_2}, and over time, there may be ongoing cellular metabolism. Accordingly, prompt measurement is always advisable. Even with prompt measurement, laboratory errors may occur, and information may be incorrectly reported. Samples drawn from indwelling lines may be diluted by fluid or drug infusions (a notorious source of error). When the situation is confusing, it is usually best to repeat the measurement.

Second, interpretation of arterial blood gas values may be problematic in patients with severe hypothermia (e.g., trauma patients undergoing damage-control interventions, who often are severely hypothermic and sometimes experience severe acidosis), in that the findings may not reflect the actual blood gas values present. Because blood samples are "normalized" to a temperature of 37 °C before undergoing analysis, the results obtained in samples from a patient whose body temperature is significantly lower than 37 °C (98.6 °F) may not be sufficiently accurate. To obviate this potential problem, the results may have to be adjusted to take the patient's actual temperature into account. At present, however, such temperature correction is not routinely done, and there has been some controversy regarding whether it has real clinical value [21, 22].

Third, whereas the aforementioned four indicators are useful for identifying an acid–base disorder, the absence of all four does not exclude a mixed acid–base disorder (i.e., alkalosis plus acidosis) in which the two components are completely matched. This, however, is rare. Apart from distinguishing a respiratory acid–base disorder from a metabolic acid–base disorder, the four indicators and the rules previously mentioned (Table 3.1) provide no information on the mechanism of an acid–base disorder.

Metabolic Acid–Base Disorders

Metabolic acid–base derangements are produced by a significantly greater number of underlying disorders than respiratory disorders and are almost always more difficult to treat. Traditionally, metabolic acidoses and alkaloses are categorized according to the ions that are responsible (e.g., lactic acidosis and chloride-responsive alkalosis).

It is important to recognize that metabolic acidosis is caused by a decrease in the SID, which produces an electrochemical force that acts to increase the free H^+ concentration. A decrease in the SID may be brought about by the generation of organic anions (e.g., lactate and ketones), by the loss of cations (as with diarrhea), by the mishandling of ions (as with renal tubular acidosis [RTA]), or by the addition of exogenous anions (as with iatrogenic acidosis or poisoning). In contrast, metabolic alkalosis is caused by an inappropriately large SID (although it may be possible for the SID to be inappropriately large without exceeding the normal range of 40–42 mEq/L). An increase in the SID may be brought about by the loss of more strong anions than strong cations (as with vomiting or diuretic therapy) or, in rare instances, by the administration of more strong cations than strong anions (as with transfusion of large volumes of banked blood containing sodium citrate).

Because metabolic acid–base disorders are caused by changes in the SID, their treatment necessarily involves normalization of the SID. Metabolic acidoses is corrected by increasing the plasma Na^+ concentration more than the plasma Cl^- concentration (e.g., by administering $NaHCO_3$), and metabolic alkaloses are corrected by replacing lost Cl^- (e.g., by giving sodium chloride [NaCl], potassium chloride [KCl], or even hydrochloric acid [HCl]). So-called chloride-resistant metabolic alkalosis (see sections "Metabolic Alkalosis" and "Chloride-Resistant Alkalosis") are resistant to chloride administration only because of ongoing renal Cl^- loss that increases in response to increased Cl^- replacement (as with hyperaldosteronism).

Metabolic Acidoses

Pathophysiology

Disorders of metabolic acid–base balance occur in one of three ways: (1) of a dysfunction of the primary regulating organs, (2) exogenous administration of drugs or fluids or (3) abnormal metabolism that overwhelms the normal defense mechanisms. As mentioned before, the organ systems responsible for regulating the SID in both health and disease are the renal system and, to a lesser extent, the GI tract.

Effect of Acidosis

Anion Gap Acidoses

Determination of Anion Gap

The AG has been used by clinicians for more than 30 years and has evolved into a major tool for evaluating acid–base disorders [23]. It is calculated—or, rather, estimated—from the difference between the routinely measured concentrations of serum cations (Na^+ and K^+) and the routinely measured concentrations of anions (Cl^- and HCO_3^-). Normally, albumin accounts for the bulk of this difference, with phosphate playing a lesser role. Sulfate and lactate also contribute a small amount to the gap (normally, <2 mEq/L); however, there are also unmeasured cations (e.g., Ca^{2+} and Mg^{2+}), which tend to offset the effects of sulfate and lactate except when the concentration of either one is abnormally increased. Plasma proteins other than albumin can be either positively or negatively charged, but in the aggregate,

they tend to be electrically neutral [24], except in rare cases of abnormal paraproteins (as in multiple myeloma). In practice, the AG is calculated as follows:

$$AG = \left(Na^+ + K^+\right) - \left(Cl^- + HCO_3^-\right)$$

Because of its low extracellular concentration, K^+ is often omitted from the calculation. In most laboratories, normal values fall into the range of 12P4 mEq/L (if K^+ is considered) or 8P4 mEq/L (if K^+ is not considered). In the past few years, the introduction of more accurate methods of measuring Cl^- concentration has led to a general lowering of the normal AG range [25, 26]. Because of the various measurement techniques employed at various institutions, however, each institution is expected to report its own normal AG values.

Clinical Utility of Anion Gap

The primary value of the AG is that it quickly and easily limits the differential diagnosis in a patient with metabolic acidosis. When the AG is increased, the explanation is almost invariably one of the following five disorders: ketosis, lactic acidosis, poisoning, renal failure, and sepsis [27].

In addition to these disorders, however, there are several conditions that can alter the accuracy of AG estimation and are particularly frequent in critical illness [28, 29]. Dehydration increases the concentrations of all of the ions. Severe hypoalbuminemia lowers the AG, with each 1 g/dL decline in the serum albumin reducing the apparent AG by 2.5–3 mEq/L; accordingly, some recommend adjusting the AG for the prevailing albumin concentration [30]. Alkalosis (respiratory or metabolic) is associated with an increase of as much as 3–10 mEq/L in the apparent AG as a consequence of enhanced lactate production (from stimulated phosphofructokinase enzymatic activity), reduction in the concentration of ionized weak acids (A^-) (as opposed to Atot, the total concentration of weak acids), and, possibly, the additional effect of dehydration (which, as noted, has its own impact on AG calculation). A low Mg^{2+} concentration with associated low K^+ and Ca^{2+} concentrations is a known cause of an increased AG, as is the administration of sodium salts of poorly reabsorbable anions (e.g., β-lactam antibiotics) [31]. Certain parenteral nutrition formulations (e.g., those containing acetate) may increase the AG. In rare cases, citrate may have the same effect in the setting of multiple blood transfusions, particularly if massive doses of banked blood are used (as during liver transplantation) [32]. None of these rare causes, however, will increase the AG significantly [33], and they usually are easily identified.

In the past few years, some additional causes of an increased AG have been reported. The nonketotic hyperosmolar state of diabetes has been associated with an increased AG that remains unexplained [34]. Unmeasured anions have been reported in the blood of patients with sepsis [35, 36], patients with liver disease [37, 38], and experimental animals that received endotoxin [39]. These anions may be the source of much of the unexplained acidosis seen in patients with critical illness [40].

The accepted clinical utility of the AG notwithstanding, doubt has been cast on its diagnostic value in certain situations [28, 36]. Some investigators have found routine reliance on the AG to be "fraught with numerous pitfalls" [28]. The primary problem with the AG is its reliance on the use of a supposedly normal range produced by albumin and, to a lesser extent, phosphate. Concentrations of albumin and phosphate may be grossly abnormal in patients with critical illness, and these abnormalities may change the normal AG range in this setting. Moreover, because these anions are not strong anions, their charge is altered by changes in pH. These concerns have led some authors to advocate adjusting the normal AG range on the basis of the patient's albumin [30] or even phosphate [11] concentration. Each 1 g/dL of albumin carries a charge of 2.8 mEq/L at a pH of 7.4 (2.3 mEq/L, pH = 7.0; 3.0 mEq/L, pH = 7.6), and each 1 mg/dL of phosphate carries a charge of 0.59 mEq/L at a pH of 7.4 (0.55 mEq/L, pH = 7.0; 0.61 mEq/L, pH = 7.6). Thus, the normal AG for a given patient can be conveniently estimated as follows [14]:

$$\text{Normal AG} = 2\left(\text{albumin}\left[\text{g/dL}\right]\right) + 0.5\left(\text{phosphate}\left[\text{mg/dL}\right]\right)$$

or, in international units,

$$\text{Normal AG} = 0.2\left(\text{albumin}\left[\text{g/L}\right]\right) + 1.5\left(\text{phosphate}\left[\text{mmol/L}\right]\right)$$

In one study, when this formula for calculating a patient-specific normal AG range was used to determine the presence of unmeasured anions in the blood of critically ill patients, its accuracy was 96 %, compared with an accuracy of 33 % with the routine AG (normal range = 12 mEq/L) [14]. This technique should be employed only when the pH is less than 7.35; even in this situation, it is accurate only within 5 mEq/L. When more accuracy is needed, a slightly more complicated method of estimating unmeasured anions is required [37, 41].

Strong Ion Gap

An alternative to relying on the traditional AG is to use a parameter derived from the SID. By definition, the SID must be equal and opposite to the sum of the negative charges contributed by A^- and total CO_2. This latter value (A^- + total CO_2) has been termed the effective strong ion difference (SIDe) [34]. The apparent strong ion difference (SIDa) is obtained by measuring concentrations of each individual ion. The SIDa and the SIDe should both equal the true SID. If the SIDa differs from the SIDe, unmeasured ions must be present. If the SIDa is greater than the SIDe, these unmeasured ions are anions; if the SIDa is less than the SIDe, they are cations. The difference between the SIDa and the SIDe has been termed the strong ion gap (SIG) to distinguish it from the AG [37]. Unlike the AG, the SIG is normally 0 and is not affected by changes in the pH or the albumin concentration. SIG has been shown to have prognostic value in the setting of trauma-related shock. In a study performed in 78 trauma patients, SIG measured early in the course of shock predicted mortality better than any other parameter, including AG, anion gap corrected (AGc), SBE, pH, and lactate with an area under the curve (AUC) of 0.96 [42].

Lactic Acidosis

In many forms of critical illness, lactate is the most important cause of metabolic acidosis [43]. Lactate concentrations have been shown to correlate with outcomes in patients with hemorrhagic [44] and septic shock [45]. Traditionally, lactic acid has been viewed as the predominant source of the metabolic acidosis that occurs in sepsis [46]. In this view, lactic acid is released primarily from the musculature and the gut as a consequence of tissue hypoxia, and the amount of lactate produced is believed to correlate with the total oxygen debt, the magnitude of hypoperfusion, and the severity of shock [43]. This view has been challenged by the observation that during sepsis, even in profound shock, resting muscle does not produce lactate. Indeed, various studies have shown that the musculature may actually consume lactate during endotoxemia [6, 47, 48].

The data on lactate release by the gut are less clear. There is little question that the gut can release lactate if it is underperfused. It appears, however, that if the gut is adequately perfused, it does not release lactate during sepsis. Under such conditions, the mesentery either is neutral with respect to lactate release or takes up lactate [6, 47]. Perfusion is likely to be a major determinant of mesenteric lactate metabolism. In a canine model of sepsis induced by infusion of endotoxin, production of lactate by the gut could not be demonstrated when flow was maintained with dopexamine [48].

Both animal studies and human studies have shown that the lung may be a prominent source of lactate in the setting of acute lung injury [6, 49–52]. These studies do not address the underlying pathophysiologic mechanisms of hyperlactatemia in sepsis, but they do suggest that the conventional wisdom regarding lactate as evidence of tissue dysoxia is, at best, an oversimplification [53]. Indeed, many investigators have begun to offer alternative explanations for the development of hyperlactatemia in this setting [50, 53–57]. One proposed mechanism is metabolic dysfunction from mitochondrial enzymatic derangements, which can and do lead to lactic acidosis. In particular, pyruvate dehydrogenase (PDH), the enzyme responsible for moving pyruvate into the

Krebs cycle, is inhibited by endotoxin [58]. Current data, however, suggest that increased aerobic metabolism may be more important than metabolic defects or anaerobic metabolism. In a 1996 study, production of glucose and pyruvate and oxidation were increased in patients with sepsis [59]. Furthermore, when PDH was stimulated by dichloroacetate, there was an additional increase in oxygen consumption but a decrease in glucose and pyruvate production. These results suggest that hyperlactatemia in sepsis occurs as a consequence of increased aerobic metabolism rather than of tissue hypoxia or PDH inhibition.

Such findings are consistent with the known metabolic effects of lactate production on cellular bioenergetics [51]. Lactate production alters cytosolic, and hence mitochondrial, redox states, so that the increased ratio of reduced nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide (NADH/NAD) supports oxidative phosphorylation as the dominant source of ATP production. Finally, the use of catecholamines, especially epinephrine, also results in lactic acidosis, presumably by stimulating cellular metabolism (e.g., increasing hepatic glycolysis), and may be a common source of lactic acidosis in the ICU [52, 60]. It is noteworthy that this phenomenon does not appear to occur with either dobutamine or norepinephrine [61] and does not appear to be related to decreased tissue perfusion.

Although the source and interpretation of lactic acidosis in critically ill patients remain controversial, there is no question about the ability of lactate accumulation to produce acidemia. Lactate is a strong ion because at a pH within the physiologic range, it is almost completely dissociated. (The pK of lactate is 3.9; at a pH of 7.4, 3,162 ions are dissociated for every one ion that is not.) Because lactate is rapidly produced and disposed of by the body, it functions as one of the most dynamic components of the SID. Therefore, a rise in the concentration of lactic acid can produce significant acidemia. Just as often, however, critically ill patients have a degree of hyperlactatemia that far exceeds the degree of acidosis observed. In fact, hyperlactatemia may exist without any metabolic acidosis at all. This is not because acid generation is separate from lactate production (e.g., through "unreversed ATP hydrolysis"), as some have suggested [61]. Phosphate is a weak acid and does not contribute substantially to metabolic acidosis, even under extreme circumstances. Furthermore, the H^+ concentration is determined not by how much H^+ is produced or removed from the plasma but by changes in the dissociation of water and weak acids. Virtually anywhere in the body, the pH is higher than 6.0, and lactate behaves as a strong ion. Generation of lactate reduces the SID and results in an increased H^+ concentration; however, the plasma lactate concentration may also be increased without an accompanying increase in the H^+ concentration.

There are two possible explanations for these observations. First, if lactate is added to the plasma, not as lactic acid but rather as the salt of a strong acid (e.g., sodium lactate), the SID will not change significantly, because a strong cation (Na^+) is being added along with a strong anion. Indeed, as lactate is metabolized and removed, the remaining Na^+ will increase the SID, resulting in metabolic alkalosis. Hence, it would be possible to give enough lactate to increase the plasma lactate concentration without increasing the H^+ concentration. However, given that normal metabolism results in the turnover of approximately 1,500–4,500 mmol of lactic acid each day, rapid infusion of a very large amount of lactate would be required to bring about an appreciable increase in the plasma lactate concentration. For example, the use of lactate-based hemofiltration fluid may result in hyperlactatemia with an increased plasma HCO_3^- concentration and an elevated pH.

A more important mechanism whereby hyperlactatemia can exist without acidemia (or with less acidemia than expected) involves correction of the SID by the elimination of another strong anion from the plasma. In a study of sustained lactic acidosis induced by lactic acid infusion, Cl^- was found to move out of the plasma space, thereby normalizing the pH [62]. Under these conditions, hyperlactatemia may persist, but compensatory mechanisms may normalize the base excess and thus restore the SID.

Traditionally, lactic acidosis has been subdivided into type A, in which the mechanism is tissue hypoxia, and type B, in which there is no hypoxia [63]. This distinction may, however, be an artificial one. Disorders such as sepsis may be associated with lactic acidosis through a variety of mechanisms some conventionally labeled type A and others type B. A potentially useful method of distinguishing between anaerobically produced lactate and lactate from other sources is to measure the serum pyruvate concentration. The normal lactate-to-pyruvate ratio is 10:1 [64], with ratios greater than 25:1 considered to be evidence of anaerobic metabolism [57]. This approach makes biochemical sense because pyruvate is shunted into lactate during anaerobic metabolism, dramatically increasing the lactate-to-pyruvate ratio. However, the precise test characteristics, including normal ranges and sensitivity and specificity data, have not yet been defined for patients. Accordingly, this method remains investigational.

Treatment of lactic acidosis continues to be a subject to debate. At present, the only noncontroversial approach is to treat the underlying cause; however, this approach assumes that the underlying cause can be identified with a significant degree of certainty, which is not always the case. The assumption that hypoperfusion is always the most likely cause has been seriously challenged, especially in well-resuscitated patients (see above). Thus, therapy aimed at increasing oxygen delivery may not be effective. Indeed, if epinephrine is used, lactic acidosis may worsen.

The vast majority of acidosis due to lactate are caused by the L-isomer. The D-isomer of lactate may also cause an acidosis, but this is not detected by normal lactate analysis and must be requested as a separate test. This is typically only seen in patients with abnormal bowel anatomy which allows for bacterial overgrowth [65].

Sodium Bicarbonate

Administration of $NaHCO_3$ to treat lactic acidosis remains unproven [66]. In perhaps the most widely quoted study on this topic, hypoxic lactic acidosis was induced in anesthetized dogs by ventilating them with gas containing very little oxygen [67]. These animals were then assigned to treatment with $NaHCO_3$ or placebo, and, surprisingly, the group receiving $NaHCO_3$ actually had higher plasma concentrations of both lactate and H^+ than the control group did. Furthermore, the $NaHCO_3$-treated animals exhibited decreases in cardiac output and blood pressure that were not seen in the control group. One possible explanation for these findings is that the HCO_3^- was converted to CO_2, and this conversion raised the P_{CO_2} not only in the blood but also inside the cells of these animals with a fixed minute ventilation; the resulting intracellular acidosis might have been detrimental to myocardial function. This hypothesis has not, however, been supported by subsequent experimental studies, which have not documented paradoxical intracellular acidosis or even detrimental hemodynamic effects after $NaHCO_3$ treatment of hypoxic lactic acidosis [68]. Furthermore, it is not clear how this type of hypoxic lactic acidosis, induced in well-perfused animals, relates to the clinical conditions in which lactic acidosis occurs. The results of clinical studies have been mixed, but, overall, they do not support the use of $NaHCO_3$ therapy for lactic acidosis [66].

Ketoacidosis

Another common cause of a metabolic acidosis with a positive AG is excessive production of ketone bodies, including acetone, acetoacetate, and β-hydroxybutyrate. Both acetoacetate and β-hydroxybutyrate are strong anions (pK 3.8 and 4.8, respectively) [69]. Their presence, like the presence of lactate, decreases the SID and increases the H^+ concentration.

Ketones are formed through beta oxidation of fatty acids, a process that is inhibited by insulin. In insulin-deficient states (e.g., diabetes), ketone formation may quickly get out of control. The reason is that severely elevated blood glucose concentrations produce an osmotic diuresis that may lead to volume contraction. This state is associated with elevated cortisol and catecholamine secretion, which further stimulates free

fatty acid production [70]. In addition, an increased glucagon level relative to the insulin level leads to a decreased malonyl coenzyme A level and an increased carnitine palmityl acyl transferase level—a combination that increases ketogenesis.

Ketoacidosis may be classified as either diabetic ketoacidosis (DKA) or alcoholic ketoacidosis (AKA). The diagnosis is established by measuring serum ketone levels. It must be kept in mind, however, that the nitroprusside reaction measures only acetone and acetoacetate, not β-hydroxybutyrate. Thus, the measured ketosis is dependent on the ratio of acetoacetate to β-hydroxybutyrate. This ratio is low when lactic acidosis coexists with ketoacidosis because the reduced redox state characteristic of lactic acidosis favors production of β-hydroxybutyrate [71]. In such circumstances, therefore, the apparent degree of ketosis is small relative to the degree of acidosis and the elevation of the AG. There is also a risk of confusion during treatment of ketoacidosis in that ketone levels, as measured by the nitroprusside reaction, sometimes rise even though the acidosis is resolving. This occurs because the nitroprusside reaction does not detect β-hydroxybutyrate, and as β-hydroxybutyrate is cleared, ketosis persists despite improvement in acid–base balance. Furthermore, conversion of β-hydroxybutyrate to acetoacetate may cause an apparent increase in ketone levels—again, because the nitroprusside reaction detects the rising levels of acetoacetate but misses the falling levels of β-hydroxybutyrate. Hence, it is better to monitor the success of therapy by measuring the pH and the AG than by assaying serum ketones.

Treatment of DKA includes administration of insulin and large amounts of fluid (0.9 % saline is usually recommended); potassium replacement is often required as well. Fluid resuscitation reverses the hormonal stimuli for ketone body formation, and insulin allows the metabolism of ketones and glucose. Administration of $NaHCO_3$ may produce a more rapid rise in the pH by increasing the SID, but there is little evidence that this result is desirable. Furthermore, to the extent that the SID is increased by increasing the plasma Na^+ concentration, the SID will be too high once the ketosis is cleared, thus resulting in a so-called overshoot alkalosis. In any case, such measures are rarely necessary and should probably be avoided except in extreme cases [72].

A more common problem in the treatment of DKA is the persistence of acidemia after the ketosis has resolved. This hyperchloremic metabolic acidosis occurs as Cl^- replaces ketoacids, thus maintaining a decreased SID and pH. There appear to be two reasons for this phenomenon. First, exogenous Cl^- is often provided in the form of 0.9 % saline, which, if given in large enough quantities, will result in a so-called dilutional acidosis (see below). Second, some degree of increased Cl^- reabsorption apparently occurs as ketones are excreted in the urine. It has also been suggested that the increased tubular Na^+ load produces electrical–chemical forces that favor Cl^- reabsorption [73].

AKA is usually less severe than DKA. It typically is the result of patients, who suffer from chronic alcoholism, discontinuing solid food while continuing to consume alcohol. This syndrome occurs when the alcohol consumption is acutely discontinued. These patients typically present with a history of vomiting and acute abdominal pain which has forced them to stop drinking. Treatment consists of administration of fluids and (in contrast to treatment of DKA) glucose rather than insulin [74]. Insulin is contraindicated in AKA patients because it may cause precipitous hypoglycemia [75]. Thiamine must also be given to keep from precipitating Wernicke encephalopathy.

Acidosis Secondary to Toxin Ingestion

Metabolic acidosis with an increased AG is a major feature of various types of intoxication (Table 3.2). Generally, it is more important to recognize these conditions and provide specific therapy for them than it is to treat the acid–base imbalances that they produce.

Salicylates

Toxic ingestion of salicylates in adults typically presents with respiratory alkalosis, mixed metabolic acidosis-respiratory alkalosis, or a pure metabolic acidosis. Often, the anion gap that is

Table 3.2 Anion gap acidosis causes

Methanol
Uremia
Diabetic ketoacidosis
Paraldehydes
Isoniazid (or Idiopathic)
Lactic acidosis
Ethylene glycol
Salicylates

seen in these patients is due to lactic acid rather than from the salicylates directly. Treatment is focused initially upon removing the offending agent by performing gastric lavage with normal saline and subsequently attempting to deactivate the salicylate with charcoal. Refractory acidosis and toxicity is treated with aggressive hydration and subsequent alkalinization of the urine with $NaHCO_3$. Hemodialysis may be necessary for severe poisoning [76].

Alcohols

When serum osmolality as measured by $P_{osm} = 2 \times Na^+ + Glucose/18 + BUN/2.8$ is elevated, the cause is usually a decreased serum sodium as seen with hyperlipidemia or hyperproteinemia, or additional osmolytes in the blood, such as mannitol, contrast, or an alcohol, are causing the osmolar gap. Along with clinical presentation and history, this simple test can help to confirm alcohol toxicity as the cause of metabolic acidosis [77].

Ethylene Glycol

Antifreeze ingestion may present as a patient who appears intoxicated but with an atypical sweet oral odor. Over time, these patients may progress to having severe neurological impairments, including seizures or coma. Treatment should not be delayed for laboratory confirmation and includes: aggressive volume resuscitation, ethanol ingestion, thiamine and pyridoxine supplementation, oral or intravenous ethanol, and, if necessary, hemodialysis. Fomepizole, an alcohol dehydrogenase inhibitor, may be a better choice than ethanol as it is dialyzable, titratable and has a predictable rate of elimination [78].

Methanol

The acidemia caused by methanol may be related to the production of lactate as well as from the intoxicant itself. Without rapid treatment, similar as that for ethylene glycol, CNS toxicity and optic nerve damage, specifically, may occur.

Isopropyl Alcohol

Intoxication with isopropyl alcohol may be the result of ingestion or excessive absorption through the skin. Although it and its metabolite, acetone, may cause an osmolar gap; they do not typically cause a metabolic acidosis. Treatment is centered around symptomatic control; however, if lactic acidosis or cardiovascular collapse ensue, hemodialysis may be necessary in severe cases [77].

Renal Failure

Renal failure may produce a hyperchloremic metabolic acidosis, especially when it is chronic, the buildup of sulfates and other acids frequently increases the AG; however, the increase usually is not large [79]. Uncomplicated renal failure rarely produces severe acidosis, except when it is accompanied by high rates of acid generation (e.g., from hypermetabolism) [80]. In all cases, the SID is decreased and will remain unchanged until therapy is provided. An observational study on 64 maintenance hemodialysis patients and 14 control subjects showed that acidosis was secondary to three causes: hyperphosphatemia, hyperchloremia, and increased unmeasured anions [81]. Hyperchloremia and the accumulation of unmeasured anions accounted for similar acidifying effects and for almost 90 % of the acidosis in this type of patient. Hemodialysis permits the removal of sulfate and other ions and allows the restoration of normal Na^+ and Cl^- balance, thus returning the SID to a normal (or near-normal) value. However, those patients who do not yet require dialysis and those who are between treatments often require some other therapy aimed at increasing the SID. $NaHCO_3$ may be used for this purpose, provided that the plasma Na^+ concentration is not already elevated.

Acidosis Secondary to Rhabdomyolysis

The extensive muscle tissue breakdown associated with myonecrosis may also be a source of positive-AG metabolic acidosis. The acidosis results from accumulation of organic acids, but the myoglobinuria associated with the disorder may also induce renal failure. In most cases, the diagnosis is a clinical one and can be facilitated by measuring creatinine kinase or aldolase levels. Early identification and aggressive resuscitation may prevent the onset of renal failure and improve the prognosis [82].

Acidosis of Unknown Origin

Several causes of an increased AG have been reported that have yet to be elucidated. An unexplained AG in the nonketotic hyperosmolar state of diabetes has been reported [34]. In addition, even when very careful measurement techniques have been employed, unmeasured anions have been reported in the blood of patients with sepsis [35, 36, 83], patients with liver disease [37], and animals to which endotoxin had been administered [38]. Furthermore, unknown cations also appear in the blood of some critically ill patients [17, 36, 84, 85]. The significance of these findings remains to be determined.

Prognostic Significance of Positive-AG Metabolic Acidosis

Several studies have examined whether the presence of unmeasured anions in the blood is associated with particular outcomes in critically ill patients. Two such studies focused on trauma patients. In one, the investigators examined 2,152 sets of laboratory data from 427 trauma patients and found that the SIG altered the acid–base disorder diagnosis in 28 % of the datasets [86]. Simultaneous measurements of blood gas, serum electrolyte, albumin, and lactate values were used to calculate the base deficit, the AG, and the SIG. Unmeasured anions (defined by the presence of an elevated SIG) were present in 92 % of patients (mean SIG 5.9P3.3); hyperlactatemia and hyperchloremia occurred in only 18 % and 21 % of patients, respectively. The arterial SBE at ICU admission was poorly predictive of hospital survival, and its predictive ability was only slightly improved by controlling for unmeasured ions. In this dataset, survivors could not be differentiated from nonsurvivors in the group as a whole on the basis of the SIG. However, in the subgroup of patients whose lactate level was normal at admission, there was a significant difference in the SIG between survivors and nonsurvivors, although no such differences were noted in the conventional measures (i.e., SBE and AG).

The poor predictive ability of the SBE, the AG, and even the SIG has been confirmed by studies of general ICU patients. In one study, analysis of data from 300 adult ICU patients demonstrated statistically significant but weak correlations between these measures and hospital mortality [87]. In another study, however, pretreatment SIG was found to be a very strong predictor of outcome in 282 patients who had sustained major vascular injury [88]. All but one of the nonsurvivors had an initial emergency department (ED) pH of 7.26 or lower, an SBE of −7.3 mEq/L or lower, a lactate concentration of 5 mmol/L or higher, and an SIG of 5 mEq/L or higher. All of the acid–base descriptors were strongly associated with outcome, but the SIG was the one that discriminated most strongly. The investigators concluded that initial ED acid–base variables, especially SIG, could distinguish survivors of major vascular injury from nonsurvivors. A subsequent prospective study in 78 trauma patients by the same group showed again the high predictive ability of SIG with an AUC of 0.96 (95 % CI 0.89–0.99) when predicting mortality, which was superior to SBE (0.63), lactate (0.60), AG (0.8), AGc (0.86), and pH (0.50) [42].

Even though the uncorrected AG and the SBE correlate poorly with the arterial lactate concentration in trauma patients [89], several investigators have proposed that these parameters be used as surrogate measures of the severity of shock or lack of resuscitation. Various studies have shown that the SBE is a poor predictor of lactic acidosis and mortality in both medical patients and surgical or trauma patients and that it cannot be substituted for direct measurement of the serum lactate concentration [28, 90, 91]. Some investigators, however, have found that the SBE can be used as

a marker of injury severity and mortality and as a predictor of transfusion requirements [92–94]. Unfortunately, the SBE can determine only the degree of acid–base derangement, never the cause. In many critically injured patients, abnormalities in body water content, electrolyte levels, and albumin concentration limit any potential correlation between SBE and lactate concentration, even when other sources of acid are absent.

Several reports in the trauma literature have focused on the prognostic value of persistently elevated lactic acid levels during the first 24–48 h after injury. In one study, involving 76 patients with multiple injuries who were admitted directly to the ICU from the operating room or the ED, serum lactate levels and oxygen transport were measured at ICU admission and at 8, 16, 24, 36, and 48 h [95]. In those patients whose lactate levels returned to normal within 24 h, the survival rate was 100 %, and in those whose lactate levels returned to normal between 24 and 48 h, the survival rate was 75 %. However, in those whose lactate levels did not return to normal by 48 h, the survival rate was only 14 %. Thus, the rate of normalization of the serum lactate level is an important prognostic factor for survival in a severely injured patient.

It is important, however, to understand that metabolic acidosis can no longer be considered as a generic term when trying to assess outcome early in the course of disease, given that the type of metabolic acidosis (i.e., lactic, hyperchloremic, SIG) influences outcome as pointed out by Gunnerson and colleagues [96, 97].

Non-Anion Gap Acidosis (Hyperchloremic)

Hyperchloremic metabolic acidosis occurs as a result of either an increase in the level of Cl^- relative to the levels of strong cations (especially Na^+) or a loss of cations with retention of Cl^-. The various causes of such an acidosis (Tables 3.3 and 3.4) can be distinguished on the basis of the history and the measured Cl^- concentration in the urine [98]. When acidosis occurs, the kidney normally responds by increasing Cl^- excretion; the absence of this response identifies the kidney as the source of the problem. Extrarenal hyperchloremic acidoses occurs because of exogenous Cl^- loads (iatrogenic acidosis) or because of loss of cations from the lower GI tract without proportional loss of Cl^- (gastrointestinal acidosis).

Table 3.3 Non-anion gap metabolic acidosis

Renal tubular acidosis
Types I, II & IV
Diarrhea
High output enterocutaneous fistula
Pancreatic fistula
Iatrogenesis
Parenteral nutrition

Table 3.4 Causes of elevated lactate

Tissue hypoxia
Uncompensated shock
Hypermetabolism
Increased aerobic glycolysis
Increased protein catabolism
Hematologic malignancies
Decreased lactate clearance
Hepatic failure
Inhibition of pyruvate dehydrogenase
Thiamine deficiency

Gastrointestinal Tract Loss

Fluid secreted into the gut lumen contains more Na^+ than Cl^-; the proportions are similar to those seen in plasma. Massive loss of this fluid, particularly if lost volume is replaced with fluid containing equal amounts of Na^+ and Cl^-, will result in a decreased plasma Na^+ concentration relative to the Cl^- concentration and a reduced SID. Such a scenario can be prevented by using solutions such as lactated Ringer solution (LRS) instead of water or saline. LRS has a more physiologic SID than water or saline and therefore does not produce acidosis except in rare circumstances (see sections "Positive–Anion Gap Acidosis"and "Lactic Acidosis").

Renal Tubular Acidosis

Most cases of RTA can be correctly diagnosed by determining urine and plasma electrolyte levels and pH and calculating the SIDa in the urine (Table 3.3) [99]. However, caution must be exercised when the plasma pH is greater than 7.35 because urine Cl^- excretion may be turned off. In such circumstances, it may be necessary to infuse sodium sulfate or furosemide. These agents stimulate excretion of Cl^- and K^+ and may be used to unmask the defect and to probe K^+ secretory capacity.

Establishing the mechanisms of RTA has proved difficult. It is likely that much of the difficulty results from the attempt to understand the physiology from the perspective of regulation of H^+ and HCO_3^- concentrations. As noted, however (see above), this approach is simply inconsistent with the principles of physical chemistry. The kidney does not excrete H^+ to any greater extent as NH_4^+ than it does as H_2O. The purpose of renal ammoniagenesis is to allow the excretion of Cl^-, which balances the charge of NH_4^+. In all types of RTA, the defect is the inability to excrete Cl^- in proportion to excretion of Na^+, although the precise reasons for this inability vary by RTA type. Treatment is largely dependent on whether the kidney will respond to mineralocorticoid replacement or whether there is Na^+ loss that can be counteracted by administering $NaHCO_3$.

Classic distal (type I) RTA responds to $NaHCO_3$ replacement; generally, the required dosage is in the range of 50–100 mEq/day. K^+ defects are also common in this type of RTA; thus, K^+ replacement is also required. A variant of the classic distal RTA is a hyperkalemic form, which is actually more common than the classic type. The central defect in this variant form appears to be impaired Na^+ transport in the cortical collecting duct. Patients with this condition also respond to $NaHCO_3$ replacement.

Proximal (type II) RTA is characterized by defects in the reabsorption of both Na^+ and K^+. It is an uncommon disorder and usually occurs as part of Fanconi syndrome, in which reabsorption of glucose, phosphate, urate, and amino acids is also impaired. Treatment of type II RTA with $NaHCO_3$ is ineffective; increased ion delivery merely results in increased excretion. Thiazide diuretics have been used to treat this disorder, with varying degrees of success.

Type IV RTA is caused by aldosterone deficiency or resistance. It is diagnosed on the basis of the high serum K^+ and the low urine pH (<5.5). The most effective treatment usually involves removal of the cause (most commonly a drug, such as a nonsteroidal anti-inflammatory agent, heparin, or a potassium-sparing diuretic). Occasionally, mineralocorticoid replacement is required.

Iatrogenic Acidosis

Two of the most common causes of a hyperchloremic metabolic acidosis are iatrogenic, and both involve administration of Cl^-. One of these potential causes is parenteral nutrition. Modern parenteral nutrition formulas contain weak anions (e.g., acetate) in addition to Cl^-, and the proportions of these anions can be adjusted according to the acid–base status of the patient. If sufficient amounts of weak anions are not provided, the plasma Cl^- concentration will increase, reducing the SID and causing acidosis.

The other potential cause is fluid resuscitation with saline, which can give rise to a so-called dilutional acidosis (a problem first described more than 40 years ago) [100, 101]. Some authors have argued that dilutional acidosis is, at most, a minor issue [102]. This argument is based on studies showing that in healthy animals, large doses of NaCl produce only a minor hyperchloremic acidosis [103]. These studies have been interpreted as indicating that dilutional acidosis occurs only in extreme cases and even then is mild. However, this line of reasoning cannot be applied to critically ill patients, for two reasons. First, it is common for patients with sepsis or trauma to require large-volume resuscitation; sometimes, such patients receive crystalloid infusions equivalent to 5–10 times their plasma volumes in a single day. Second, critically ill patients frequently are not in

a state of normal acid–base balance to begin with. Often they have lactic acidosis or renal insufficiency. Furthermore, critically ill patients may not be able to compensate for acid–base imbalance normally (e.g., by increasing ventilation), and they may have abnormal buffer capacity as a result of hypoalbuminemia. In ICU and surgical patients [104–106], as well as in animals with experimentally induced sepsis [107], saline-induced acidosis does occur and can produce significant acidemia.

The reason why administration of saline causes acidosis is that solutions containing equal amounts of Na^+ and Cl^- affect plasma concentrations of Na^+ and Cl^- differently [108]. Although some authors continue to argue that a simple "dilutional" effect of fluids on the amount of base (HCO_3) is sufficient to explain the phenomenon [109], this concept has been discredited [110]. The normal Na^+ concentration is 35–45 mEq/L higher than the normal Cl^- concentration. Thus, adding (for example) 154 mEq/L of each ion in 0.9 % saline will result in a greater relative increase in the Cl^- concentration than in the Na^+ concentration. This does not explain, however, why critically ill patients are more susceptible to this disorder than healthy persons are.

It appears that many critically ill patients have a significantly lower SID than healthy persons do, even when these patients have no evidence of a metabolic acid–base derangement [111]. The positive charge of the SID is balanced by the negative charges of A^- and total CO_2, but many critically ill patients are hypoalbuminemic, and A^- tends to be reduced. Because the body maintains P_{CO_2} for other reasons, a reduction in A^- leads to a reduction in SID so that a normal pH can be maintained. Thus, a typical ICU patient may have an SID of 30 mEq/L rather than 40–42 mEq/L. If a metabolic acidosis (e.g., lactic acidosis) then develops in this patient, the SID will decrease further. If this patient is subsequently resuscitated with large volumes of 0.9 % saline, a significant metabolic acidosis will result.

The clinical implication for management of ICU patients is that if large volumes of fluid are to be given for resuscitation, fluids that are more physiologic than saline should be used. One alternative is LRS, which has a more physiologic ratio of Na^+ content to Cl^- content and thus has an SID that is closer to normal (roughly 28 mEq/L, compared with an SID of 0 mEq/L for saline). Of course, the assumption here is that the lactate in LRS is metabolized, which, as noted (see above), is almost always the case. Volume resuscitation also reduces the weak acid concentration, thereby moderating the acidosis. One ex vivo study concluded that administration of a solution with an SID of approximately 24 mEq/L will have a neutral effect on the pH as blood is progressively diluted [112].

Unexplained Hyperchloremic Acidosis

Critically ill patients sometimes manifest hyperchloremic metabolic acidosis for reasons that cannot be determined. Often other coexisting types of metabolic acidosis are present, making the precise diagnosis difficult. For example, some patients with lactic acidosis have a greater degree of acidosis than can be explained by the increase in the lactate concentration [35], and some patients with sepsis and acidosis have normal lactate levels [113]. In many instances, the presence of unexplained anions may be the cause [35–37]. However, anions such as amino acids, uric acid, and organic acids were shown to contribute to SIG only in 7.9 % in critically ill patients with metabolic acidosis [114], whereas in other cases, there is a hyperchloremic acidosis [83]. Saline resuscitation may be responsible for much of this acidosis (see above), but experimental evidence from endotoxemic animals suggests that as much as a third of the acidosis cannot be explained in terms of current knowledge [107].

One potential explanation for unexplained hyperchloremic acidosis is partial loss of the Donnan equilibrium between plasma and interstitial fluid. The severe capillary leakage that accompanies this loss of equilibrium results in loss of albumin from the vascular space, which means that another ion must move into this space to maintain the charge balance between the two compartments. If Cl^- moves into the plasma space to restore the charge balance, a strong anion

is replacing a weak anion, and a hyperchloremic metabolic acidosis results. This hypothesis appears reasonable but, at present, remains unproven.

Metabolic Alkaloses

Pathogenesis and Differential Diagnosis

Metabolic alkalosis occurs as a result of an increased SID or a decreased Atot, secondary either to loss of anions (e.g., Cl^- from the stomach and albumin from the plasma) or increases in cations (rare). Metabolic alkaloses can be divided into those in which Cl^- losses are temporary and can be effectively replaced (chloride-responsive alkaloses) and those in which hormonal mechanisms produce ongoing losses that, at best, can be only temporarily offset by Cl^- administration (chloride-resistant alkaloses) (see Table 3.5). Like hyperchloremic acidosis, metabolic alkalosis can be confirmed by measuring the urine Cl^- concentration.

Table 3.5 Metabolic alkalemia causes

Chloride loss ($Cl^- < Na^+$)
Chloride-responsive alkalosis (urine Cl^- concentration < 10 mmol/L)
Vomiting
Gastric drainage
Chloride-wasting diarrhea (villous adenoma)
Diuretic use
Hypercapnia
Chloride-resistant alkalosis (urine Cl^- concentration > 20 mmol/L)
Mineralocorticoid excess
Primary hyperaldosteronism (Conn syndrome)
Secondary hyperaldosteronism
Cushing syndrome
Liddle syndrome
Bartter syndrome
Exogenous corticoids
Excessive licorice intake
Ongoing diuretic use
Exogenous sodium load ($Na^+ > Cl^-$)
Sodium salt administration (acetate, citrate)
Massive blood transfusions
Parenteral nutrition
Plasma volume expanders
Sodium lactate (lactated Ringer solution)
Other
Severe deficiency of intracellular cations (Mg^{2+}, K^+)

Chloride Sensitive Metabolic Alkaloses

Chloride-responsive metabolic alkalosis usually occurs as a result of loss of Cl^- from the stomach (e.g., through vomiting or gastric drainage). Treatment consists of replacing the lost Cl^-, either slowly (with NaCl) or relatively rapidly (with KCl or even HCl). Because chloride-responsive alkalosis is usually accompanied by volume depletion, the most common therapeutic choice is to give saline along with KCl. Dehydration stimulates aldosterone secretion, which results in reabsorption of Na^+ and loss of K^+. Saline is effective even though it contains Na^+ because the administration of equal amounts of Na^+ and Cl^- yields a larger relative increase in the Cl^- concentration than in the Na^+ concentration (see above). In rare circumstances, when neither K^+ loss nor volume depletion is a problem, it may be desirable to replace Cl^- by giving HCl.

Diuresis and other forms of volume contraction cause metabolic alkalosis mainly by stimulating aldosterone secretion; however, diuretics also directly stimulate excretion of K^+ and Cl^-, further complicating the problem and inducing metabolic alkalosis more rapidly.

Chloride-Resistant Metabolic Alkaloses

Chloride-resistant alkalosis (Table 3.5) is characterized by an increased urine Cl^- concentration (>20 mmol/L) and ongoing Cl^- loss that cannot be abolished by Cl^- replacement. Most commonly, the proximate cause is increased mineralocorticoid activity. Treatment involves identification and correction of the underlying disorder.

Other Causes of Metabolic Alkalosis

In rare situations, an increased SID—and therefore metabolic alkalosis—occurs secondary to cation administration rather than to anion depletion. Examples include milk–alkali syndrome and intravenous administration of strong cations without strong anions. The latter occurs with massive blood transfusion because Na^+ is given with citrate (a weak anion) rather than with Cl^-. Similar results ensue when parenteral nutrition formulations contain too much acetate and not enough Cl^- to balance the Na^+ load.

Diagnostic Evaluation and Management

Metabolic Acidosis

Traditionally, metabolic acidoses is categorized according to the presence or absence of unmeasured anions. These unmeasured anions are routinely detected by examining the plasma electrolytes and calculating the anion gap (AG) (see below). The differential diagnosis for a positive-AG acidosis includes various common and rare causes (Table 3.2). Generally speaking, non-AG acidoses can be divided into three types: renal, GI, and iatrogenic (see Table 3.3). In the intensive care unit (ICU), the most common types of metabolic acidosis are lactic acidosis, ketoacidosis, iatrogenic acidosis, and acidosis secondary to toxins.

Even extreme acidosis appears to be well tolerated by healthy persons, particularly when the duration of the acidosis is short. For example, healthy individuals may achieve an arterial pH lower than 7.15 and a lactate concentration higher than 20 mEq/L during maximal exercise, with no lasting effects [115]. Over the long term, however, even mild acidemia (pH < 7.35) may lead to metabolic bone disease and protein catabolism. Furthermore, critically ill patients may not be able to tolerate even brief episodes of acidemia [116]. There do appear to be significant differences between respiratory and metabolic acidosis (and even between different types of metabolic acidosis) with respect to patient outcome, and these differences suggest that the underlying disorder may be more important than the absolute degree of acidemia [96, 97, 117].

If prudence dictates that symptomatic therapy is to be provided, the likely duration of the disorder should be taken into account. When the disorder is expected to be a short-lived one (e.g., diabetic ketoacidosis), maximizing respiratory compensation is usually the safest approach. Once the disorder resolves, ventilation can be quickly reduced to normal levels, and there will be no lingering effects from therapy. If the SID is increased (e.g., by administering $NaHCO_3$), there is a risk of alkalosis when the underlying disorder resolves. When the disorder is likely to be a more chronic one (e.g., renal failure), therapy aimed at restoring the SID to normal is indicated. In all cases, the therapeutic target can be accurately determined from the SBE. As noted (see above), the SBE corresponds to the amount by which the current SID differs from the SID necessary to restore the pH to 7.4, given a P_{CO_2} of 40 mm Hg [17]. Thus, if the SID is 30 mEq/L and the SBE is −10 mEq/L, the target SID is 40 mEq/L. Accordingly, the plasma Na^+ concentration would have to increase by 10 mEq/L for $NaHCO_3$ administration to correct the acidosis completely.

It should be noted that the target SID is the SID at the equilibrium point between the SID, P_{CO_2}, and Atot and that it may not be equal to 40 mEq/L, as in the example given. By convention, P_{CO_2} is set at 40 mm Hg, but the SBE is not corrected for abnormalities in Atot. In many hypoalbuminemic patients, Atot is lower than normal; thus, the SID at the equilibrium point will be less than 40 mEq/L [118]. Also, it is rare that the choice would be made to correct the acid–base abnormality completely. Therefore, the target SID should be used as a reference value, but in most cases, partial correction is all that is required.

If increasing the plasma Na^+ concentration is inadvisable for other reasons (e.g., hypernatremia), $NaHCO_3$ administration is inadvisable. It is noteworthy that $NaHCO_3$ administration has not been shown to improve outcome in patients with lactic acidosis [66]. In addition, $NaHCO_3$ administration

is associated with certain disadvantages [119]. Large (hypertonic) doses, if given rapidly, may actually reduce blood pressure [120] and may cause sudden, severe increases in Pa_{CO_2} [121]. Accordingly, it is important to assess the patient's ventilatory status before $NaHCO_3$ is administered, particularly if the patient is not on a ventilator. $NaHCO_3$ infusion also affects serum K^+ and Ca^{2+} concentrations, which must be monitored closely.

To avoid some of the disadvantages of $NaHCO_3$ therapy, alternative therapies for metabolic acidosis have been developed. Carbicarb is an equimolar mixture of sodium carbonate (Na_2CO_3) and $NaHCO_3$ [119, 122]. Like $NaHCO_3$, carbicarb works by increasing the plasma Na^+ concentration, except that it does not raise the P_{CO_2}. Results with carbicarb in animal studies have been mixed [123], and experience in humans is extremely limited.

Dicholoroacetate has also been utilized for treatment of metabolic acidosis due to its ability to stimulate pyruvate dehydrogenase, which results in a decrease in the production of lactate. However; due to the observation of toxicity, including limb paralysis and other neuropathies, it is no longer recommended for use in the treatment of lactic acidosis [124, 125].

THAM (tris-hydroxymethyl aminomethane) is a synthetic buffer that consumes CO_2 and readily penetrates cells [119, 126]. It is a weak base (pK = 7.9) and, as such, is unlike other plasma constituents. The major advantage of THAM is that it does not alter the SID, which means that there is no need to be concerned about having to increase the plasma Na^+ concentration to achieve a therapeutic effect. Accordingly, THAM is often used in situations where $NaHCO_3$ cannot be used because of hypernatremia. Although THAM has been available since the 1960s, there is surprisingly little information available regarding its efficacy in humans with acid–base disorders. In small uncontrolled studies, THAM appears to be capable of reversing metabolic acidosis secondary to ketoacidosis or renal failure without causing obvious toxicity [127]; however, adverse reactions have been reported, including hypoglycemia, respiratory depression, and even fatal hepatic necrosis, when concentrations exceeding 0.3 mol/L are used. In Europe, a mixture of THAM, acetate, $NaHCO_3$, and disodium phosphate is available. This mixture, known as tribonate (Tribonat, Pharmacia and Upjohn, Solna, Sweden), seems to have fewer side effects than THAM alone does, but as with THAM, experience with its use in humans is still quite limited.

Respiratory Acid–Base Disorders

Respiratory disorders are far easier to diagnose and treat than metabolic disorders, because the mechanism is always the same, even though the underlying disease process may vary. CO_2 is produced by cellular metabolism or by the titration of HCO_3^- by metabolic acids. Normally, alveolar ventilation is adjusted to maintain the Pa_{CO_2} between 35 and 45 mm Hg. When alveolar ventilation is increased or decreased out of proportion to the Pa_{CO_2}, a respiratory acid–base disorder exists.

Pathophysiology

CO_2 is produced by the body at a rate of 220 mL/min, which equates to production of 15 mol/L of carbonic acid each day [128]. By way of comparison, total daily production of all the nonrespiratory acids managed by the kidney and the gut amounts to less than 500 mmol/L. Pulmonary ventilation is adjusted by the respiratory center in response to Pa_{CO_2}, pH, and Po_2, as well as in response to exercise, anxiety, wakefulness, and other signals. Normal Pa_{CO_2} (40 mm Hg) is attained by precisely matching alveolar ventilation to metabolic CO_2 production. Pa_{CO_2} changes in predictable ways as a compensatory ventilatory response to the altered arterial pH produced by metabolic acidosis or alkalosis (see Table 3.1).

Respiratory Acidosis

Mechanism

When the rate of CO_2 elimination is inadequate relative to the rate of tissue CO_2 production, the Pa_{CO_2} rises to a new steady state, determined by the new relation between alveolar

ventilation and CO_2 production. In the short term, this rise in the Pa_{CO_2} increases the concentrations of both H^+ and HCO_3^- according to the carbonic acid equilibrium equation. Thus, the change in the HCO_3^- concentration is mediated not by any systemic adaptation but by chemical equilibrium. The higher HCO_3^- concentration does not buffer the H^+ concentration. The SID does not change, nor does the SBE. Tissue acidosis always occurs in respiratory acidosis because CO_2 inevitably builds up in the tissue.

If the Pa_{CO_2} remains elevated, a compensatory response will occur, and the SID will increase to return the H^+ concentration to the normal range. The increase in the SID is accomplished primarily by removing Cl^- from the plasma space. If Cl^- moves into tissues or red blood cells, it will result in intracellular acidosis (complicated by the elevated tissue P_{CO_2}); thus, to exert a lasting effect on the SID, Cl^- must be removed from the body. The kidney is designed to do this, whereas the GI tract is not (although the adaptive capacity of the GI tract as a route of Cl^- elimination has not been fully explored). Accordingly, patients with renal disease have a very difficult time adapting to chronic respiratory acidosis.

Patients whose renal function is intact can eliminate Cl^- in the urine; after a few days, the SID rises to the level required to restore the pH to a value of 7.35. It is unclear whether this amount of time is necessary because of the physiologic constraints of the system or because the body benefits from not being overly sensitive to transient changes in alveolar ventilation. In any case, this response yields an increased pH for any degree of hypercapnia. According to the Henderson–Hasselbalch equation, the increased pH results in an increased HCO_3^- concentration for a given P_{CO_2}. Thus, the "adaptive" increase in the HCO_3^- concentration is actually the consequence, not the cause, of the increased pH. Although the HCO_3^- concentration is a convenient and reliable marker of metabolic compensation, it is not the mechanism of the compensatory response. This point is not merely a semantic one: as noted (see above), only changes in the independent variables of acid–base balance (P_{CO_2}, Atot, and SID) can affect the plasma H^+ concentration, and HCO_3^- concentration is not an independent variable.

Management

Treatment of Underlying Ventilatory Impairment

As with virtually all acid–base disorders, treatment begins by addressing the underlying disorder. Acute respiratory acidosis may be caused by central nervous system (CNS) suppression; neuromuscular diseases or conditions that impair neuromuscular functions (e.g., myasthenia gravis, hypophosphatemia, and hypokalemia); or diseases affecting the airway or the lung parenchyma (e.g., asthma and acute respiratory dysfunction syndrome [ARDS]). The last category of conditions produces not only alveolar hypoventilation but also primary hypoxia. The two can be distinguished by means of the alveolar gas equation:

$$P_AO_2 = P_IO_2 - Pa_{CO_2} / R$$

where R is the respiratory exchange coefficient (generally taken to be 0.8) and P_IO_2 is the inspired oxygen tension (approximately 150 mm Hg in room air). Thus, as the Pa_{CO_2} increases, the P_AO_2 should also decrease in a predictable fashion. If the P_AO_2 falls by more than the predicted amount, there is a defect in gas exchange.

In most cases, chronic respiratory acidosis is caused by either chronic lung disease (e.g., chronic obstructive pulmonary disease [COPD]) or chest wall disease (e.g., kyphoscoliosis). In rare cases, it is caused by central hypoventilation or chronic neuromuscular disease.

Control of Hypoxemia

The alveolar gas equation also illustrates that the primary threat to life with respiratory acidosis does not come from the acidosis but from hypoxemia. In patients breathing room air, the Pa_{CO_2} cannot exceed 80 mm Hg before life-threatening hypoxemia results. Accordingly, supplemental oxygen is required in the treatment of these patients. Unfortunately, oxygen administration is almost never sufficient treatment by itself, and it generally proves

necessary to address the ventilatory defect. When the underlying cause can be addressed quickly (as when the effects of narcotics are reversed with naloxone), endotracheal intubation may be avoidable. In the majority of patients, however, this is not the case, and mechanical ventilation must be initiated. Mechanical support is indicated for patients who are unstable or at risk for instability and patients whose CNS function is deteriorating. In patients who exhibit signs of respiratory muscle fatigue, mechanical ventilation should be instituted before respiratory failure occurs. Therefore, it is not the absolute Pa_{CO_2} value that is the most important consideration in this situation but, rather, the clinical condition of the patient.

Chronic hypercapnia must be treated if the patient's clinical condition is deteriorating acutely. In this setting, it is important not to try to restore the Pa_{CO_2} to the normal range of 35–45 mm Hg. Instead, the patient's baseline Pa_{CO_2}, if known, should be the therapeutic target; if the baseline Pa_{CO_2} is not known, a target Pa_{CO_2} of 60 mm Hg is perhaps a reasonable choice. Overventilation can have two undesirable consequences. First, if the Pa_{CO_2} is rapidly normalized in a patient with chronic respiratory acidosis and an appropriately large SID, life-threatening alkalemia may ensue. Second, even if the Pa_{CO_2} is corrected slowly, the plasma SID may decrease over time, making it impossible to wean the patient from mechanical ventilation.

One option for treatment of hypercapnia is noninvasive ventilation with a bi-level positive airway pressure (BiPAP) system. This technique may be useful in the management of some patients, particularly those whose sensorium is not impaired [129]. Rapid infusion of $NaHCO_3$ in patients with respiratory acidosis may induce acute respiratory failure if alveolar ventilation is not increased to account for the increased CO_2. Thus, if $NaHCO_3$ is to be given, it must be administered slowly, with alveolar ventilation adjusted appropriately. Furthermore, it must be remembered that $NaHCO_3$ works by increasing the plasma Na^+ concentration; if this effect is not possible or not desirable, $NaHCO_3$ should not be given.

Occasionally, it is useful to reduce CO_2 production. This can be accomplished by reducing the amount of carbohydrates supplied in feedings (in patients requiring nutritional support), controlling body temperature (in febrile patients), or providing sedation (in anxious or combative patients). In addition, treatment of shivering in the postoperative period can reduce CO_2 production. Rarely, however, can hypercapnia be controlled with these CO_2-reducing techniques alone.

Permissive Hypercapnia

In the recent past, there has been considerable interest in ventilator-associated lung injury. Overdistention of alveoli can result in tissue injury and microvascular permeability, which lead to interstitial and alveolar edema. In animal studies, prolonged use of elevated airway pressures and increased lung volumes resulted in increased pathologic pulmonary changes and decreased survival when compared with ventilatory strategies employing lower pressures and volumes [130, 131]. In a large multicenter clinical trial, simply lowering the tidal volume on the ventilator from 12 mL/kg to 6 mL/kg in patients with acute lung injury resulted in a 9 % absolute reduction in mortality risk [132]. Although the protocol followed in this trial did not advocate a reduced minute ventilation and hence an elevated Pa_{CO_2}, this approach, often referred to as permissive hypercapnia or controlled hypoventilation, has been increasingly used clinically. Uncontrolled studies suggest that permissive hypercapnia may reduce mortality in patients with severe ARDS [117]. This strategy is not, however, without risks. Sedation is mandatory, and neuromuscular blocking agents are frequently required. Intracranial pressure rises, as does transpulmonary pressure; consequently, this technique is unusable in patients with brain injury or right ventricular dysfunction. There is controversy regarding how low the pH can be allowed to fall. Some authors have reported good results with pH values of 7.0 or even lower [4], but most have advocated more modest pH reductions (i.e., g7.25).

Respiratory Alkalosis

Respiratory alkalosis may be the most frequently encountered acid–base disorder. It occurs in residents of high-altitude locales and in persons with any of a wide range of pathologic conditions, the most important of which are salicylate intoxication, early sepsis, hepatic failure, and hypoxic respiratory disorders. Respiratory alkalosis also occurs in association with pregnancy and with pain or anxiety. Hypocapnia appears to be a particularly strong negative prognostic indicator in patients with critical illness [133]. Like acute respiratory acidosis, acute respiratory alkalosis results in a small change in the HCO_3^- concentration, as dictated by the Henderson–Hasselbalch equation. If hypocapnia persists, the SID begins to decrease as a consequence of renal Cl^- reabsorption. After 2–3 days, the SID assumes a new and lower steady state [134].

Severe alkalemia is unusual in respiratory alkalosis. Management therefore is typically directed toward the underlying cause [135]. In general, these mild acid–base changes are clinically important more for what they can alert the clinician to, in terms of underlying disease, than for any direct threat they pose to the patient. In rare cases, respiratory depression with narcotics is necessary.

Pseudorespiratory Alkalosis

The presence of arterial hypocapnia in patients experiencing profound circulatory shock has been termed pseudorespiratory alkalosis [101]. This condition occurs when alveolar ventilation is supported, but the circulation is grossly inadequate. In such circumstances, the mixed venous P_{CO_2} is significantly elevated, but the Pa_{CO_2} is normal or even decreased as a consequence of reduced CO_2 delivery to the lung and increased pulmonary transit time. Overall CO_2 clearance is therefore markedly decreased, and profound tissue acidosis—usually both metabolic and respiratory—ensues. The metabolic component of the acidosis comes from tissue hypoperfusion and hyperlactatemia. Arterial oxygen saturation may also appear adequate despite tissue hypoxemia. Pseudorespiratory alkalemia is rapidly fatal unless the patient's systemic hemodynamic status can be normalized.

References

1. Corey HE. Stewart and beyond: new models of acid-base balance. Kidney Int. 2003;64(3):777–87.
2. Bourke E, Haussinger D. pH homeostasis: the conceptual change. Contrib Nephrol. 1992;100:58–88.
3. Oliver J, Bourke E. Adaptations in urea ammonium excretion in metabolic acidosis in the rat: a reinterpretation. Clin Sci Mol Med Suppl. 1975;48(6):515–10.
4. Atkinson DE, Bourke E. pH homeostasis in terrestrial vertebrates; Ammonium ion as a proton source. In: Norbert H, editor. Mechanisms of systemic regulation: acid–base regulation, ion-transfer and metabolism. New York: Springer; 1995. p. 3–26.
5. Moore EW. The alkaline tide. Gastroenterology. 1967;52(6):1052–4.
6. Bellomo R, Kellum JA, Pinsky MR. Transvisceral lactate fluxes during early endotoxemia. Chest. 1996;110(1):198–204.
7. Kellum JA, Bellomo R, Kramer DJ, Pinksky MR. Splanchnic buffering of metabolic acid during early endotoxemia. J Crit Care. 1997;12(1):7–12.
8. Schlichtig R, Grogono AW, Severinghaus JW. Human $PaCO_2$ and standard base excess compensation for acid-base imbalance. Crit Care Med. 1998;26:1173–9.
9. Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. J Appl Physiol. 2003;95(6):2333–44.
10. Fidkowski C, Helstrom J. Diagnosing metabolic acidosis in the critically ill: bridging the anion gap, Stewart, and base excess methods. Can J Anaesth. 2009;56:247–56.
11. Kellum JA. Clinical review: reunification of acid-base physiology. Crit Care. 2005;9(5):500–7.
12. Kurtz I, Kraut J, Ornekian V, Nguyen MK. Acid-base analysis: a critique of the Stewart and bicarbonate-centered approaches. Am J Physiol Renal Physiol. 2008;294(5):F1009–31.
13. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol. 1983;61(12):1444–61.
14. Kellum JA. Determinants of blood pH in health and disease. Crit Care. 2000;4(1):6–14.
15. Sirker AA, Rhodes A, Grounds RM, Bennett ED. Acid-base physiology: the 'traditional' and the 'modern' approaches. Anaesthesia. 2002;57(4):348–56.
16. Wooten EW. Science review: quantitative acid-base physiology using the Stewart model. Crit Care. 2004;8(6):448–52.
17. Kellum JA. Disorders of acid-base balance. Crit Care Med. 2007;35(11):2630–6.

18. Corey HE. Bench-to-bedside review: fundamental principles of acid-base physiology. Crit Care. 2005; 9(2):184–92.
19. Jones NL. A quantitative physicochemical approach to acid-base physiology. Clin Biochem. 1990;23(3): 189–95.
20. Leblanc Martine KJ. Biochemical and biophysical principles of hydrogen ion regulation. In Critical care nephrology. Philadelphia: Saunders; 1998. p. 261–77.
21. Hansen JE, Sue DY. Should blood gas measurement be corrected for the patient's temperature? N Engl J Med. 1980;303(6):341.
22. Delaney KA, Howland MA, Vassallo S, Goldfrank LR. Assessment of acid-base disturbances in hypothermia and their physiologic consequences. Ann Emerg Med. 1989;18(1):72–82.
23. Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. Medicine. 1980; 59(3):161–87.
24. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. J Lab Clin Med. 1992;120(5):713–9.
25. Sadjadi SA. A new range for the anion gap. Ann Intern Med. 1995;123(10):807.
26. Winter SD, Pearson JR, Gabow PA, Schultz AL, Lepoff RB. The fall of the serum anion gap. Arch Intern Med. 1990;150(2):311–3.
27. Harrison TR. Harrison's principles of internal medicine. In: Braunwald E, Isselbacher KJ, Petersdorp RG, editors. Acidocis and alkalosis. 11th ed. New York: McGraw-Hill; 1987.
28. Salem MM, Mujais SK. Gaps in the anion gap. Arch Intern Med. 1992;152(8):1625–9.
29. Oster JR, Perez GO, Materson BJ. Use of the anion gap in clinical medicine. South Med J. 1988;81(2): 229–37.
30. Gabow PA. Disorders associated with an altered anion gap. Kidney Int. 1985;27(2):472–83.
31. Whelton A, Carter GG, Garth MA, Darwish MO, Walker WG. Carbenicillin-induced acidosis and seizures. JAMA. 1971;218(13):1942–3.
32. Kang Y, Aggarwal S, Virji M, Pasculle AW, Lewis JH, Freeman JA, Martin LK. Clinical evaluation of autotransfusion during liver transplantation. Anesth Analg. 1991;72(1):94–100.
33. Narins R. Metabolic acid-base disorders: pathophysiology, classification and treatment. In Fluid, electrolyte, and acid-base disorders. New York: Churchill Livingstone; 1985. p. 269–384.
34. Arieff AI, Carroll HJ. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. Medicine. 1972;51(2): 73–94.
35. Mecher C, Rackow EC, Astiz ME, Weil MH. Unaccounted for anion in metabolic acidosis during severe sepsis in humans. Crit Care Med. 1991; 19(5):705–11.
36. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. J Crit Care. 1993;8(4):187–97.
37. Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care. 1995;10(2):51–5.
38. Kirschbaum B. Increased anion gap after liver transplantation. Am J Med Sci. 1997;313(2):107–10.
39. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Hepatic anion flux during acute endotoxemia. J Appl Physiol. 1995;78(6):2212–7.
40. Mehta KK, Janes A, Carlson RW. The relationship between anion gap and elevated lactate. Crit Care Med. 1986;14(4):405.
41. Schlichtig R. [Base excess] vs [strong ion difference]. Which is more helpful? Adv Exp Med Biol. 1997;411:91–5.
42. Kaplan LJ, Kellum JA. Comparison of acid-base models for prediction of hospital mortality after trauma. Shock. 2008;29(6):662–6.
43. Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med. 1992;20(1):80–93.
44. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation. 1970;41(6):989–1001.
45. Blair E. Acid-base balance in bacteremic shock. Arch Intern Med. 1971;127(4):731–9.
46. Madias NE. Lactic acidosis. Kidney Int. 1986; 29(3):752–74.
47. van Lambalgen AA, Runge HC, van den Bos GC, Thijs LG. Regional lactate production in early canine endotoxin shock. Am J Physiol. 1988;254 (1 Pt 1):E45–51.
48. Cain SM, Curtis SE. Systemic and regional oxygen uptake and delivery and lactate flux in endotoxic dogs infused with dopexamine. Crit Care Med. 1991;19(12):1552–60.
49. Brown SD, Clark C, Gutierrez G. Pulmonary lactate release in patients with sepsis and the adult respiratory distress syndrome. J Crit Care. 1996; 11(1):2–8.
50. Kellum JA, Kramer DJ, Mankad S, Bellomo R, Lee K, Pinsky MR. Release of lactate by the lung in acute lung injury. Chest. 1997;111(5):1301–5.
51. Connett RJ, et al. Defining hypoxia: a systems view of VO_2, glycolysis, energetics, and intracellular PO_2. J Appl Physiol. 1990;68(3):833–42.
52. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, Nabet P, Larcan A. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med. 1997; 23(3):282–7.
53. De Backer D. Lactic acidosis. Intensive Care Med. 2003;29(5):699–702.
54. De Backer D, Creteur J, Zhang H, Norrenberg M, Vincent JL. Lactate production by the lungs in acute

lung injury. Am J Respir Crit Care Med. 1997;156 (4 Pt 1):1099–104.
55. Stacpoole PW. Lactic acidosis and other mitochondrial disorders. Metabolism. 1997;46(3):306–21.
56. Fink MP. Does tissue acidosis in sepsis indicate tissue hypoperfusion? Intensive Care Med. 1996; 22(11):1144–6.
57. Gutierrez G, Wulf ME. Lactic acidosis in sepsis: a commentary. Intensive Care Med. 1996;22(1):6–16.
58. Kilpatrick-Smith L, Kilpatrick-Smith L, Deas J, Erecińska M, Silver IA. Cellular effects of endotoxin in vitro. II. Reversibility of endotoxic damage. Circ Shock. 1983;11(2):101–11.
59. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. Ann Surg. 1996;224(1):97–102.
60. Bearn AG, Billing B, Sherlock S. The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. J Physiol. 1951;115(4):430–41.
61. Zilva JF. The origin of acidosis in hyperlactatemia. Ann Clin Biochem. 1978;15:40–3.
62. Madias NE, Homer SM, Johns CA, Cohen JJ. Hypochloremia as a consequence of anion gap metabolic acidosis. J Lab Clin Med. 1984;104(1): 15–23.
63. Cohen RD, Woods HF. Lactic acidosis revisited. Diabetes. 1983;32(2):181–91.
64. Kreisberg RA. Lactate homeostasis and lactic acidosis. Ann Intern Med. 1980;92(2 Pt 1):227–37.
65. Uribarri J, Oh MS, Carroll HJ. D-lactic acidosis. A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. Medicine. 1998;77(2):73–82.
66. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. Chest. 2000;117(1): 260–7.
67. Graf H, Leach W, Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science. 1985;227(4688):754–6.
68. Rhee KH, Toro LO, McDonald GG, Nunnally RL, Levin DL. Carbicarb, sodium bicarbonate, and sodium chloride in hypoxic lactic acidosis. Effect on arterial blood gases, lactate concentrations, hemodynamic variables, and myocardial intracellular pH. Chest. 1993;104(3):913–8.
69. Magder S. Pathophysiology of metabolic acid-base disturbances in patients with critical illness. In Critical care nephrology. Philadelphia: Saunders; 1998. p. 279–96.
70. Alberti KG. Diabetic emergencies. Br Med Bull. 1989;45(1):242–63.
71. Bakerman S, Bakerman P, Strausbauch P. ABC's of interpretive laboratory data. In Bakerman's ABC's of interpretive laboratory data. 4th ed. Scottsdale, AZ: Interpretive Laboratory Data; 2002.
72. Androque HJ, Tannen RL. Fluids and electrolytes. In: Kokko JP, Tannen RL, editors. Ketoacidosis, hyperosmolar states, and lactic acidosis. Philadelphia: WB Saunders; 1996.
73. Good DW. Regulation of bicarbonate and ammonium absorption in the thick ascending limb of the rat. Kidney Int Suppl. 1991;33:S36–42.
74. Fulop M. Alcoholic ketoacidosis. Endocrinol Metab Clin North Am. 1993;22(2):209–19.
75. Wrenn KD, Slovis CM, Minion GE, Rutkowski R. The syndrome of alcoholic ketoacidosis. Am J Med. 1991;91(2):119–28.
76. Proudfoot AT, Krenzelok EP, Brent J, Vale JA. Does urine alkalinization increase salicylate elimination? If so, why? Toxicol Rev. 2003;22(3):129–36.
77. Whiteney GM, Szerlip HM. Acid base and electrolyte disorders. In: Dubose Jr TD, Hamm LL, editors. Acid-base disorders in the critical care setting. Philadelphia: WB Saunders; 2002.
78. Fraser AD. Clinical toxicologic implications of ethylene glycol and glycolic acid poisoning. Ther Drug Monit. 2002;24(2):232–8.
79. Widmer B, Gerhardt RE, Harrington JT, Cohen JJ. Serum electrolyte and acid base composition. The influence of graded degrees of chronic renal failure. Arch Intern Med. 1979;139(10):1099–102.
80. Harrington JT, Cohen JJ. Metabolic acidosis. In: Kasirer JP, Cohen JJ, editors. Acid-base. Boston: Little, Brown and Co; 1982.
81. Liborio AB, Daher EF, de Castro MC. Characterization of acid-base status in maintenance hemodialysis: physicochemical approach. J Artif Organs. 2008; 11(3):156–9.
82. Abassi ZA, Hoffman A, Better OS. Acute renal failure complicating muscle crush injury. Semin Nephrol. 1998;18(5):558–65.
83. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJ, Libório AB, Park M. Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. Crit Care Med. 2009;37(10):2733–9.
84. Forni LG, McKinnon W, Lord GA, Treacher DF, Peron JM, Hilton PJ. Circulating anions usually associated with the Krebs cycle in patients with metabolic acidosis. Crit Care. 2005;9(5):R591–5.
85. Forni LG, McKinnon W, Hilton PJ. Unmeasured anions in metabolic acidosis: unravelling the mystery. Crit Care. 2006;10(4):220.
86. Martin M, Murray J, Berne T, Demetriades D, Belzberg H. Diagnosis of acid-base derangements and mortality prediction in the trauma intensive care unit: the physiochemical approach. J Trauma. 2005; 58(2):238–43.
87. Rocktaeschel J, Morimatsu H, Uchino S, Bellomo R. Unmeasured anions in critically ill patients: can they predict mortality? Crit Care Med. 2003;31(8): 2131–6.
88. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med. 2004;32(5):1120–4.

89. Mikulaschek A, Henry SM, Donovan R, Scalea TM. Serum lactate is not predicted by anion gap or base excess after trauma resuscitation. J Trauma. 1996;40(2):218–22. discussion 222–4.
90. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP. Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. Crit Care Med. 1990;18(3):275–7.
91. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg. 2003; 185(5):485–91.
92. Rutherford EJ, Morris Jr JA, Reed GW, Hall KS. Base deficit stratifies mortality and determines therapy. J Trauma. 1992;33(3):417–23.
93. Davis JW, Kaups KL, Parks SN. Base deficit is superior to pH in evaluating clearance of acidosis after traumatic shock. J Trauma. 1998;44(1):114–8.
94. Davis JW, Kaups KL. Base deficit in the elderly: a marker of severe injury and death. J Trauma. 1998;45(5):873–7.
95. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. J Trauma. 1993;35(4):584–8. discussion 588–9.
96. Gunnerson KJ. Clinical review: The meaning of acid-base abnormalities in the intensive care unit part I - epidemiology. Crit Care. 2005;9(5):508–16.
97. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006;10(1):R22.
98. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med. 1988;318(10):594–9.
99. Ring T, Frische S, Nielsen S. Clinical review: Renal tubular acidosis–a physicochemical approach. Crit Care. 2005;9(6):573–80.
100. Cheek DB. Changes in total chloride and acid-base balance in gastroenteritis following treatment with large and small loads of sodium chloride. Pediatrics. 1956;17(6):839–48.
101. Shires GT, Holman J. Dilution acidosis. Ann Intern Med. 1948;28(3):557–9.
102. Garella S, Chang BS, Kahn SI. Dilution acidosis and contraction alkalosis: review of a concept. Kidney Int. 1975;8(5):279–83.
103. Garella S, Tzamaloukas AH, Chazan JA. Effect of isotonic volume expansion on extracellular bicarbonate stores in normal dogs. Am J Physiol. 1973; 225(3):628–36.
104. Waters JH, Bernstein CA. Dilutional acidosis following hetastarch or albumin in healthy volunteers. Anesthesiology. 2000;93(5):1184–7.
105. Waters JH, Miller LR, Clack S, Kim JV. Cause of metabolic acidosis in prolonged surgery. Crit Care Med. 1999;27(10):2142–6.
106. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg. 2001;93(4):811–6.
107. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock. 1998;9(5): 364–8.
108. Gattinoni L, Carlesso E, Maiocchi G, Polli F, Cadringher P. Dilutional acidosis: where do the protons come from? Intensive Care Med. 2009;35(12): 2033–43.
109. Doberer D, Funk GC, Kirchner K, Schneeweiss B. A critique of Stewart's approach: the chemical mechanism of dilutional acidosis. Intensive Care Med. 2009;35(12):2173–80.
110. Ring T. Mixing bicarbonates: dilution acidosis from first principles. Intensive Care Med. 2009;35(12): 2183–4; author reply 2185–6.
111. Kellum JA. Recent advances in acid-base physiology applied to critical care. In: Vincent J-L, editor. Yearbook of intensive care and emergency medicine. Heidelberg: Springer; 1998.
112. Morgan TJ, Venkatesh B, Hall J. Crystalloid strong ion difference determines metabolic acid-base change during in vitro hemodilution. Crit Care Med. 2002;30(1):157–60.
113. Gilbert EM, Haupt MT, Mandanas RY, Huaringa AJ, Carlson RW. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Respir Dis. 1986;134(5):873–8.
114. Moviat M, Terpstra AM, Ruitenbeek W, Kluijtmans LA, Pickkers P, van der Hoeven JG. Contribution of various metabolites to the "unmeasured" anions in critically ill patients with metabolic acidosis. Crit Care Med. 2008;36:752–8.
115. Lindinger MI, Heigenhauser GJ, McKelvie RS, Jones NL. Blood ion regulation during repeated maximal exercise and recovery in humans. Am J Physiol. 1992;262(1 Pt 2):R126–36.
116. Forrest David WK, Russell J. Impact of acid-base disorders on individual organ systems. In Critical care nephrology. Philadelphia: Saunders; 1998. p. 313–26.
117. Hickling KG, Walsh J, Herderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med. 1994;22:1568–78.
118. Gunnerson KJ, Srisawat N, Kellum JA. Is there a difference between strong ion gap in healthy volunteers and intensive care unit patients? J Crit Care. 2010; 25:520–4.
119. Gehlbach BK, Schmidt GA. Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit - the role of buffers. Crit Care. 2004;8:259–65.
120. Kette F, Weil MH, Gazmuri RJ. Buffer solutions may compromise cardiac resuscitation by reducing

coronary perfusion pressure. JAMA. 1991;266: 2121–6.
121. Hindman BJ. Sodium bicarbonate in the treatment of subtypes of acute lactic acidosis: physiologic considerations. Anesthesiology. 1990;72:1064–76.
122. Bersin RM, Arieff AI. Improved hemodynamic function during hypoxia with Carbicarb, a new agent for the management of acidosis. Circulation. 1988;77: 227–33.
123. Spital Aaron GS. Correction of acid-base derangements. In Critical care nephrology. Philadelphia: Saunders; 1998. p. 327–44.
124. Stacpoole PW, Moore GW, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, et al. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. N Engl J Med. 1992;327:1564–9.
125. Stacpoole PW, Moore GW, Kornhauser DM. Toxicity of chronic dichloroacetate. N Engl J Med. 1979; 300:372.
126. Bleich HL, Schwartz WB. Tris buffer (THAM). An appraisal of its physiologic effects and clinical usefulness. N Engl J Med. 1966;274(14):782–7.
127. Arieff AI. Bicarbonate therapy in the treatment of metabolic acidosis. In: Chernow B, editor. The pharmacologic approach to the critically ill patient. Philadelphia: Williams & Wilkins; 1994.
128. Gattinoni L, Lissoni A. Pathophysiology and diagnosis of respiratory acid-base disturbances in patients with critical illness. In Critical care nephrology. Philadelphia: Saunders; 1998, p. 297–311.
129. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
130. Tsuno K, Miura K, Takeya M, Kolobow T, Morioka T. Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. Am Rev Respir Dis. 1991;143(5 Pt 1): 1115–20.
131. Sugiura M, McCulloch PR, Wren S, Dawson RH, Froese AB. Ventilator pattern influences neutrophil influx and activation in atelectasis-prone rabbit lung. J Appl Physiol. 1985;77:1355–65.
132. [no authors listed]. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18): 1301–8.
133. Gennari FJ. Acid-base. In: Cohen JJ, editor. Respiratory alkalosis. Boston: Little Brown and Co.; 1982.
134. Cohen JJ, Madias NE, Wolf CJ, Schwartz WB. Regulation of acid-base equilibrium in chronic hypocapnia. Evidence that the response of the kidney is not geared to the defense of extracellular (H^+). J Clin Invest. 1976;57:1483–9.
135. Adrogue HJ, Madias NE. Management of life-threatening acid-base disorders. Second of two parts. N Engl J Med. 1998;338(2):107–11.
136. Ashley SW, editor. ACS surgery: principles and practice. Hamilton, ON: B. C. Decker; 2014.

Starvation

4

Charles Weissman and Rawhi Hashem

Starvation is a multifaceted condition commonly encountered by surgeons (Table 4.1). The inability to ingest sufficient calories and/or an appropriate mixture of nutrients results in changes in the underlying metabolic milieu that can affect the outcome of both illnesses and their treatments. Therefore, surgeons and other clinicians must be cognizant of the consequences of these changes and take measures to reverse these detrimental effects.

Starvation and Surgery

Surgical patients have reduced caloric intake at various times during their illness, ranging from preoperative overnight fasts to prolonged periods of decreased caloric and energy intake. With surgical scheduling being imprecise, patients can be fasted for as long as 12–15 h prior to undergoing surgery. This leads patients to begin surgery in a fasting state. Both preoperatively and postoperatively diminished caloric and/or nutrient intake can be due to loss of appetite; inability to eat; holding nutritional intake prior to diagnostic procedures; and gastrointestinal tract dysfunction such as obstruction, ilieus, maldigestion, and malabsorption. Furthermore, the prevailing tradition of not permitting patient to eat for the few days after abdominal surgery—"to let the bowel rest" results in prolonged starvation or semistarvation. Insufficient caloric and nutrient intake can delay wound healing; weaken the immune system leading to vulnerability to infection; cause muscle weakness secondary to proteolysis; and weight loss due to lipolysis.

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Short-Term Starvation: Metabolic Consequences

The lack or severe reduction in nutrient intake results in a continuum of metabolic changes aimed at providing sufficient energy substrate to preserve vital bodily functions. Organisms slowly adapt their metabolic functions by gradually reducing energy output, producing endogenous substrates, and attempting to preserve muscle mass at the expense of adipose tissue.

Carbohydrate Metabolism

The postabsorptive state (Table 4.1), seen mainly during the late morning, late afternoon, and overnight, is characterized by metabolic changes that aim to preserve the body's blood glucose concentration within a range of 90–100 mg/dL. Maintaining blood glucose concentrations is particularly critical for brain and red blood cells which exclusively use

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Table 4.1 Definitions

Starvation—The most extreme form of malnutrition, which involves severe deficiency in caloric energy, nutrient, and vitamin intake
Fasting—The act of refraining from food, drink or both, for a finite time period
Postabsorptive State—After the complete absorption of a meal (3–5 h after a meal), the metabolism changes to that of a fasting state
Cachexia—loss of weight, muscle atrophy, fatigue, weakness, and significant loss of appetite in someone who is not actively trying to lose weight
Sarcopenia—degenerative loss of skeletal muscle mass
Marasmus—chronic undernourishment caused by a diet deficient in energy intake in all its forms, including protein
Kwashiorkor—a condition where there is a dietary protein deficiency but an adequate energy intake
Wasting—Unintentional loss of weight, due to decreases in both fat and fat-free compartments. Surgical patients who suffer from decreased caloric and nutrient intake are described as patients who "should not, would not and/or could not eat"

glucose as their energy source. The postabsorptive state is triggered by falling blood glucose concentrations which result in declining insulin concentrations. As the glucose and insulin concentrations decrease, glucagon is secreted by pancreatic α-cells likely in response to intrinsic (within the α-cell itself) and paracrine (mediated by factors released by pancreatic β- and/or δ-cells) stimulation [1]. Among the latter is a reduction in intra-islet insulin-mediated suppression of glucagon secretion. Mitochondrial uncoupling protein-2 (UCP2) likely plays a role in α-cell glucose sensing [2]. Glucagon is synthesized as a 160 amino acid prohormone (proglucagon) from a gene on chromosome 2. Proglucagon undergoes cleavage by prohormone convertase 2 into four peptides including 29-amino acid glucagon. Much of the secreted glucagon is then transported to the liver where the high glucagon:insulin ratio triggers glycogenolysis and gluconeogenesis while inhibiting glycolysis and glycogenesis. Activation of the β-adrenergic system and increased cortisol further promotes this metabolic activity [3]. After 48-h of fasting, insulin concentrations are reduced by about 80 % resulting in decreased insulin receptor activation which in turn leads to reduced protein kinase B/AKT activity (i.e., decreased AKT phosphorylation [4]). The reduced plasma insulin concentrations decrease tissue glucose uptake, increase protein catabolism and increase lipolysis. Interestingly, after 48 h of fasting there was no change in skeletal muscle AKT or insulin receptor substrates 1 and 2 compared to prefasting levels reflecting other functional alterations in metabolism. However there was reduced AKT phosphorylation after 62-h of starvation [5, 6]. The contribution of the adrenergic system is variable. However, after a 72-h fast in normal subjects, 24-h urinary norepinephrine and dopamine concentrations and heart rate were increased, while cardiac vagal modulation decreased [7].

During the initial few hours of fasting, blood glucose concentration is maintained by hepatic glycogenolysis—the conversion of glycogen stored in the liver to glucose (Fig. 4.1). As these hepatic stores become depleted, glycogenolysis can also occur within skeletal muscles (Fig. 4.1). However, muscle lacks glucose-6-phospatase so that intramuscular gluconeogenesis cannot occur, instead the glycogen is converted to lactate which is then transported to the liver and kidney to undergo gluconeogenesis. Gluconeogenesis occurs in parallel with the hepatic glycogenolysis, even when liver glycogen stores are still maximal. At this stage gluconeogenesis contributes approximately 50 % of the endogenous glucose production. [8]. After 24 h of no caloric or nutrient intake blood glucose concentrations decrease to the low "normal" ranges. Concomitantly, plasma concentrations of free fatty acids and ketones increase, which differentiate the postabsorptive from the fasting state [9]. During starvation liver glycogen stores remain very low while those in skeletal muscle remain unchanged or even slightly increased.

The secreted glucagon binds to G-protein coupled glucagon receptors located on hepatocytes and other cells activating adenylate cyclase and inhibiting cyclic AMP (cAMP) phosphodiesterase thus causing a rise in intracellular cAMP [10]. β-adrenergic stimulation also enhances cAMP formation. The increased

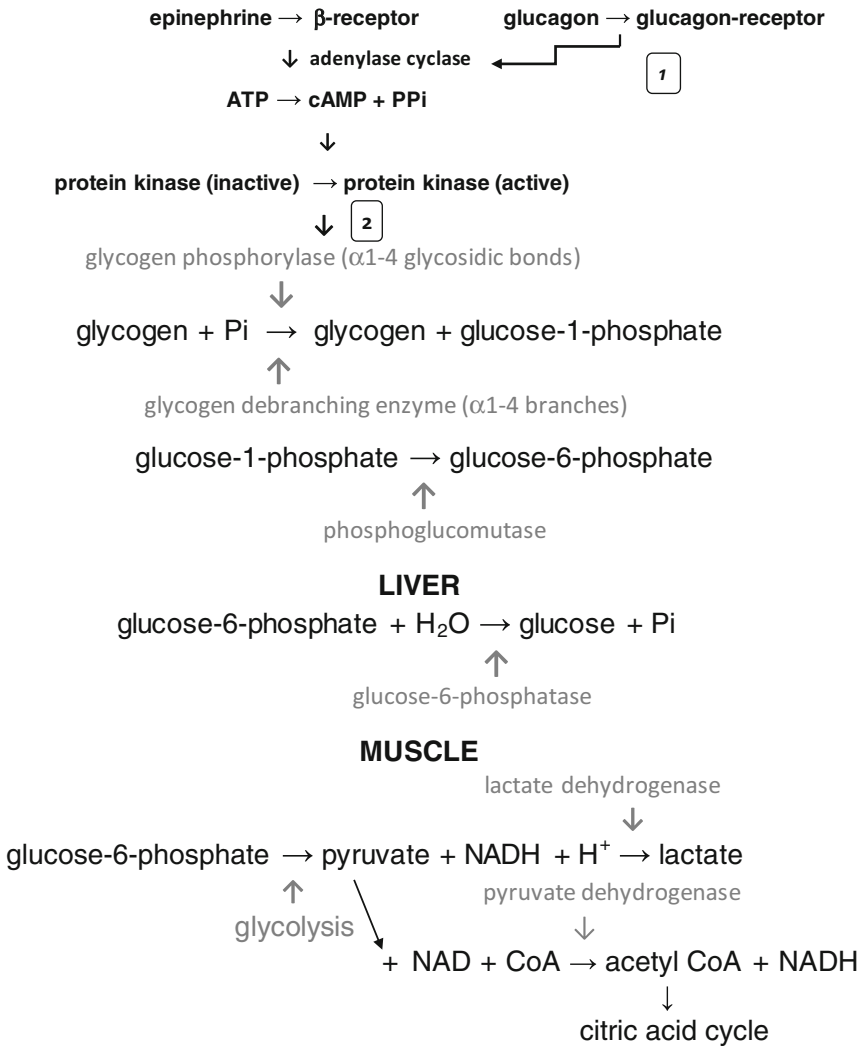

Fig. 4.1 Glycogenolysis is the initial source of glucose in the postabsorptive state and early starvation. However, the supply of hepatic and muscle glycogen is limited, lasting only a few hours. Muscle lacks glucose-6-phosphatase so that it cannot produce glucose directly but produces lactate which is transported to the liver where it undergoes gluconeogenesis. *Note 1*—Glucagon increases cAMP via its own G-protein coupled receptors i.e., a mechanism not requiring β-adrenergic receptors. Glucagon receptors are found mainly in the liver and kidney and less in adipose tissue. *Note 2*—Active protein kinase A catalyzes the transformation of inactive dephospho-phosphorylase kinase to active phospho-phosphorylase. Phospho-phosphorylase kinase then activates glycogen phosphorylase. *Pi* inorganic phosphate

cAMP activates protein kinase A leading to greater glycogen phosphorylation causing glycogenolysis. In addition there is upregulation of gluconeogenic enzymes leading to increased glucose production. Protein kinase A enters the nucleus to phosphorylate cAMP-responsive element binding protein (CREB). Phosphorylated CREB is transcriptionally active and binds to cAMP-responsive element (CRE) located in the promotor region of the target genes. CREB binds to its coactivator to form CREB-regulated transcription coactivator 2 (CRTC2; also known as TORC2). This complex is a major regulator of gluconeogenesis promoting the synthesis of major enzymes such a glucose-6-phosphatase. Parallel decreases in insulin signaling augment

this gluconeogenic gene expression through the dephosphorylation and nuclear shuttling of forkhead box protein 1 (FOXO1—transcription factors involved in regulating gene expression) in concert with the TORC2 [11, 12] FOXO1 and the peroxisome proliferator-activated receptor-γ, synergistically increase transcription of gluconeogenic genes [13]. The role of peroxisome proliferator-activated receptor-γ in human gluconeogenesis is still unclear. Glucocorticoids also stimulate gluconeogenesis by increasing the transcription of the glucose-6-phosphatase and phosphoenolpyruvate carboxylkinase genes. Glucocorticoids bind to glucocorticoid receptors and the resulting complex translocates to the nucleus where it binds to glucocorticoid responsive elements located on genes associated with gluconeogenesis.

Gluconeogenesis is the key process for maintaining the body's glucose supply becoming the main mechanism for glucose production once glycogen stores have been depleted. After 42 h of fasting by healthy subjects it provides practically all (93 %) of the glucose production [14]. Gluconeogenesis takes place in the liver and kidney using the breakdown products of adipose and muscle tissues that supply glycerol and amino acids, respectively, as substrates for glucose production [15]. After 60 h of starvation, glycerol accounts for about 15 % of glucose production. This proportion increases as starvation continues and proteolysis diminishes [16]. In addition, lactate from red blood cells, muscle activity, and renal medulla is used as a substrate [3]. The amino acid gluconeogenic substrate is mainly alanine in the liver and mainly glutamine in the kidney [17]. The liver produces about 60 % of the glucose with the remainder produced by the kidneys [18]. As fasting progresses, the total hepatic glucose production decreases largely because of reduced glycogenolysis, with little change in gluconeogenesis [19]. As the period of starvation continues the rate of gluconeogenesis begins to fall as the body tries to preserve muscle mass. Compared to overnight fast, endogenous glucose production falls by about 12 % after 38 h of starvation and by 30 % after 62 h [16]. The reduction in hepatic glucose production after 64 h of fasting was greater in females than in males [20]. In its stead, both fat oxidation and ketone body formation increase [16]. This is reflected in a reduction of about 40 % in insulin-mediated glucose uptake with an increase in non-insulin-mediated nonoxidative disposal [16]. After 40–48 h of starvation, the increase in muscle and liver concentration of acetyl-CoA activates pyruvate dehydrogenase kinase isozyme 4 (PDK4), a mitochondrial enzyme that phosphorylates thus inhibiting the pyruvate dehydrogenase complex. This inhibition reduces the conversion of pyruvate to acetyl-coenzyme A (CoA), resulting in decreased glucose oxidation [16]. In liver and kidney pyruvate dehydrogenase kinase isozyme 2 (PDK2) activity is also increased [21]. The mechanism of PDK2 and PDK4 activation include reduced insulin signaling attributed to reduced insulin concentrations and/or insulin resistance. The reduction in insulin stimulation leads to activation of FOXO1 and FOXO3. Simultaneously, FOXO proteins are involved in the transcription of gluconeogenic genes responsible for glucose-6-phosphatase and phosphoenolpyruvate carboxylkinase activities [21]. The latter enzyme, along with fructose-1,6-diphosphatase, regulate gluconeogenesis.

Lipid Metabolism

Humans have limited stores of carbohydrates and protein, so it is the fat stores that possess the surplus calories that maintain body functions during fasting and starvation. Stored triglycerides are excellent sources of energy providing 9 kcal/g as opposed to 4 kcal/g for protein and carbohydrate. The dominant fuels for energy production during fasting are thus free fatty acids and ketones derived from stored triglycerides. Lipolysis, the breakdown of stored triglycerides to free fatty acids and glycerol, occurs in response to increased epinephrine, growth hormone and glucagon stimulation plus decreased insulin stimulation [4, 22]. Not only is there a decrease in the serum insulin concentration but also reduced end-organ sensitivity [23]. The stimulation of β2-adrenergic receptors causes cAMP concentrations to rise thereby increasing the cAMP-dependent protein

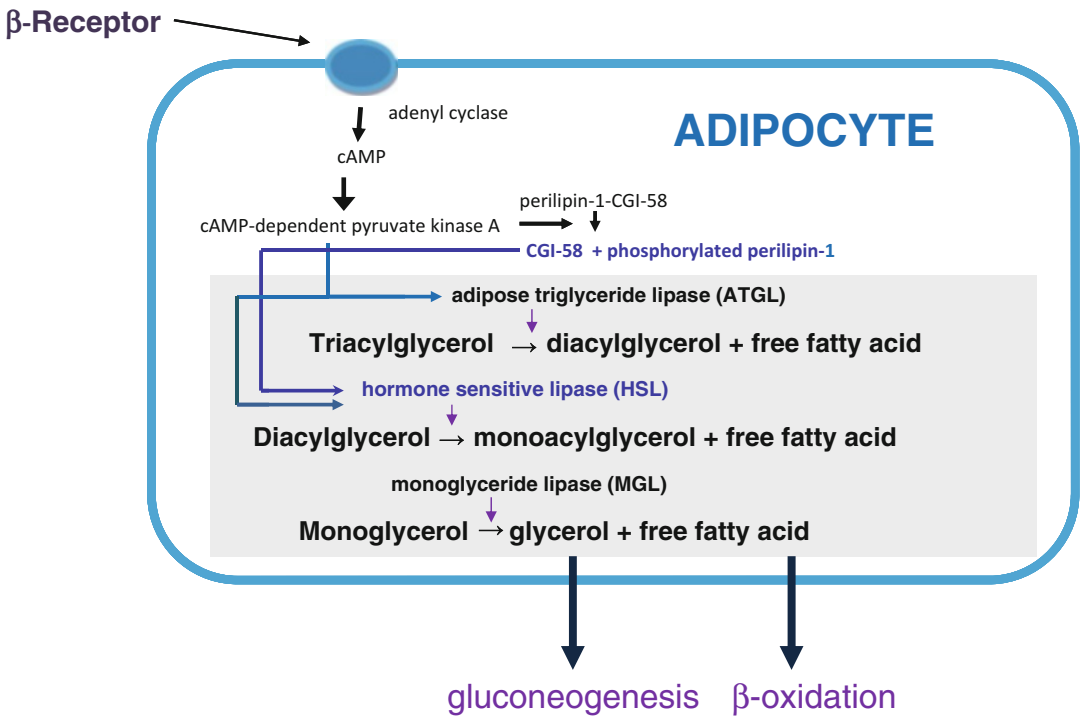

Fig. 4.2 Lipolysis—the breakdown of stored triglycerides into glycerol and fatty acids—is a key pathway in the adaptive response to starvation. During starvation it is triggered by β-adrenergic stimulation and possibly also growth hormone, glucagon, and cortisol. Perilipin (also called lipid droplet-associated protein) coats lipid droplets located in adipocytes and forms a protective coating to protect the stored lipid from lipases. During lipolysis perilipin is phosphorylated by cAMP-dependent pyruvate kinase A and undergoes a change in conformation exposing the stored lipids to hormone-sensitive lipase. Although, cAMP-dependent pyruvate kinase A also activates hormone-sensitive lipase, phosphorylated perilipin is more potent an activator

kinase A phosphorylation of the various lipolytic enzymes, especially hormone-sensitive lipase (Fig. 4.2). The rate of lipolysis, measured by palmitate turnover, doubles from postabsorptive levels after 84 h of fasting, releasing glycerol and free fatty acids [17]. The former is converted to glucose via gluconeogenesis and the latter undergoes β-oxidation and ketone body formation. This shift to lipid oxidation and ketogenesis is reflected by the decrease in respiratory quotient from 0.85 prior to fasting to 0.70 after 4 days of starvation [24].

The rate of free fatty acid appearance after 87 h of starvation is double that required to provide substrate for energy production. Many of the remaining free fatty acids are reesterified to triglycerides in adipose tissue and skeletal muscle and to a much lower extent in the liver. Teleologically, the reesterification cycles permit rapid increases and decreases in the metabolism of lipolytic substrates. Some of the free fatty acids are converted to bioactive intermediates, e.g., ceramide and acylcarnitines [16].

Lipolysis occurs differentially among the body's fat stores. In the postabsorptive state, 80–90 % of the lipolysis in lean subjects occurs within the upper body nonsplanchnic (subcutaneous) fat. In individuals with larger visceral fat stores, a greater portion of the lipolysis occurs within the visceral adipose tissue. This situation is accentuated in women compared to men [25]. After 72 h of fasting, lipolysis occurs predominantly in skeletal muscle; upper body subcutaneous fat and abdominal adipose tissue, while sparing peripheral adipose tissue [26]. In addition, 15–20 % of glycerol turnover is attributable to intravascular hydrolysis of very low-density lipoprotein triglycerides [27].

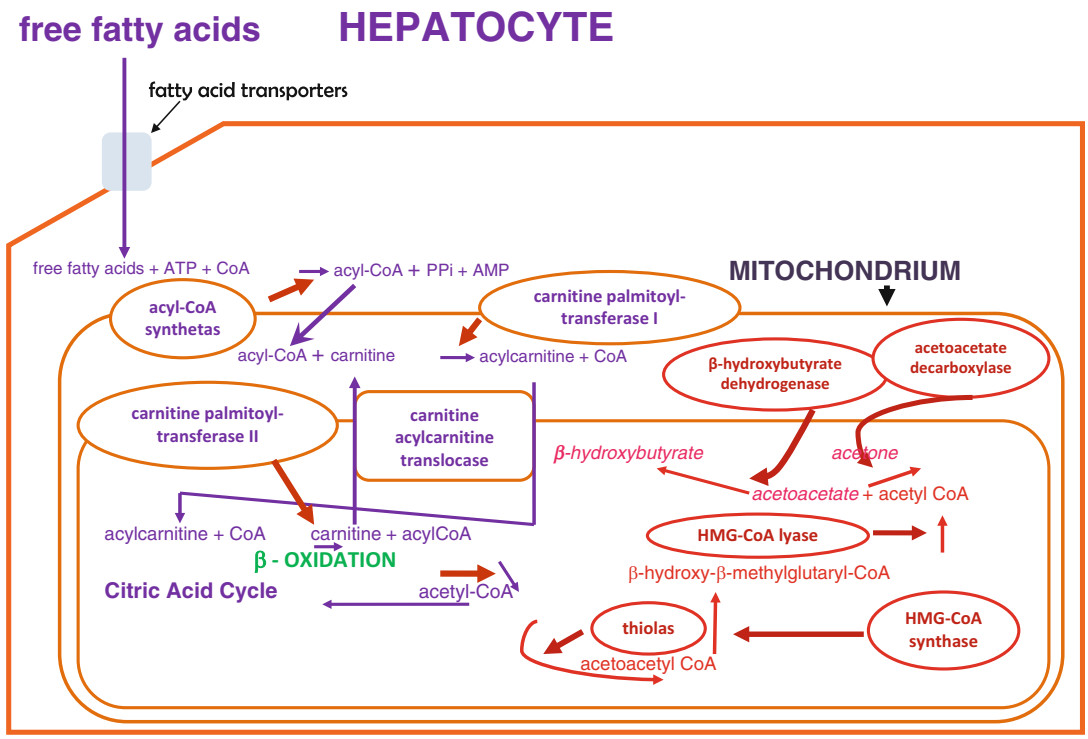

Fig. 4.3 Hepatocyte fatty acid β-oxidation and ketogenesis—fatty acids released by lipolysis undergo β-oxidation and ketogenesis within hepatocytes. The acetyl-CoA produced either enters the citric acid cycle (tricarboxylic acid cycle or the Krebs cycle) where the NADH generated enters the oxidative phosphorylation pathway to produce ATP or it is converted to ketone bodies (β-hydroxybutyrate and acetoacetate). The ketone bodies are transported to other organs to be used as energy substrate

Within 24 h of the onset of fasting, blood concentrations of glycerol and free fatty acids begin to increase. Average plasma free fatty acid concentrations were higher in women than men during 4–24 h of fasting, a difference not seen during 24–48 h of fasting due to the increases in free fatty acid concentrations being fourfold greater in males [9]. Free fatty acids, released into blood plasma where they bind to albumin, are taken up by the liver, skeletal muscle, heart, and kidney where they undergo β-oxidation in the mitochondria to acetyl-CoA (Fig. 4.2). The elevated fatty acid concentrations in hepatocytes (and monocytes) activate nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR-alpha), a transcription factor [28]. PPAR-alpha activation, along with the transcription factors FOXA2 and Sp1 (Specificity Protein 1) promotes uptake, utilization, and metabolism of the fatty acids by upregulation of genes involved in fatty acid transport, mitochondrial fatty acid β-oxidation, and ketogenesis. These genes code for enzymes such as pyruvate dehydrogenase, and carnitine/acylcarnitine carrier. β-oxidation of fatty acids coupled with oxidative phosphorylation is the key pathway for producing energy during fasting. Fatty acid acyl groups are transported from the cytosol into the mitochondrial matrix by means of the carnitine shuttle system (Fig. 4.3). In the cytosol, fatty acid units are transferred from acyl-CoAs to carnitine by the action of carnitine-palmitoyl-transferase-1 located on the external surface of the outer mitochondrial membrane. Metabolomic studies demonstrate an increase in cytosolic carnitine [29]. The acylcarnitines are translocated through the inner mitochondrial membrane by the carnitine/acylcarnitine carrier in exchange for intramitochondrial free

carnitine. Within the mitochondrial matrix, fatty acid acyl units are transferred from carnitine to matrix CoA by carnitine-palmitoyl-transferase 2 (CPT2) and these mitochondrial acyl-CoAs are oxidized by the β-oxidation enzymes. The acetyl-CoA produced from the fatty acids enters either the Krebs cycle or is used to form ketone bodies [30]. As starvation persists, acetyl-CoA accumulates within the hepatic mitochondria leading to the increased formation of the three ketone molecules: acetone, acetoacetate, and β-hydroxybutyrate (Fig. 4.2). The latter two are synthesized from acetyl-CoA, in the mitochondria of liver cells and can be used as a source of energy by the heart and brain. Acetone, formed by spontaneous decarboxylation of acetoacetate, is a waste product excreted in urine or breath.

As starvation persists, tissues begin to use ketones as energy sources and by weeks 5 and 6 of starvation become the main energy substrate [31]. The brain, which under most circumstances is dependent on glucose for energy, adapts to the use of ketones as its major energy source. In the brain, acetoacetate and β-hydroxybutyrate are reconverted to acetyl-CoA and enter the citric acid cycle to produce energy. β-hydroxybutyrate is a good source of energy providing 4.7 kcal/g [18]. During starvation the brain can use ketones for up to 70 % of its energy needs. The concentrations of β-hydroxybutyrate observed during starvation are usually 1–2 mM/L during the initial period of fasting, reaching levels of 4–7 mM/L after 2 weeks of starvation. This is much below the concentrations of 15–25 mM/L seen in ketoacidosis [9, 18]. Breakdown of ketone bodies in peripheral tissues increases acetyl-CoA bringing about reduce insulin signaling thus reducing cellular glucose uptake. Although, neuronal glucose uptake and oxidation during starvation is reduced, its influx (transport) through the blood–brain barrier is not reduced [31]. Furthermore, the increase in the amount of ketone bodies transported across the blood–brain barrier appears to be passive and depended on the greatly increased arterial concentrations appearing during starvation. The increased capacity of the blood–brain barrier monocarboxylic carrier contributes only a small fraction of the transported ketones [31].

The hyperketonemia is accompanied by hyperketonuria caused by a lack of reabsorption of a significant proportion of acetoacetate ($AcAc^-$) and β-hydroxybutyrate (β-OHB^-) by the renal tubule. To prevent systemic acidosis, near urinary electroneutrality is maintained by obligate isomolar excretion of cations, mainly NH_4^+. The NH_4^+ is obtained largely from renal deamination and deamidation of glutamine [9]. Persistent ketonuria, thus, results in the loss of valuable fuels derived from fat and also depletes protein stores to provide NH_4^+ [32]. Suppression of glucagon secretion by free fatty acids and ketone bodies may be part of a negative feedback system regulating ketogenesis.

After 7 days of fasting normal weight volunteers had increased serum concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B, while triglyceride and high-density lipoprotein (HDL) cholesterol concentrations were unchanged. The latter were found to be decreased after 6 days of fasting, while triglyceride concentrations were increased [33]. The increasing LDL levels were associated with decreasing serum insulin grown factor-1 (IGF-1) concentrations which is in keeping with the inverse correlation between the two [34]. In another study of normal weight individuals, 3 days of fasting resulted in increases in plasma triglyceride, as well as very low-density lipoprotein cholesterol and apolipoprotein B concentrations [35].

Insulin Resistance

In addition to the low concentrations of insulin during fasting and starvation, there is end-organ insulin resistance that some have called "diabetes of starvation." The teleological explanation for this resistance insures minimal insulin effects thus assuring that gluconeogenesis and lipolysis are not inhibited by insulin. The insulin resistance also reduces peripheral glucose utilization thus decreasing the need for greater proteolysis to supply gluconeogenic substrate while also assuring an adequate glucose supply for the brain and erythrocytes. Within 2–3 days of starvation, pronounced insulin resistance develops, possibly

mediated by increased lipid load [19]. Lean subjects subjected to 6-days of fasting developed insulin intolerance [36]. Compared to lean subjects, obese subjects had less of a decrease in insulin action after a 48-h fast. The greater reduction in insulin action after 48 h of fasting in lean subjects was ascribed to greater increases in FFA and β-hydroxybutyrate concentrations [19]. The reduced whole body insulin sensitivity manifests as reduced insulin-stimulated glucose disposal caused by decreased insulin stimulation of glucose oxidation and reduced nonoxidative glucose disposal [37]. However, insulin-induced suppression of endogenous glucose production, reflecting hepatic insulin sensitivity, was only marginally affected by 60 h of fasting [37]. Furthermore, one exercise session increased mitochondrial fatty acid oxidation and reverses starvation-induced insulin resistance [38]. However, other investigators observed that after a 3-day fast, intramyocellular lipid content was increased over prefasting levels in subjects who did not exercise, but did not accumulate in those who did moderate-intensity exercise. However, exercise did not change the concentration of free fatty acid or insulin sensitivity [39].

Protein Metabolism

The postabsorptive and initial fasting periods are characterized by the release into the blood stream of amino acids derived from the breakdown of muscle tissue. These amino acids are used for protein synthesis or endogenous glucose production. About 1.75 g of muscle protein must be broken down to produce 1 g of glucose [40–43]. The carbon skeletons of the amino acids are substrates for gluconeogenesis and/or enter the citric acid cycle. The greater amount of nitrogenous waste, urea, uric acid (urate), creatinine, ammonium (NH_4^+) manifests as increased urinary nitrogen excretion. With the enhanced proteolysis, plasma concentrations of branched-chain amino acids (leucine, isoleucine, valine) are increased. However, as the fasting continues past its initial few days, nitrogen excretion decreases as the body begins to utilize stored fat to produce energy. Some have ascribed this decreased nitrogen excretion to also being due to the total body reduction in metabolic rate [41]. This protein sparing phenomenon can continue for much time, during which adipose tissue becomes the main source of energy substrate. The greater the adipose tissue stores the longer the time that the organism can survive. The etiology for this decreased proteolysis is unclear and has been ascribed to the reduced T3 concentrations and increased growth hormone concentrations which stimulate lipolysis [42].

Nitrogen balance is always negative during starvation due to the lack of protein and amino acid intake. During the initial 1–3 weeks of starvation there is significant excretion of nitrogen occasioned by accelerated proteolysis of skeletal muscle (myofibrillar protein). This accelerated protein catabolism subsides thereafter, as evidenced by the pattern of 3-methylhistidine (an index of myofibrillar proteolysis) excretion. The excretion of 3-methylhistidine increases after 2–3 days of starvation and decreases substantially by the third week. The amino acids released by proteolysis are utilized as gluconeogenic substrates by the liver (alanine) and kidney (glutamine). The decline in proteolysis is accompanied by an increase in lipid oxidation, enhanced ketone production, increased use of glycerol as a gluconeogenic substrate and the reduced demand for glucose by various tissues such as the brain. The rate of protein catabolism remains low until the supply of lipid substrates is exhausted at which point protein catabolism again increases. This resumption of high levels of proteolysis is associated with impending death.

The triggers for proteolysis are unclear but might include decreased insulin levels along with increased cortisol and glucagon concentrations, but not growth hormone [4]. Furthermore, the mechanisms of proteolysis in myocytes are thought to be a combination of autophagic (lysosomal) and ubiquitin-proteasomic protein breakdown, although their relative contributions are still unclear [4]. However, in many other tissues (except, the brain), lysosomal proteolysis pathways are stimulated during fasting [43]. It appears that short-term starvation activates macroautophagy, a nonselective mechanism, while as

starvation progresses there is a switch to chaperone-mediated autophagy, which is more selective in identifying cellular components for degradation.

Macroautophagy involves the formation of vesicles called autophagosomes that incorporate many types of cytoplasmic materials. These autophagosomes then fuse with lysosomes where the material is degraded. The trigger for autophagy is the dissociation of the ULK1 (Unc-51-like kinase-1; an autophagy related [atg] gene)—mTORC1 (mammalian target of rapamycin complex-1) complex which is promoted by adenosine monophosphate-activated protein kinase (AMPK) [44]. The latter in turn is activated by increased cytosolic AMP (a sign of energy depletion) or amino acid depletion. ULK1 then phosphorylates Beclin 1 complex (Beclin-1 bound to class III phosphoinositide 3-kinase (PI3K;Vps34)) giving rise to autophagosome membranes that engulf proteins, organelles, and other cytosolic material (lipids, nucleosides) to form vesicles that fuse with lysosomes (called autolysosomes). Lysosomal enzymes then metabolize this material which is subsequently released into the cytosol as amino acids, fatty acids, and ribose-phosphate. The latter can be converted to glucose via the nonoxidative pentose phosphate pathway.

Chaperone-mediated autophagy increases the selectivity of the autophagy-lysosomal pathway since proteins with the exposed peptide sequence KFERQ (sequences biochemically related to Lys–Phe–Glu–Arg–Gln) are selectively broken down. This sequence targets cytosolic proteins, such as ribonuclease A, for lysosomal degradation. The targeted protein is initially recognized by heat shock cognate 70 kDa (hsc70). Multiple co-chaperones (e.g., heat shock protein-90) interact with the protein–chaperone complex which attaches to its receptor, lysosome-associated membrane protein 2 (LAMP2), on the lysosomal membrane. The substrate proteins then translocate across the lysosomal membrane of lysosomes containing hsc-70. During starvation the number of hsc-70 rich lysosomes may double, facilitating chaperone-mediated autophagy. Among the proteins degraded are those involved with glycolysis; an enzyme pathway not particularly active during starvation [45].

The ubiquitin-proteasome system is another proteolytic mechanism active during starvation. Proteins are tagged for degradation with a 76 amino acid protein called ubiquitin. This reaction is catalyzed by a group of enzymes: ubiquitin-activating enzymes, ubiquitin-conjugating enzymes, and ubiquitin ligases. A protein tagged with an ubiquitin molecule is a target for other ligases to attach additional ubiquitin molecules. The resulting polyubiquitin chain is bound by a cytosolic 26S proteasome which then cleaves the chain via a threonine-dependent nucleophilic attack to very short peptide fragments. These fragments are then further cleaved to individual amino acids.

Hepatic protein synthesis is also affected by starvation. After a 3-day fast the albumin concentration significantly increased, while the concentration of retinal binding protein fell by 16 %, unrelated to changes in hydration state [46]. During short-term (3 days) fasting the overall protein synthetic rate decreases as much as 13 %, although overall protein turnover is increased [4, 47]. However, with a 5 % weight loss after 6 days of starvation in lean individuals, whole body protein oxidation increased while the fractional synthetic rates of specific hepatic export proteins increased (high-density lipoprotein apolipoprotein A1, retinol binding protein, α1-antitrypsin). However, the plasma concentrations of binding proteins, such as retinol, retinol binding protein, and transthyretin were decreased [48]. Four days of starvation produced marked reductions (approximately 30 %) in the circulating concentrations of retinol binding protein and prealbumin, but did not significantly affect the plasma concentration of immunoglobulins (Igs) G, A, M or other proteins (orosomucoid, haptoglobin, alpha(1) antitrypsin), albumin, and total protein [49]. In ten healthy volunteers starved for 4.5 days, daily measurements showed a rapid reduction in plasma fibronectin, no alteration in either C3 or plasma transferrin and, at the end of the starvation period, an elevated serum albumin [50]. Proteomic analysis of murine small intestines revealed that during the first 12 h of starvation there was a decline in proteins associated with energy production and glycolysis, while after 24 h substances related to protein synthesis

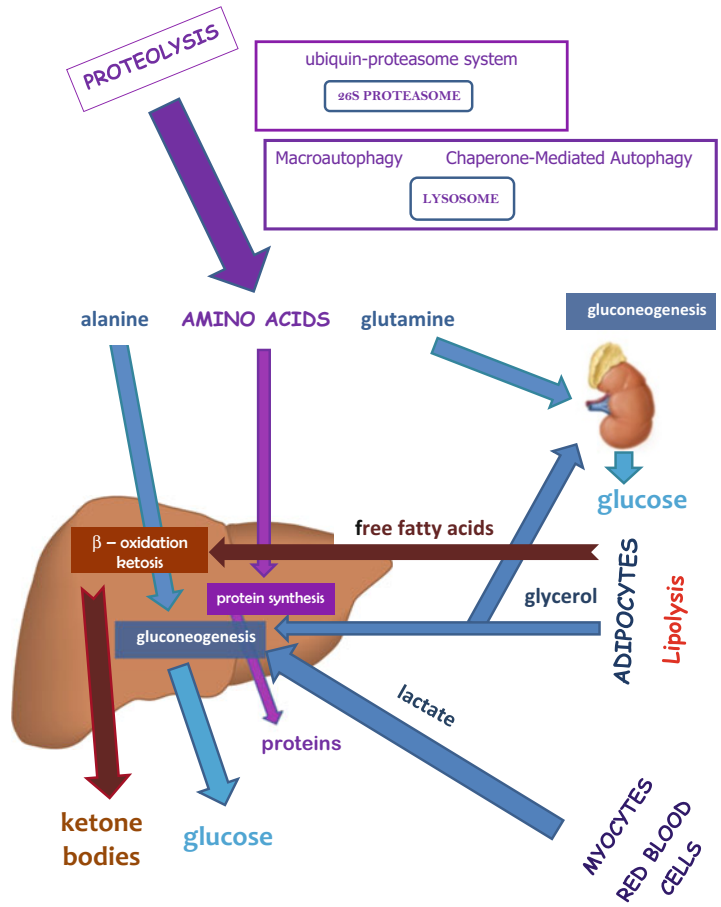

Fig. 4.4 The adaptive response to starvation—Gluconeogenesis uses glycerol from fat stores, amino acids from muscles, and lactate from red blood cells and muscle activity to produce glucose. Lipolysis of adipose tissue triglycerides releases free fatty acids for β-oxidation and ketone body formation. Endogenous glucose production via gluconeogensis occurs in the kidney and liver. Hepatic protein synthesis occurs, but at a reduced rate

and amino acids were decreased. Additionally, after 24 h extracellular enzymes that reduce oxidative stress were increased [51].

Starvation also affects bone formation with increased urinary calcium and phosphorous excretion, increased serum calcium concentrations and decreased concentrations of serum osteocalcin and procollagen carboxyl-terminal propeptide. The former indicate enhanced bone resorption while the latter two substances are markers of bone formation. Fasting-induced metabolic acidosis appears to play an important role in bone resorption [52].

Energy Expenditure

Among the adaptive responses to starvation (Fig. 4.4) is a decrease in total body energy expenditure, attributed to reduced basal energy expenditure and decreased physical activity. However, at the onset of fasting resting energy expenditure increased significantly from day 1 to day 3 associated with more than a doubling of norepinephrine concentrations from day 1 to day 4 [53]. Epinephrine concentrations did not increase concomitantly, leading to the conclusion that the increased norepinephrine was due to sympathetic nervous system stimulation. As the dearth of caloric and nutrient intake continues, the resting energy expenditure has been reported by most, but not all, investigators to decrease [54]. This decreased energy expenditure is accompanied by diminished catecholamine and thyroid hormone stimulation [55]. The decrease in basal energy expenditure is greater than can be accounted for by changes in body weight or composition. This reduction in basal energy expenditure increases metabolic efficiency thus reducing the rate of tissue depletion [56]. In addition, total daily energy expenditure is also decreased because of reduced activity and exercise on the part of the weakened starving individual.

Furthermore, starvation can effect thermoregulation as demonstrated by a reduced thermoregulatory response to a cooling stimulus in normal weight young females after 48 h of starvation [57].

As starvation progresses there is continuous loss of lean body mass, along with decreases in both basal energy expenditure and protein oxidation. Lean subjects, who have less lean body mass than obese subjects, maintain higher daily nitrogen excretion in absolute terms, in relation to weight loss and in relation to energy expenditure. Moreover, in lean subjects the contribution of protein oxidation to basal energy expenditure does not decrease as starvation progresses (up to 45 weeks) while in obese individuals it decreases reaching values more than twofold lower than observed in lean subjects [58]. Therefore, pre-starvation conditions play an important role in the energy expenditure response to starvation.

Hydration

Starvation due to the lack of ingestion of nutrients should be differentiated from dehydration, the lack of water ingestion. Death from the lack of any food or water intake occurs with a week to ten days depending on the rate of external water loss, e.g., sweating, and the body's intrinsic water supply. The continuum of dehydration is characterized by headaches, orthostatic hypotension, decreased resting blood pressure, reduced or no urine output, delirium, unconsciousness and, eventually, death. In studies of starvation, subjects are routinely provided with oral or intravenous solutions containing water and electrolytes to prevent dehydration and electrolyte disturbances. Hunger strikers are generally provided with such solutions and in prolonged starvation also with vitamins to prevent vitamin deficiencies.

Weight Loss

Total cessation of nutrient intake results in substantial weight loss. Early in fasting weight loss is rapid, averaging 0.9 kg/day during the first week due to negative water and sodium balance. The losses slow to about 0.3 kg/day by the third week [59]. During a 10-day fast a 54-year-old male lost 0.25 kg/day [60], while hunger strikers had lost 18 % of their pre-fast body weight by days 28–35 [61]. Some of the weight loss during the initial period of fasting is due to loss of water in association with glycogenolysis [16]. With a 5 % weight loss secondary to starvation the fraction of fat-free mass to total weight loss was 46 % indicating much loss of muscle tissue. In obese individuals subject to total starvation, weight loss was biphasic, with more rapid losses observed during the first 14 days followed by slower more linear losses from day 15 to days 30. Over the first 14 days males lost significantly more weight (8 %) than females (7 %) [62].

Hormonal Changes

Starvation is accompanied by substantial changes in the hormonal milieu that helps the organism to adapt its metabolism to reduced nutrient intake. Plasma concentrations of thyroid hormones are decreased; glucagon, catecholamine, and growth hormone concentrations increase [63]. There are increases in serum cortisol and urinary free cortisol concentrations, but without changes in adrenocorticotropic hormone (ACTH) levels. There are substantial reductions in serum testosterone concentrations as the result of alternations in the pulsatility of luteinizing hormone (LH) secretion likely mediated by reduced hypothalamic GnRH pulses. This situation appears related to the decrease in leptin concentrations [64]. Among premenopausal women amenorrhea occurs while fertility is reduced in males.

Short-term fasting results in a drop in thyroid-stimulating hormone (TSH) pulse amplitude, a decrease in serum T3 levels with an increase in rT3, a reduced TSH response to thyrotropin-releasing hormone (TRH) and little change in thyroid-binding globulin (TBG). T4 concentrations are unchanged due to its longer half-life. It has been proposed that the decreased T3 and thyroid receptor protein concentrations are involved in the reduced energy expenditure during fasting. As starvation continues, TBG

concentrations begin to decrease so that after a 10-day fast free-T4 levels were still normal [60, 64].

Adipose tissue is an endocrine organ that secrets cytokines and unique substances dubbed adipocytokines or adipokines which have both metabolic and immunological effects. After 72 h of fasting, leptin (a satiety factor that regulates body weight by appetite suppression and stimulation of energy expenditure) decreased by 21 % of baseline values [65–69]. Alternately, the concentration of adiponectin (enhances insulin sensitivity, reduces energy expenditure and negatively regulates hematopoiesis) is increased. It has been hypothesized that adiponectin ("the starvation gene") evolved to help organisms survive malnutrition [70]. The serum concentrations of the adipokines vaspin (an endogenous insulin sensitizer) and visfatin (which has insulin-mimetic effects) were unchanged after 72 h of fasting [68].

Growth hormone is secreted by the somatotropic cells of the anterior pituitary gland and its secretion is enhanced by hypothalamic growth hormone releasing hormone (GHRH) and stomach-derived ghrelin. Secretion is reduced by somatostatin and circulating concentrations of IGF-1. Growth hormone secretion is increased after 24-h of fasting, with both free and total growth hormone concentrations increasing since there is little change in growth hormone binding protein [66]. There is some tissue level resistance to growth hormone's effects associated with reduced IGF-1 concentrations. The reduced IGF-1 effects are due to both reduced IGF-1 production and increased IGF-specific binding protein concentrations thus reducing the amount of circulating IGF-1 [42]. This situation appears to reduce the anabolic effects of IGF-1, while permitting the lipolytic effects of growth hormone. By stimulating lipolysis growth hormone preserves muscle tissue by reducing the need for proteolysis to supply gluconeogenic substrate. During fasting, circulating ghrelin has been reported to be increased by some, but not all, investigators [42]. Ghrelin secretion is likely increased due to the increased adrenergic stimulation [67].

The central control of energy balance involves the complex interaction of a variety of substances and neuronal centers including alpha melanocyte-stimulating hormone (α-MSH—an anorexigenic substance) and its antagonism at the melanocortin-4 receptor by agouti related protein (AgRP—an orexigenic, or appetite stimulating substance that increases food intake and decreases energy expenditure in times of negative energy balance). During a 6-day fast in lean subjects, coincident with a decrease in plasma leptin concentrations, there was increased AgRP, but no change in α-MSH. This increase in AgRP, along with increased neuropeptide-Y (another orexigenic substance), appears to inhibit the thyroid axis at the level of the pituitary gland [71].

Another substance active during starvation is FGF21 (fibroblast growth factor 21), whose plasma concentrations are increased after a 7-day fast [72]. It is secreted by the liver, pancreas, and white adipose tissue [73]. In the liver, FGF21 stimulates metabolic changes characteristic of fasting including gluconeogenesis, fatty acid oxidation, and ketogenesis, but does not stimulate glycogenolysis [73].

Prolonged Starvation: Metabolic Consequences

Starvation for over 30 days is considered long-term starvation, with serious complications and death occurring from the 40th day. Although, such prolonged starvation is a rare event, hunger strikes have provided information on the metabolic and other effects of such extended food deprivation. Among Northern Ireland hunger strikers death occurred between days 57–73 and after the loss of 40–50 % of body weight [74]. A male subject who had fasted for 44 days was found to have lost 25 % of his weight, 24 % of his fat-free body mass (20 % of total body protein) and 33 % of his fat mass [75, 76]. To survive for over a month requires the oral ingestion and/or intravenous infusion of water, electrolytes, and vitamins. The most common cause of death in these extreme cases of starvation is myocardial infarction, pneumonia, or organ failure. It occurs almost inevitably when the body mass index reaches about 12.5 kg/m^2. Obese individuals can survive longer than the 60–70 day survival times

seen in lean individuals. Survivals of 200–300 days have been seen in obese individuals ascribed to their greater fat stores and thus lower need to derive energy from protein [77, 78].

Protein Metabolism

During prolonged fasting, hormonal and metabolic changes reduce protein and muscle breakdown so that protein catabolism produces only about 10 % of total energy. Muscle and other tissues use ketone bodies and fatty acids as their main energy source. Therefore, the human brain derives energy from fat stores, permitting survival in starving normal weight persons for up to 2 to 2.5 months. After 44 days of starvation, a 30-year-old subject had normal plasma glucose, cholesterol, and triacyl-glycerol, but substantially elevated free fatty acid and 3-hydroxybutyrate concentrations [75]. Only 13–17 % of total energy expenditure was from protein oxidation [76]. Once fat stores are depleted, catastrophic protein catabolism of all organs, including the heart, develops leading to death [78].

Medical problems that develop during long-term starvation include dehydration leading to shock, renal failure and stroke; hypoglycemia; metabolic disturbances causing arrhythmias; vitamin deficiencies resulting in Wernicke-Korsakoff syndrome, confusion; dizziness; peptic ulcers and nephrolithiasis. Myocardial dysfunction can occur due to significant changes in myocardial muscle structure as well as function, leading to pulmonary edema formation. Close medical monitoring is recommended after a 10 % weight loss in lean healthy individuals. Serious medical problems begin at a loss of approximately 18–20 % from initial body weight.

Vitamin Deficiencies

Neurological problems are encountered and they are often secondary to vitamin deficiencies. For example, thiamine (vitamin B_1) deficiency (beriberi—distal motor and sensory neuropathy plus heart failure) occurs when fasting is accompanied by the exclusive intake of sugar and liquids [79]. Of 25 hunger strikers admitted to hospital after more than 153 days of fasting, one third had ophthalmoparesis (paresis of the lateral rectus muscle), about half had some form of paresis, and a quarter had truncal ataxia. At discharge, 16 % had persistent ophthalmoparesis and 36 % had nystagmus. Only four patients (16 %) could walk independently [80]. In half the patients nystagmus and ataxia had not resolved after 1 year.

Semistarvation

Most surgical patients are not in a state of total starvation, but in a semistarved state attributed to very low caloric intake, intermittent intake or both. The classical intravenous fluid containing 5 % dextrose (3.4 kcal/g) infused at rates of 1–3 L/day (50–150 g/day) has mild protein sparing effects as evidenced by lower nitrogen excretion. The provision of at least 100 g/day of glucose also prevents the appearance of ketones. Furthermore, many patients eat only intermittently or inadequately so that they are in a perpetual semistarved state.

Metabolic and Hormonal Changes

Many of the metabolic and hormonal changes observed during total starvation are also seen during semistarvation. However, the magnitude of these changes is smaller and depends on the caloric intake and its composition. Studies performed with very low caloric intakes (450 kcal/day for 16 weeks) in obese patients showed that in adipocytes there was decreased expression of genes encoding leptin, adiponectin, de novo lipogenesis and rate-limiting enzymes for fatty acid β-oxidation and carnitine palmitoyltransferase 1B. This pattern reflects increased adipocyte fatty acid oxidation [81]. Furthermore, genes associated with protein synthesis were downregulated [81]. The 1950 Minnesota semistarvation study of Keys and colleagues [82] demonstrated that normal lean subjects who had lost 25 % of their body weight over 24 weeks and had little measureable fat remaining (i.e., <5 % of body weight) were catabolizing substantial amounts of their lean mass.

Other studies which examined serum concentrations of proteins, fatty acids, hematologic parameters, liver function tests, electrolytes, and vitamins showed little or no change from pre-semistarvation levels [82]. However, despite these normal results, T3 declined significantly while the changes in T4 and T4/TBG were smaller but demonstrated statistically significant declines that paralleled the changes in T3. TSH was elevated over baseline through most of the course. Cortisol concentrations increased significantly and testosterone declined to levels well below the normal range for men. A large rise in sex hormone binding globulin (SHBG) to outside of the normal male range paralleled similar changes in TBG. This increase in SHBG further reduced bioavailable testosterone to 10 % of pre-semistarvation levels. LH also decreased significantly. Similarly, among female victims of famine, menstrual irregularities were observed secondary to impaired gonadotropin secretion [83].

Substrate Metabolism

A computational model used a simulated semistarvation diet averaging 1,100 kcal/day of carbohydrates, 290 kcal/day of fat, and 195 kcal/day of protein for 24 weeks. After the first week of this diet, the simulated carbohydrate oxidation dropped by 35 % and accounted for ~42 % of the total energy expenditure [84]. The simulated protein oxidation decreased by 12 % after the first week of semistarvation and remained suppressed, while the simulated fat oxidation increased by 12 % during the initial days of semistarvation due to enhanced lipolysis associated with the reduced carbohydrate intake. After a week of semistarvation, fat oxidation was 46 % of the total energy expenditure. This led to a negative fat balance of more than 1,000 kcal/day that slowly became less negative as the semistarvation progressed and body fat was catabolized. At the end of the semistarvation period, all three macronutrient oxidation rates were roughly equal to their respective dietary intakes [84].

Both the total caloric intake and composition of the semistarvation diet are important in determining the composition of tissue loss. After a 5 % weight loss, the fraction of fat-free mass to total weight loss was 30 % and 18 % for a very low calorie diet (600 kcal/day) and low calorie diet (1,200 kcal/day), respectively, indicating that slower weight loss with a higher caloric intake results in greater loss of fat than muscle [74]. Meta-regression analysis of patients on weight loss diets showed that higher protein intakes (>1.05 g/kg) reduce the loss of lean body mass [85]. This conclusion was confirmed on subsequent studies, which also showed higher concentrations of the anabolic substance IGF-1 with higher protein intakes [86, 87].

The reduction in the basal metabolic rate during semistarvation is highly associated with the loss of body fat [56].

Long-Term Consequences of Semistarvation

Semistarvation can have especially detrimental long-term effects. Early gestation appeared to be the most vulnerable period. People who were conceived during famine were at increased risk of schizophrenia and depression, they had a more atherogenic plasma lipid profile, were more responsive to stress and had double the rate of coronary heart disease. They also performed worse on cognitive tasks which may be a sign of accelerated aging. People exposed during any period of semistarvation during gestation had more type 2 diabetes [88].

Marasmus

Chronic malnutrition caused by deficient and insufficient dietary intakes result in major changes in body composition and homeostasis. Any form of illness in such patients is frequently life threatening because of altered metabolism, lack of glycogen and adipose tissue reserves and immune deficiency. Marasmus is derived from the Greek marasmos, which means withering or wasting. Marasmus is one of the three forms of serious chronic protein-energy malnutrition (PEM). The other two forms are kwashiorkor and marasmic-kwashiorkor. Marasmus involves insufficient intake

of both protein and calories and is characterized by emaciation whereas kwashiorkor is due to protein deficiency, resulting in an edematous appearance [2]. Marasmic-kwashiorkor indicates the often encountered difficulty in separating these entities and indicates that features of both marasmus and kwashiorkor are present. These forms of serious PEM represent a group of pathologic conditions that occur mainly in young children from developing countries. They are classically observed around time of weaning from their mother's milk. The reasons why a nutritional deficit progresses to marasmus rather than kwashiorkor are unclear and cannot be solely explained by the composition of the deficient diet (i.e., a diet deficient in energy for marasmus and a diet deficient in protein for kwashiorkor). The study of these entities is considerably limited by the lack of appropriate animal models.

Body Composition in Marasmus

Marasmus results from negative energy balance secondary to a decreased energy intake, loss of ingested calories (via. emesis and diarrhea), increased energy expenditure (due to. infections burns), or combinations of these factors. Marasmatic individuals display adaptive energy conserving behavior by reducing physical activity and growth. The basal energy metabolism is associated with lethargy which also conserves energy. In patients with marasmus, body mass is significantly reduced and fat stores can decline to as low as 5 % of total body weight [89]. The proportion of total body water content increases as the magnitude of the protein-energy malnutrition (marasmus or kwashiorkor) increases and is associated with loss of fat mass, which is poor in water. Protein mass can decrease as much as 30 % in the most serious forms of marasmus. Marasmus malnutrition does not substantially change concentrations of albumin but levels of transport proteins with very short half-lives, such as prealbumin, transferrin, or transcortin, are reduced. Muscle fibers are thin and lose their striations. Muscle cells are atrophic and muscle tissue is infiltrated with fat and fibrous tissue. The brain, skeleton, and kidney are preserved, whereas the liver, heart, pancreas, and digestive tract are the first to be affected. The loss of fat and muscle mass can be evaluated by measuring arm circumference and triceps skinfold thickness.

Minerals and Vitamins

Potassium deficits can reach 15 mEq/kg and can contribute to hypotonia, apathy, and impaired cardiac function. Plasma sodium concentrations are generally within the normal range, but they can also be reduced. Deficits in calcium, phosphorus, and magnesium stores are also observed. Iron deficiency anemia is usually seen in marasmus. Zinc, selenium, and magnesium are more often deficient in kwashiorkor but can also be deficient in marasmus.

Kwashiorkor

Kwashiorkor occurs when there is insufficient dietary protein. It generally occurs in very poor countries often during droughts, other natural disasters, or political unrest. The symptoms of kwashiorkor include edema, changes in skin pigmentation, protuberant abdomen, dermatitis, decreased muscle mass and texture, vulnerability to infections due to dysfunctional immunity, lethargy and irritability. Hepatomegaly may be present.

Carbohydrate Metabolism

Blood glucose concentrations are regulated by the fine balance between gluconeogenesis and glucose clearance. In kwashiorkor, an inability to maintain sufficient gluconeogenic glucose production can result in hypoglycemia. Glucose clearance rates correlated with plasma albumin concentrations in both marasmus and kwashiorkor. The reduced glucose clearance in both conditions appears related to impaired insulin availability as demonstrated by impaired insulin responses to a glucose load. Among the potential mechanisms of disturbed insulin secretion in these two conditions is pancreatic dysfunction [90, 91]. Pancreatic atrophy and fibrosis, as well as fatty infiltration have been consistent autopsy features in kwashiorkor [92, 93]. Pancreatic β-cells are vulnerable to

oxidative stress which is increased in kwashiorkor) and might explain the pancreatic changes [94–97]. However, there was no indication of peripheral or hepatic insulin resistance. Another cause of the hypoglycemia in kwashiorkor is impaired glucose absorption possibly related to intestinal villous atrophy [98, 99]. Lower disaccharidase activity was found in kwashiorkor compared with marasmus [100–102]. Another possible factor contributing to impaired glucose absorption could be decreased expression of the sodium-dependent hexose transporter or the glucose transporter 2, which transports glucose across the luminal membranes. A third cause of reduced glucose absorption could be a decreased gut motility and consumption of carbohydrates by small bowel bacterial overgrowth [103].

Lipid Metabolism

Lipolysis is elevated in kwashiorkor more than in marasmus while both lipolysis and fatty acid oxidation are less efficient in kwashiorkor [104]. The latter was demonstrated by slower palmitate oxidation. Additionally, there is reduced concentration of plasma carnitine in kwashiorkor which might be part of the reason there is slower fatty acid oxidation.

Protein Metabolism

Unlike marasmus, kwashiorkor is characterized by low serum albumin concentrations and slow protein breakdown and turnover. For example there is slower methionine production in kwashiorkor than marasmus because of a slower rate of release from protein breakdown [105, 106]. This slower protein breakdown in kwashiorkor might be among the reason for poorer survival in these patients [105, 106].

Anorexia Nervosa

Anorexia nervosa is an eating disorder where people lose more weight than is healthy for their age and height. It is far more common in females than males. Those suffering from this disorder may greatly fear weight gain, even when underweight. They may diet excessively, taking in only a few hundred calories a day or just water (Restricting Type), or eat and then purge, either by vomiting or taking laxatives (Binge/Purging Type). This chapter will focus on the restricting type.

Hormonal Responses

The hormonal responses observed with anorexia nervosa are similar to those seen in starved and semistarved individuals. However, in anorexia these responses may continue for years at varying intensities resulting in major changes in body composition and homeostasis even during periods of reasonable caloric and nutrient intake. Surgeons may encounter patients during these various phases. Anorectics suffer from bone loss and thus are particularly vulnerable to fractures. Low bone density is a consequence of hormonal alterations including hypoestrogenism, hypoleptinemia, hypercortisolism, and decreased IGF-1 levels [107].

Anorexia nervosa is characterized by hypothalamic–pituitary–adrenal axis hyperactivity as evidenced by increased corticotrophin releasing hormone secretion [108]. This leads to increased free plasma, salivary, urinary cortisol concentrations, and 24-h mean plasma concentrations. Circadian rhythms are normal although nocturnal spikes can occur [109]. The elevated cortisol levels are ascribed to prolonged cortisol half-life along with decreased metabolic clearance while cortisol production was normal. Studies of untreated anorexia nervosa patients showed reduced cortisol suppression after dexamethasone suppression test. Underweight anorexics showed low CSF ACTH levels but plasma ACTH levels were normal. Anorexia nervosa is characterized by adrenal sympathetic overactivity and neural sympathetic underactivity as demonstrated by a predominance of circulating epinephrine over norepinephrine levels [110]. Markedly increased subcutaneous abdominal adipose tissue norepinephrine concentrations in anorectics compared to control subjects, reflect increased sympathetic nervous system activity [111, 112]. However, not all studies have reached similar conclusions, with some actually reporting reduced sympathetic activity. Growth hormone concentrations are increased but due to relative hepatic resistance insulin-like growth

factor-1 levels are reduced. Thyroid-function studies show a "sick-euthyroid" pattern with normal TSH, low to normal total and free T4 and low T3. There is increased conversion of T4 to reverse T3. Additionally there is hypogonadotropic hypogonadism. LH, FSH and estradiol concentrations are significantly lower in anorexia nervosa than in controls, while SHBG concentrations are increased [113, 114]. This constellation leads to amenorrhea in female anorectics [115].

Adipokines are also affected by anorexia nervosa with circulating adiponectin levels inversely related to body mass index (BMI) [116]. When adiponectin isoforms were examined there were decreases in the percentage of high molecular weight and increases in the percentage of low molecular weight isoforms that correlated with BMI [116]. Serum leptin concentrations are severely decreased while serum soluble leptin receptor levels were increased [116]. This receptor increase might be a protective mechanism that decreases free leptin bioavailability thus facilitating energy conservation [116]. Mean serum resistin concentrations were significantly lower in anorexics as compared to controls, in some but not all studies. Furthermore, serum visfatin concentrations, a peptide regulating adipocyte differentiation, were decreased in anorectics [113].

Some evidence points to anorexia patients being in a state of inflammation. In one study of anorectic patients there was increased TNF-α and IL-6 mRNA expression while another study found plasma TNF-α to be significantly higher in patients than controls [117, 118]. Both TNF-R55 and TNF-R75 (receptors) were higher in those suffering with anorexia for longer than a year as compared to controls and patients with shorter disease duration [117]. However, increased TNF and IL-1 activity was not seen in all studies [119]. Concentrations of IL-1β, s-TNF-α-R-I & -II and sIL-1β-RA in plasma did not differ significantly in patients with anorexia nervosa compared with control subjects [120]. Serum IL-6 was higher in anorexic women in comparison with a control group. Serum sIL-6R (soluble IL-6 receptor) was lower and serum sgp130 (an inhibitor of the IL-6 trans-signaling pathway) was higher anorexics in comparison with controls [121]. This constellation appears directed at inhibiting IL-6 action [121].

Carbohydrate Metabolism

In chronic anorectic starvation regulation of substrates depends mainly on decreased serum insulin concentrations and increased growth hormone secretion [122]. These low plasma insulin levels are the result of greater insulin clearance rather than depressed insulin secretion [123]. Following an overnight fast, anorexics maintained normal fasting plasma glucose concentrations which were not related to body weight or BMI thus demonstrating that endogenous glucose production remains a priority providing glucose to the central nervous system [124]. Since anorectics consume some carbohydrates they do not generally develop ketosis. The role of glucagon seems to be of minor importance in this situation. Impaired recovery of plasma glucose after insulin-induced hypoglycemia in anorexia nervosa is primarily attributable to impaired pancreatic glucagon (α-cell) secretory capability [125]. Moreover, pancreatic β-cell dysfunction as evidenced by reduced insulin secretion was seen following glucagon administration to anorectic patients [126].

Insulin-stimulated glucose disposal is normal in anorexia nervosa patients, a finding that contrasts with previously reported increases in erythrocyte insulin receptors [127]. Other studies agree with the latter one by revealing that insulin-stimulated glucose disposal and nonoxidative glucose metabolism were significantly reduced in anorexia nervosa. Nonoxidative glucose metabolism reflects skeletal muscle storage of glucose as glycogen as evidenced by lower glycogen concentrations in muscles of anorectic patients. Therefore, in anorexia nervosa the nonoxidative pathway of glucose metabolism is resistant to the action of insulin (i.e., insulin stimulates glucose oxidation more than glucose storage); a situation similar to that commonly observed during prolonged starvation [128]. Furthermore, insulin sensitivity is not systemically increased and glucose effectiveness is unchanged in anorectic women when compared to normal weight controls [123].

Lipid Metabolism

Anorexia nervosa is characterized by the marked loss of adipose tissue. Therefore, it is not surprising that these individuals have increased lipolysis as evidenced by an inverse linear relationship between the rate of glycerol production and weight after an overnight fast [124]. Interestingly, concentrations of serum free fatty acid are either not or only mildly elevated in anorexia nervosa [129]. Furthermore, during exercise, but not at rest, there was a local increase in both adipose tissue norepinephrine and glycerol concentrations in anorectic patients in comparison to controls, indicating accelerated lipolysis [112].

Anorexia nervosa patients display a complex membrane fatty acid profile without characteristics of nutritional essential free fatty acid deficiency, but with a deficiency in long chain polyunsaturated fatty acids [130]. The phospholipid profile showed significantly lower (n-6) and (n-3) elongation and desaturation products with elevated short-chain saturated, short-chain monounsaturated, branched-chain and odd-chain fatty acids. This latter pattern indicates enhanced biosynthesis of alternative fatty acids that only partially compensate for the loss of polyunsaturated fatty acids in providing membrane "fluidity" [131]. The most consistent finding in the fatty acid pattern is decreased content of linoleic acid and increased content of palmitoleic acid in all lipid classes. The alteration in plasma lipids and lipoproteins in anorexia nervosa are the result of complex mechanisms including decreased catabolism of triglyceride-rich lipoproteins, normal rate of cholesterol synthesis and increased resorption of exogenous cholesterol [132]. Mean serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, apolipoprotein (apo)-A1, B, C2, C3, E, and cholesterol ester transfer protein (CETP) activity were significantly higher in anorexic compared to controls [133]. The elevated cholesterol concentrations in anorexia are generally attributed to increased LDL-cholesterol secondary to the severe loss of body fat, changes in thyroid hormones, increased lipolysis, and decreased endogenous cholesterol synthesis with resultant decrease in LDL removal. CETP activity increases cholesterol turnover as an adaptation to its low intake thus maintaining elevated cholesterol concentrations. In severe anorexia this mechanism can fail resulting in the fall of cholesterol concentrations [134].

Energy Expenditure

In patients with anorexia nervosa metabolic rate slows, with resting energy expenditures decreasing to as low as 50–70 % of predicted values [135, 136]. The low resting energy expenditure (REE) is attributed to the loss of lean body mass and to some extent the effects of reduced thyroid hormones and leptin. Schebendach et al. [137] studied 21 anorexic adolescents and found that mean measured resting energy expenditures were 62 ± 18 % of that predicted by the Harris–Benedict equation. The authors proposed a corrective formula for predicting resting energy expenditures in anorexia nervosa for use when indirect calorimetry is not available [137]. Marra et al. [138] performed indirect calorimetry on 237 females with anorexia nervosa and confirmed that both the Harris–Benedict equation and the World Health Organization equations overestimate REE in patients with anorexia nervosa. The Schebendach correction accurately predicted measured REE in the adolescents, but not in the adults, in a follow-up prospective study of 50 patients with anorexia nervosa.

The Elderly: Cachexia and Sarcopenia

Weight loss, often coinciding with frailty, is commonly observed in the elderly. It is frequently preceded by sarcopenia—the involuntary loss of skeletal muscle mass and, consequently, loss of strength—which occurs even in "successfully" aging adults [139]. In fact, after the age of 50 years, individuals lose muscle mass at the rate of about 1–2 % per year; with losses of 40 % not uncommon in octogenarians. Sarcopenia is associated with dynapenia—the loss of muscle strength secondary to reduced neural activation and reduced contractility quality [140]. The cause of sarcopenia is unknown, but might be due to a

combination of decreased physical activity; loss of spinal motor neurons; reduced endogenous growth hormone; estrogen and androgen production; insufficient protein intake; and a chronic low-grade inflammatory response (i.e., increased cytokines IL-1, TNF and IL-6 [141]). Sarcopenia is aggravated by a complex interaction of several factors among them aging, disuse, immobilization, disease, and malnutrition. Another possible mechanism is an insufficient synthetic response to protein ingestion possibly due to reduced production and/or reduced responses to the anabolic effects of anabolic hormones such as androgens, growth hormone (GH) and IGF-1. The concentrations of these anabolic hormones decrease progressively during aging. Transcriptomic studies showed older males (63–79 years) to be less responsive to anabolic stimuli and more responsive to catabolic conditions (i.e., greater proteolysis with a low protein diet) than younger males (21–43 years) [142]. The elderly have reduced numbers and sizes of type II muscle fibers apparently due to skeletal myocyte apoptosis [143]. Type I fibers are spared. When compared to tissue from young individuals the mitochondrial respiration of muscle fibers from elderly individuals was reduced 41 %. This reduction was associated with a 30 % decline in cytochrome c oxidase activity and 50 % reductions in the levels of the metabolic regulators, SIRT3 (silent mating-type information regulator number 3) and PGC-1α. (peroxisome proliferation-activated receptor gamma coactivator 1-α) Some, but not all, studies found reduced ATP concentrations in aging muscle [144]. These observations suggest that aging is associated with impaired skeletal muscle mitochondrial function [145]. Resistance or endurance exercise regimens may improve both muscle mass and function. Paradoxically, caloric restriction might reduce the development of sarcopenia.

The elderly not only lose muscle mass but many also lose weight. Age-related reduction in energy intake is a physiologic effect of healthy aging. However, harmful anorectic effects can intervene—the anorexia of aging is a physiologic decrease in food intake which gradually results in weight loss accompanied by age-related changes in body composition. Reduced food intake can be caused by appetite loss attributed to reduced caloric requirements or because of more rapid and stronger satiety signals. Early satiation is often due to a decrease in adaptive relaxation of the stomach fundus resulting in early antral filling. Increased concentrations and effectiveness of cholecystokinin may play a role. The central feeding drive (opioid and the neuropeptide Y effects) appears to decline with age. Physical factors such as poor dentition, ill-fitting dentures, or age-associated changes in taste and smell may influence food choice and limit the type and quantity of food eaten by older people [145].

The frailty syndrome is defined as unintentional weight and muscle loss accompanied by exhaustion along with declines in grip strength, gait speed, and activity [146]. Frail individuals can rapidly progress to a disabled state when another stressor such as surgery or illness ensues. This situation frequently causes a domino effect that increases mortality [146]. The cause of frailty is thought to be an imbalance between inflammatory and anti-inflammatory networks, resulting in a low-grade chronic pro-inflammatory status, dubbed, "inflamm-aging." This pro-inflammatory state is linked to immunosenescence. Genotype also plays a role, with centenarians having a high level of anti-inflammatory cytokines together with a protective genotype [147]. Poor nutritional status has been implicated in the development and progression of chronic diseases affecting the elderly. This situation, plus chronic illnesses and such problems such as impaired muscle function, decreased bone mass, immune dysfunction, anemia, reduced cognitive function and poor wound healing, delayed recovery from surgery and ultimately increased morbidity and mortality.

The Refeeding Syndrome

Refeeding syndrome describes the biochemical changes, clinical signs and symptoms and complications that can occur secondary to feeding a malnourished and often catabolic individual. This syndrome can cause serious harm and even death [148]. Initial descriptions of the syndrome were from malnourished prisoners-of-war who

developed cardiac and neurological symptoms soon after they resumed eating [149, 150]. Because of the potential for significant morbidity and mortality, healthcare professionals need to be aware of its possible appearance and effects among at-risk populations. The syndrome's presentation ranges from simple nausea, vomiting, and lethargy to respiratory insufficiency, cardiac failure, hypotension, arrhythmias, delirium, coma, and death. Peripheral edema and fluid overload leading to pulmonary edema can also occur [151]. Clinical deterioration may occur rapidly if the cause is not established and appropriate measures not instituted.

Refeeding a starved individual rapidly decreases gluconeogenesis and anaerobic metabolism mediated by a rapid rise in serum insulin concentrations [152, 153]. The elevated insulin stimulates the intracellular movement of extracellular potassium, phosphate, and magnesium. During prolonged starvation, intracellular stores of some minerals become severely depleted while their serum concentrations often remain normal. The latter is due to the contraction of the intracellular compartment during starvation along with reduction in the renal excretion of sodium and water. This can potentially lead to expansion of the extracellular compartment resulting in the possibility for fluid overload. Because of the depleted intracellular stores there is a large extra-intracellular concentration gradient resulting in a rapid decline in the extracellular concentrations of these ions [154, 155]. To maintain osmotic neutrality sodium and water are retained [156]. Reactivation of carbohydrate-dependent metabolic pathways increases the demand for thiamine which can become rapidly deficient if not replaced [157, 158]. Phosphate, magnesium, potassium, and thiamine deficiencies occur to varying degrees and have different effects in different patients [159]. Some individuals, such as chronic alcohol abusers or those suffering from long-term starvation are extremely vulnerable to the consequences of electrolyte and vitamin deficiencies [160–166]. Therefore it might be prudent to slowly increasing glucose intake to allow sufficient opportunity to replace serum electrolyte deficiencies. Furthermore, excessive fluid intake is to be avoided to prevent further reductions in phosphate, magnesium and potassium concentrations and increasing the intravascular fluid load.

Hypophosphatemia is among the markers used to diagnose the refeeding syndrome, although low serum phosphate is not pathognomonic [167]. A prospective study of 62 intensive care unit patients refed after 48 h of starvation found that 21 (34 %) experienced hypophosphatemia associated with low prealbumin concentrations [151]. Low serum albumin concentration may be an important predictor of hypophosphatemia [151]. Another study of 106 refed patients with histologically confirmed cancer, noted an incidence of hypophosphatemia of 25 % [168].

The optimum timing for correcting the biochemical and fluid abnormalities during refeeding has been the source of debate. Some investigators advocate correcting electrolyte abnormalities before beginning the refeeding. This approach has been revised and recent National Institute of Health and Clinical Excellence Guidelines in the United Kingdom recommend that careful refeeding and correction of electrolyte abnormalities can occur simultaneously without deleterious effects. There are no randomized trial data to support either approach.

Conclusions

Starvation is characterized by a series of adaptive responses aimed at preserving an organism's body mass and ultimately its survival. This adaptation contrasts with the obligate hypermetabolic, catabolic, and auto-cannibalistic state observed during stressful situations such as trauma, burns, sepsis, and surgery. In such situations adaptive responses such as ketone body formation do not occur, leading to the need for continuous high rates of gluconeogenesis and proteolysis. Therefore, caring for and feeding such patients differ from that of a starved patient and must take into consideration the underlying metabolic conditions that are not able to utilize exogenous nutrients in a "normal" fashion.

References

1. González-Vélez V, Dupont G, Gil A, González A, Quesada I. Model for glucagon secretion by pancreatic α-cells. PLoS ONE. 2012;7:e32282.
2. Allister EM, Robson-Doucette CA, Prentice KJ, Hardy AB, Sultan S, Gaisano HY, Kong D, Gilon P, Herrera PL, Lowell BB, Wheeler MB. UCP2 regulates the glucagon response to fasting and starvation. Diabetes. 2013;62:1623–33.
3. Meyer C, Stumvoll M, Dostou J, Welle S, Haymond M, Gerich J. Renal substrate exchange and gluconeogenesis in normal postabsorptive humans. Am J Physiol Endocrinol Metab. 2002;282:E428–34.
4. Sakharova AA, Horowitz JF, Surya S, Goldenberg N, Harber MP, Symons K, Barkan A. Role of growth hormone in regulating lipolysis, proteolysis, and hepatic glucose production during fasting. J Clin Endocrinol Metab. 2008;93:2755–9.
5. Tsintzas K, Jewell K, Kamran M, Laithwaite D, Boonsong T, Littlewood J, Macdonald I, Bennett A. Differential regulation of metabolic genes in skeletal muscle during starvation and refeeding in humans. J Physiol. 2006;575(1):291–303.
6. Soeters MR, Sauerwein HP, Dubbelhuis PF, Groener JE, Ackermans MT, Fliers E, Aerts JM, Serlie MJ. Muscle adaptation to short-term fasting in healthy lean humans. J Clin Endocrinol Metab. 2008;93:2900–3.
7. Chan JL, Mietus JE, Raciti PM, Goldberger AL, Mantzoros CS. Short-term fasting-induced autonomic activation and changes in catecholamine levels are not mediated by changes in leptin levels in healthy humans. Clin Endocrinol (Oxf). 2007; 66:49–57.
8. Petersen KF, Price T, Cline GW, Rothman DL, Shulman GI. Contribution of net hepatic glycogenolysis to glucose production during the early postprandial period. Am J Physiol. 1996;270(1 Pt 1): E186–91.
9. Browning JD, Baxter J, Santhosh S, Burgess SC. The effects of short-term fasting on liver and skeletal muscle lipid, glucose and energy metabolism in healthy women and men. J Lipid Res. 2012;53: 577–86.
10. Robles-Flores M, Allende G, Pinat E, Garcia-Sainz JA. Cross-talk between glucagon- and adenosine-mediated signalling systems in rat hepatocytes: effects on cyclic AMP-phosphodiesterase activity. Biochem J. 1995;312:763–7.
11. Liu Y, Dentin R, Chen D, Hedrick S, Ravnskjaer K, Schenk S, Milne J, Meyers DJ, Cole P, Yates 3rd J, Olefsky J, Guarente L, Montminy M. A fasting inducible switch modulates gluconeogenesis via activator/coactivator exchange. Nature. 2008;456: 269–723.
12. Dentin R, Liu Y, Koo SH, Hedrick S, Vargas T, Heredia J, Yates 3rd J, Montminy M. Insulin modulates gluconeogenesis by inhibition of the coactivator TORC2. Nature. 2007;449:366–9.
13. Jitrapakdee S. Transcription factors and coactivators controlling nutrient and hormonal regulation of hepatic gluconeogenesis. Int J Biochem Cell Biol. 2012;44:33–45.
14. Landau BR, Wahren J, Chandramouli V, Schumann WC, Ekberg K, Kalhan SC. Contributions of gluconeogenesis to glucose production in the fasted state. J Clin Invest. 1996;98:378–85.
15. Marsenic O. Glucose control by the kidney: an emerging target in diabetes. Am J Kidney Dis. 2009;53:875–83.
16. Soeters MR, Soeters PB, Schooneman MG, Houten SM, Romijin JA. Adaptive reciprocity of lipid and glucose metabolism in human short-term starvation. Am J Physiol Endocrinol Metab. 2012;303: E1397–407.
17. Stumvoll M, Meyer C, Perriello G, Kreider M, Welle S, Gerich J. Human kidney and liver gluconeogenesis: evidence for organ substrate selectivity. Am J Physiol. 1998;274:E817–26.
18. Cahill GF. Fuel metabolism in starvation. Annu Rev Nutr. 2006;26:1–22.
19. Bergman BC, Cornier MA, Horton TJ, Bessesen DH. Effects of fasting on insulin action and glucose kinetics in lean and obese men and women. Am J Physiol Endocrinol Metab. 2007;293:E1103–11.
20. Clore JN, Glickman PS, Helm ST, Nestler JE, Blackard WG. Accelerated decline in hepatic glucose production during fasting in normal women compared with men. Metabolism. 1989;38: 1103–7.
21. Jeong JY, Jeung NH, Park KG, Lee IK. Transcriptional regulation of pyruvate dehydrogenase kinase. Diabetes Metab J. 2012;36:328–35.
22. Young SG, Zechner R. Biochemistry and pathophysiology of intravascular and intracellular lipolysis. Genes Dev. 2013;27:459–84.
23. Horton TJ, Hill JO. Prolonged fasting significantly changes nutrient oxidation and glucose tolerance after a normal mixed meal. J Appl Physiol. 2001; 90:155–63.
24. Elia M, Lammert O, Zed C, Neale G. Energy metabolism during exercise in normal subjects undergoing total starvation. Hum Nutr Clin Nutr. 1984;38: 355–62.
25. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest. 2004;113:1582–8.
26. Gjedsted J, Gormsen LC, Nielsen S, Schmitz O, Djuhuus CB, Keiding S, Orskov H, Tonesen E, Moller N. Effects of a 3-day fast on regional lipid and glucose metabolism in human skeletal muscle and adipose tissue. Acta Physiol. 2007;191:205–16.
27. Jensen MD, Chandramouli V, Schumann WC, Ekberg K, Previs SF, Gupta S, Landau BR. Sources of blood glycerol during fasting. Am J Physiol Endocrinol Metab. 2001;281:E998–1004.

28. Bouwens M, Afman LA, Müller M. Fasting induces changes in peripheral blood mononuclear cell gene expression profiles related to increases in fatty acid beta-oxidation: functional role of peroxisome proliferator activated receptor alpha in human peripheral blood mononuclear cells. Am J Clin Nutr. 2007; 86:1515–23.
29. Krug S, Kastenmüller G, Stückler F, Rist MJ, Skurk T, Sailer M, Raffler J, Römisch-Margl W, Adamski J, Prehn C, Frank T, Engel KH, Hofmann T, Luy B, Zimmermann R, Moritz F, Schmitt-Kopplin P, Krumsiek J, Kremer W, Huber F, Oeh U, Theis FJ, Szymczak W, Hauner H, Suhre K, Daniel H. The dynamic range of the human metabolome revealed by challenges. FASEB J. 2012;26:2607–19.
30. Indiveri C, Iacobazzi V, Tonazzi A, Giangregorio N, Infantino V, Convertini P, Console L, Palmieri F. The mitochondrial carnitine/acylcarnitine carrier: function, structure and physiopathology. Mol Aspects Med. 2011;32:223–33.
31. Hasselbalch SG, Knudsen GM, Jakobsen J, Hageman LP, Holm S, Paulson OB. Blood-brain barrier permeability of glucose and ketone bodies during short-term starvation in humans. Am J Physiol Endocrinol Metab. 1995;268:E1161–6.
32. Owen OE, Smalley KJ, D'Alessio DA, Mozzoli MA, Dawson EK. Protein, fat, and carbohydrate requirements during starvation: anaplerosis and cataplerosis. Am J Clin Nutr. 1998;68:12–34.
33. Markel A, Brook JG, Aviram M. Increased plasma triglycerides, cholesterol and apolipoprotein E during prolonged fasting in normal subjects. Postgrad Med J. 1985;61:395–400.
34. Sävendahl L, Underwood LE. Fasting increases serum total cholesterol, LDL cholesterol and apolipoprotein B in healthy, nonobese humans. J Nutr. 1999;129:2005–8.
35. Fainaru M, Schafer Z. Effect of prolonged fasting on plasma lipids, lipoproteins and apolipoprotein B in 12 physicians participating in a hunger strike: an observational study. Isr Med Assoc J. 2000; 2:215–9.
36. Göschke H. Mechanism of glucose intolerance during fasting: differences between lean and obese subjects. Metabolism. 1977;26:1147–53.
37. Hoeks J, van Herpen NA, Mensink M, Moonen-Kornips E, van Beurden D, Hesselink MK, Schrauwen P. Prolonged fasting identifies skeletal muscle mitochondrial dysfunction as consequence rather than cause of human insulin resistance. Diabetes. 2010;59:2117–25.
38. Frank P, Katz A, Andersson E, Sahlin K. Acute exercise reverses starvation-mediated insulin resistance in humans. Am J Physiol Endocrinol Metab. 2013;15(304):E436–43.
39. Green JG, Johnson NA, Sachinwalla T, Cunningham CW, Thompson MW, Stannard SR. Moderate-intensity endurance exercise prevents short-term starvation-induced intramyocellular lipid accumulation but not insulin resistance. Metabolism. 2011;60: 1051–7.
40. Awad S, Consantin-Teodosiu D, Macdonald IA, Lobo DN. Short-term starvation and mitochondrial dysfunction – a possible mechanism leading to postoperative insulin resistance. Clin Nutr. 2009; 28:497–509.
41. Henry CJ, Rivers JP, Payne PR. Protein and energy metabolism in starvation reconsidered. Eur J Clin Nutr. 1988;42:543–9.
42. Norrelund H. The metabolic role of growth hormone in humans with particular reference to fasting. Growth Horm IGR Res. 2005;15:95–122.
43. Dice JF, Finn PF. Proteolytic and lipolytic responses to starvation. Nutrition. 2006;22:830–44.
44. Rabinowitz JD, White E. Autophagy and metabolism. Science. 2010;330:1344–8.
45. Bejarano E, Cuervo AM. Chaperone-medicated autophagy. Proc Am Thorac Soc. 2010;7:29–39.
46. Broom J, Fraser MH, McKenzie K, Miller JD, Fleck A. The protein metabolic response to short-term starvation in man. Clin Nutr. 1986;5:63–5.
47. Elia M, Stubbs RJ, Henry CJ. Differences in fat, carbohydrate, and protein metabolism between lean and obese subjects undergoing total starvation. Obes Res. 1999;7:597–604.
48. Afolabi PR, Jahoor F, Jackson AA, Stubbs J, Johnstone AM, Faber P, Lobley G, Gibney E, Elia M. The effect of total starvation and very low energy diet in lean men on kinetics of whole body protein and five hepatic secretory proteins. Am J Physiol Endocrinol Metab. 2007;293:E1580–9.
49. Elia M, Martin S, Price C, Hallworth MJ, Neale G. Effect of starvation and elective surgery on hand dynamometry and circulating concentration of various proteins. Clin Nutr. 1984;2:173–9.
50. Chadwick SJ, Sim AJ, Dudley HA. Changes in plasma fibronectin during acute nutritional deprivation in healthy human subjects. Br J Nutr. 1986; 55:7–12.
51. Cottingham K. Proteomics of starvation. J Proteome Res. 2006;5:2075.
52. Grinspoon SK, Baum HBA, Kim V, Coggiins C, Kilbansmi A. Decreased bone formation and increased mineral dissolution during acute fasting in young women. J Clin Endocrinol Metab. 1995; 80:3628–33.
53. Zauner C, Schneeweiss B, Kranz A, Madl C, Ratheiser K, Kramer L, Roth E, Schneider B, Lenz K. Resting energy expenditure in short-term starvation is increased as a result of an increase in serum norepinephrine. Am J Clin Nutr. 2000;71: 1511–5.
54. Leibel RL, Rosenbaum M, Hirsch JH. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332:621–8.
55. Silva JE, Bianco SD. Thyroid-adrenergic interactions: physiological and clinical implications. Thyroid. 2008;18:157–65.

56. Dulloo AG, Jacquet J. Adaptive reduction in basal metabolic rate in response to food deprivation in humans: a role for feedback signals from fat stores. Am J Clin Nutr. 1998;68:599–606.
57. Mansell PI, Macdonald IA. Effects of underfeeding and of starvation on thermoregulatory responses to cooling in women. Clin Sci (Lond). 1989;77: 245–52.
58. Elia M. Effect of starvation and very low calorie diets on protein-energy interrelationships in lean and obese subjects lean and obese subjects. http://www.unu.edu/unupress/food2/UID07E/UID07E11.HTM (accessed May 13, 2013).
59. Kerndt PR, Naughton JL, Driscoll CE, Loxterkamp DA. Fasting: the history, pathophysiology and complications. West J Med. 1982;137:379–99.
60. Heusser P, Wolf U, Vonwiller HM, Messerli N, Laederach-Hofmann. Nutrition with 'light and water'? In strict isolation for 10 days without food - a critical case study. Forsch Komplementmed. 2008;15:203–9.
61. Frommel D, Gautier M, Questiaux E, Schwarzenberg L. Voluntary total fasting: a challenge for the medical community. Lancet. 1984;1(8392):1451–2.
62. Runcie J, Hilditch TE. Energy provision, tissue utilization, and weight loss in prolonged starvation. Br Med J. 1974;2:352–6.
63. Wassif WS, McLoughlin DM, Vincent RP, Conroy S, Russell GF, Taylor NF. Steroid metabolism and excretion in severe anorexia nervosa: effects of refeeding. Am J Clin Nutr. 2011;93:911–7.
64. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest. 2003;111:1409–21.
65. Komaki G, Tamai H, Mori T, Nakagawa T, Mori S. Changes in serum angiotensin-converting enzyme in acutely starved non-obese patients. A possible dissociation between angiotensin-converting enzyme and the thyroid state. Acta Endocrinol (Copenh). 1988;118:45–50.
66. Salgin B, Marcovecchio ML, Hill N, Dunger DB, Frystyk J. The effects of prolonged fasting on levels of growth hormone-binding protein and free growth hormone. Growth Horm IGR Res. 2012;22: 76–81.
67. Goldstein JL, Zhao T-j, Li RL. Surviving starvation: essential role of the ghrelin-growth hormone axis. Cold Spring Harb Symp Quant Biol. 2011;76: 121–7.
68. Kang ES, Magkos F, Sienkiewicz E, Mantzoros CS. Circulating vaspin and visfatin are not affected by acute or chronic energy deficiency or leptin administration in humans. Eur J Endocrinol. 2011; 164:911–7.
69. Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul. 2009;43:157–68.
70. Behre CJ. Adiponectin: saving the starved and the overfed. Med Hypotheses. 2007;69:1290–2.
71. Sainsbury A, Zhang L. Role of the hypothalamus in the neuroendocrine regulation of body weight and composition during energy deficit. Obes Rev. 2012;13:234–57.
72. Galman C, Lundasen T, Kharitonenkov A, et al. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARalpha. activation in man. Cell Metab. 2008;8:169–74.
73. Kliewer SA, Mangelsdorf DJ. Fibroblast growth factor 21: from pharmacology to physiology. Am J Clin Nutr. 2010;91:254S–7.
74. Johnstone AM. Fasting - the ultimate diet? Obes Rev. 2007;8:211–22.
75. Korbonits M, Blaine D, Elia M, Powell-Tuck J. Metabolic and hormonal changes during the refeeding period of prolonged fasting. Eur J Endocrinol. 2007;157:157–66.
76. Jackson JM, Blaine D, Powell-Tuck J, Korbonits M, Carey A, Elia M. Macro- and micronutrient losses and nutritional status resulting from 44 days of total fasting in a non-obese man. Nutrition. 2006;22: 889–97.
77. Elia M. Effect of starvation and very low calorie diets on protein-energy interrelationships in lean and obese subjects. In: Scrimshaw N, Schurch B, editors. Protein-energy interactions. International Dietary Energy Consultancy Group, Proceedings of an IDECG workshop. Lausanne: Nestle Foundation; 1991. p. 249–84.
78. Chalela JA, Lopez JI. Medical management of hunger strikers. Nutr Clin Pract. 2013;28:128–35.
79. Gétaz L, Rieder JP, Nyffenegger L, Eytan A, Gaspoz JM, Wolff H. Hunger strike among detainees: guidance for good medical practice. Swiss Med Wkly. 2012;142:w13675.
80. Kirbas D, Sutlas N, Kuscu DY, Karagoz N, Tecer O, Altun U. The impact of prolonged hunger strike: clinical and laboratory aspects of twenty-five hunger strikers. Ideggyogy Sz. 2008;61:317–24.
81. Franck N, Gummesson A, Jernås M, Glad C, Svensson PA, Guillot G, Rudemo M, Nyström FH, Carlsson LM, Olsson B. Identification of adipocyte genes regulated by caloric intake. J Clin Endocrinol Metab. 2011;96:E413–8.
82. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. Minneapolis, MN: University of Minnesota Press; 1950.
83. Elias SG, van Noord PA, Peeters PH, den Tonkelaar I, Kaaks R, Grobbee DE. Menstruation during and after caloric restriction: the 1944-1945 Dutch famine. Fertil Steril. 2007;88(4 Suppl):1101–10.
84. Hall KD. Computational model of in vivo human energy metabolism during semistarvation and refeeding. Am J Physiol Endocrinol Metab. 2006; 291:E23–37.
85. Kreiger JW, Sitren HS, Daniels MJ, Langkemp-Henken B. Effects of variation in protein and

carbohydrate intake on body mass and composition during energy restriction: a meta regression. Am J Clin Nutr. 2006;83:260–74.
86. Bopp MJ, Houston DK, Lenchik L, Easter L, Kritchevsky SB, Nicklas BJ. Lean mass loss is associated with low protein intake during dietary-induced weight loss in postmenopausal women. J Am Diet Assoc. 2008;108:1216–20.
87. Sukumar D, Ambia-Sobhan H, Zurfluh R, Schlussel Y, Stahl TJ, Gordon CL, Shapses SA. Areal and volumetric bone mineral density and geometry at two levels of protein intake during caloric restriction: a randomized, controlled trial. J Bone Miner Res. 2011;26:1339–48.
88. Roseboom TJ, Painter RC, van Abeelen AF, Veenendaal MV, de Rooij SR. Hungry in the womb: what are the consequences? Lessons from the Dutch famine. Maturitas. 2011;70:141–5.
89. Buchanan N, Moodley G, Eyberg C, Bloom SR, Hansen JD. Hypoglycemia associated with severe kwashiorkor. S Afr Med J. 1976;50:1442–6.
90. Becker DJ, Pimstone BL, Hansen JD, et al. Patterns of insulin response to glucose in protein- calorie malmutrition. Am J Clin Nutr. 1972;25:499–505.
91. Das BK, Ramesh J, Agarwal JK, et al. Blood sugar and serum insulin response in protein-energy malnutrition. J Trop Pediatr. 1998;44:139–41.
92. Brooks SE, Golden MH. The exocrine pancreas in kwashiorkor and marasmus. Light and electron microscopy. West Indian Med J. 1992;41:56–60.
93. Campbell JA. The morbid anatomy of infantile malnutrition in Cape Town. Arch Dis Child. 1956; 31:310–3104.
94. Golden MH, Ramadath D. Free radicals in pathogenesis of kwashiorkor. Proc Nutr Soc. 1987;46: 53–68.
95. Manary MJ, Leeuwenburgh C, Heinecke JW. Increased oxidative stress in kwashiorkor. J Pediatr. 2000;137:421–4.
96. Fechner A, Bohme C, Gromer S, et al. Antioxidant status and nitric oxide in the malnutrition syndrome kwashiorkor. Pediatr Res. 2001;49:237–43.
97. Tiedge M, Lortz S, Drinkgern J, et al. Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin- producing cells. Diabetes. 1997;46:1733–42.
98. Robert HJ, Geert TH, et al. Impaired glucose absorption in children with severe malnutrition. J Pediatr. 2011;158:282–7.
99. Stanfield JP, Hutt MS, Tunnicliffe R. Intestinal biopsy in kwashiorkor. Lancet. 1965;2:519–23.
100. Sullivan PB, Marsh MN, Mirkian R, Hill SM, Milla PJ, Neale G. Chronic diarrhea and malnutrition-histology of the small intestinal lesion. J Pediatr Gastroenterol Nutr. 1991;12:195–203.
101. James WP. Jejunal disaccharidase activities in children with marasmus and kwashiorkor. Response to treatment. Arch Dis Child. 1971;46:218–20.
102. James WP. Intestinal absorption in protein-calorie malnutrition. Lancet. 1968;1:333–5.
103. Gracey M, SuharjonoSunotoStone DE. Microbial contamination of the gut: another feature of malnutrition. Am J Clin Nutr. 1973;26:1170–4.
104. Badaloo AV, Forrester T, Reid M, Jahorr F. Lipid kinetic differences between children with kwashiorkor and those with marasmus. Am J Clin Nutr. 2006;83:1283–8.
105. Jahoor F, Badaloo A, Reid M, Forrester T. Protein kinetic differences between children with edematous and nonedematous severe childhood undernutrition in the fed and postabsorptive states. Am J Clin Nutr. 2005;82:792–800.
106. Jahoor F, Badaloo A, Reid M, Forrester T. Sulfur amino acid metabolism in children with severe childhood undernutrition: methionine kinetics. Am J Clin Nutr. 2006;84:1400–5.
107. Fernández-Soto ML, González-Jiménez A, Chamorro-Fernández M, Leyva-Martínez S. Clinical and hormonal variables related to bone mass loss in anorexia nervosa patients. Vitam Horm. 2013;92:259–69.
108. Amitani H, Asakawa A, Ogiso K, Nakahara T, Ushikai M, Haruta I, Koyama K, Amitani M, Cheng KC, Inui A. The role of adiponectin multimers in anorexia nervosa. Nutrition. 2013;29:203–6.
109. Boyar RM, Hellman LD, Roffwarg H, Katz J, Zumoff B, O'Connor J, Bradlow HL, Fukushima DK. Cortisol secretion and metabolism in anorexia nervosa. N Engl J Med. 1977;296:190–3.
110. Lechin F, van der Dijs B, Pardey-Maldonado B, Rivera JE, Baez S, Lechin ME. Anorexia nervosa depends on adrenal sympathetic hyperactivity: opposite neuroautonomic profile of hyperinsulinism syndrome. Diabetes Metab Syndr Obes. 2010;3: 311–7.
111. Nedvídková J, Dostálová I, Barták V, Papezov H, Pacák K. Increased subcutaneous abdominal tissue norepinephrine levels in patients with anorexia nervosa: an in vivo microdialysis study. Physiol Res. 2004;53:409–13.
112. Bartak V, Vybiral S, Papezova H, Dostalova I, Pacak K, Nedvidkova J. Basal and exercise-induced sympathetic nervous activity and lipolysis in adipose tissue of patients with anorexia nervosa. Eur J Clin Invest. 2004;34:371–7.
113. Ziora K, Oświęcimska J, Swiętochowska E, Ziora D, Stojewska M, Suwała A, Ostrowska Z, Gorczyca P, Klimacka-Nawrot E, Lukas W, Błońska-Fajfrowska B. Assessment of serum visfatin levels in girls with anorexia nervosa. Clin Endocrinol (Oxf). 2012; 76:514–9.
114. Estour B, Germain N, Diconne E, Frere D, Cottet-Emard JM, Carrot G, Lang F, Galusca B. Hormonal profile heterogeneity and short-term physical risk in restrictive anorexia nervosa. J Clin Endocrinol Metab. 2010;95:2203–10.
115. Tomasik PJ, Sztefko K, Starzyk J, Rogatko I, Szafran Z. Entero-insular axis in children with anorexia nervosa. Psychoneuroendocrinology. 2005;30:364–72.
116. Housova J, Anderlova K, Krizová J, Haluzikova D, Kremen J, Kumstyrová T, Papezová H, Haluzik

M. Serum adiponectin and resistin concentrations in patients with restrictive and binge/purge form of anorexia nervosa and bulimia nervosa. J Clin Endocrinol Metab. 2005;90:1366–70.
117. Agnello E, Malfi G, Costantino AM, Massarenti P, Pugliese M, Fortunati N, Catalano MG, Palmo A. Tumour necrosis factor alpha and oxidative stress as maintaining factors in the evolution of anorexia nervosa. Eat Weight Disord. 2012;17:e194–9.
118. Kahl KG, Kruse N, Rieckmann P, Schmidt MH. Cytokine mRNA expression patterns in the disease course of female adolescents with anorexia nervosa. Psychoneuroendocrinology. 2004;29:13–20.
119. Shimizu T, Satoh Y, Kaneko N, Suzuki M, Lee T, Tanaka K, Iijima M, Yamashiro Y. Factors involved in the regulation of plasma leptin levels in children and adolescents with anorexia nervosa. Pediatr Int. 2005;47:154–8.
120. Brambilla F, Monti D, Franceschi C. Plasma concentrations of interleukin-1-beta, interleukin-6 and tumor necrosis factor-alpha, and of their soluble receptors and receptor antagonist in anorexia nervosa. Psychiatry Res. 2001;103(2–3):107–14.
121. Karczewska-Kupczewska M, Adamska A, Nikołajuk A, Otziomek E, Górska M, Kowalska I, Strączkowski M. Circulating interleukin 6 and soluble forms of its receptors in relation to resting energy expenditure in women with anorexia nervosa. Clin Endocrinol (Oxf). 2013;79(6):812–6.
122. Blickle JF, Reville P, Stephan F, Meyer P, Demangeat C, Sapin R. The role of insulin, glucagon and growth hormone in the regulation of plasma glucose and free fatty acid levels in anorexia nervosa. Horm Metab Res. 1984;16:336–40.
123. Letiexhe MR, Scheen AJ, Lefèbvre PJ. Plasma leptin levels, insulin secretion, clearance and action on glucose metabolism in anorexia nervosa. Eat Weight Disord. 1997;2:79–86.
124. Swenne I, Gustafsson J. Endogenous glucose production and lipolysis in anorexia nervosa–a study using stable isotope-labelled compounds. Acta Paediatr. 2004;93:1446–8.
125. Fujii S, Tamai H, Kumai M, Takaichi Y, Nakagawa T, Aoki TT. Impaired glucagon secretion to insulin-induced hypoglycemia in anorexia nervosa. Acta Endocrinol (Copenh). 1989;120:610–5.
126. Kobayashi N, Tamai H, Takii M, Matsubayashi S, Nakagawa T. Pancreatic B-cell functioning after intravenous glucagon administration in anorexia nervosa. Acta Psychiatr Scand. 1992;85:6–10.
127. Castillo M, Scheen A, Lefebvre PJ, Luyckx AS. Insulin-stimulated glucose disposal is not increased in anorexia nervosa. J Clin Endocrinol Metab. 1985;60:311–4.
128. Pannacciulli N, Vettor R, Milan G, Granzotto M, Catucci A, Federspil G, De Giacomo P, Giorgino R, De Pergola GJ. Anorexia nervosa is characterized by increased adiponectin plasma levels and reduced nonoxidative glucose metabolism. Clin Endocrinol Metab. 2003;88:1748–52.
129. Ohwada R, Hotta M, Oikawa S, Takano K. Etiology of hypercholesterolemia in patients with anorexia nervosa. Int J Eat Disord. 2006;39:598–601.
130. Caspar-Bauguil S, Montastier E, Galinon F, Frisch-Benarous D, Salvayre R, Ritz P. Anorexia nervosa patients display a deficit in membrane long chain poly-unsaturated fatty acids. Clin Nutr. 2012;31:386–90.
131. Holman RT, Adams CE, Nelson RA, Grater SJ, Jaskiewicz JA, Johnson SB, Erdman Jr JW. Patients with anorexia nervosa demonstrate deficiencies of selected essential fatty acids, compensatory changes in nonessential fatty acids and decreased fluidity of plasma lipids. J Nutr. 1995;125:901–7.
132. Zák A, Vecka M, Tvrzická E, Hrubý M, Novák F, Papezová H, Lubanda H, Veselá L, Stanková B. Composition of plasma fatty acids and non-cholesterol sterols in anorexia nervosa. Physiol Res. 2005;54:443–51.
133. Matzkin VB, Geissler C, Coniglio R, Selles J, Bello M. Cholesterol concentrations in patients with Anorexia Nervosa and in healthy controls. Int J Psychiatr Nurs Res. 2006;11:1283–93.
134. Rigaud D, Tallonneau I, Vergès B. Hypercholesterolaemia in anorexia nervosa: frequency and changes during refeeding. Diabetes Metab. 2009;35:57–63.
135. Schebendach J, Golden NH, Jacobson MS, Arden M, Pettei M, Hardoff D, Bauman N, Reichert P, Copperman N, Hertz S. Indirect calorimetry in the nutritional management of eating disorders. Int J Eat Disord. 1995;17:59–66.
136. Vaisman N, Rossi MF, Goldberg E, Dibden LJ, Wykes LJ, Pencharz PB. Energy expenditure and body composition in patients with anorexia nervosa. J Pediatr. 1988;113:919–24.
137. Schebendach JE, Golden NH, Jacobson MS, Hertz S, Shenker IR. The metabolic responses to starvation and refeeding in adolescents with anorexia nervosa. Ann NY Acad Sci. 1997;817:110–9.
138. Marra M, Polito A, De Filippo E, Cuzzolaro M, Ciarapica D, Contaldo F, Scalfi L. Are the general equations to predict BMR applicable to patients with anorexia nervosa? Eat Weight Disord. 2002;7:53–9.
139. Ronenn R. The pathophysiology of wasting in the elderly. J Nutr. 1999;129:256S–9.
140. Clark BC, Manini TC. Functional consequences of sarcopenia and dynapenia in the elderly. Curr Opin Clin Nutr Metab Care. 2010;13:271–6.
141. Bautmans I, Van Puyvelde K, Mets T. Sarcopenia and functional decline: pathophysiology, prevention and therapy. Acta Clin Belg. 2009;64:303–16.
142. Thalacker-Mercer AE, Fleet JC, Craig BA, Campbell WW. The skeletal muscle transcript profile reflects accommodative responses to inadequate protein intake in younger and older males. J Nutr Biochem. 2010;21:1076–82.
143. Marzetti E, Calvani R, Bernabei R, Leeuwenburgh C. Apoptosis in skeletal myocytes: a potential target for interventions against sarcopenia and physical frailty - a mini-review. Gerontology. 2012;58:99–106.

144. Nair KS. Aging muscle. Am J Clin Nutr. 2005; 81:953–63.
145. Joseph AM, Adhihetty PJ, Buford TW, Wohlgemuth SE, Lees HA, Nguyen LM, Aranda JM, Sandesara BD, Pahor M, Manini TM, Marzetti E, Leeuwenburgh C. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. Aging Cell. 2012;11:801–9.
146. Heuberger RA. The frailty syndrome: a comprehensive review. J Nutr Gerontol Geriatr. 2011;30: 315–68.
147. Candore G, Caruso C, Colonna-Romano G. Inflammation, genetic background and longevity. Biogerontology. 2010;11:565–73.
148. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001;17:632–7.
149. Fayeulle S, Renou F, Protais E, Hedouin V, Wartel G, Yvin JL. Management of the hunger strike in prison. Presse Méd. 2010;39(10):e217–22.
150. Hearing SD. Refeeding syndrome. BMJ. 2004; 328: 908–9.
151. Marik E, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg. 1996;131: 1043–7.
152. Ekberg KB, Landau R, Wajngot A, Chandramouli V, Efendic S, Brunengraber H, Wahren J. Contributions by kidney and liver to glucose production in the postabsorptive state and after 60 h of fasting. Diabetes. 1999;48:292–8.
153. Hill GL, Bradley JA, Bradley JA. Changes in body weight and body protein with intravenous nutrition. JPEN J Parenter Enteral Nutr. 1979;3:215–8.
154. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr. 1990;14:90–7.
155. Bloom WL. Inhibition of salt excretion by carbohydrate. Arch Int Med. 1962;109:26–32.
156. Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. N Engl J Med. 1985;312:1035–9.
157. Drenick EJ, Joven CB, Swendseid ME. Occurrence of acute Wernicke's encephalopathy during prolonged starvation for the treatment of obesity. N Engl J Med. 1966;274:937–9.
158. Cumming AD, Farquhar JR, Bouchier IAD. Refeeding hypophosphataemia in anorexia nervosa and alcoholism. BMJ. 1987;295:490–1.
159. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, Lobo DN. Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62:687–94.
160. Kohn MR, Golden NH, Shenker IR. Cardiac arrest and delirium: presentations of the refeeding syndrome in severely malnourished adolescents with anorexia nervosa. J Adolesc Health. 1998;22: 239–43.
161. Baltasar A, Del Rio J, Escrivá C, Arlandis F, Martínez R, Serra C. Preliminary results of the duodenal switch. Obes Surg. 1997;7:500–4.
162. Mason EE. Starvation injury after gastric reduction for obesity. World J Surg. 1998;22:1002–7.
163. Rudman D, Millikan WJ, Richardson TJ, Bixler 2nd TJ, Stackhouse J, McGarrity WC. Elemental balances during intravenous hyperalimentation of underweight adult subjects. J Clin Invest. 1975;55: 94–104.
164. Walike JW. Tube feeding syndrome in head and neck surgery. Arch Otolaryngol. 1969;89:533–6.
165. Holroyde CP, Myers RN, Smink RD. Metabolic response to total parenteral nutrition in cancer patients. Cancer Res. 1977;37:3109–14.
166. Meier R, Stratton RJ. Basic concepts in nutrition: epidemiology of malnutrition. Eur J Clin Nutr Metab. 2008;3:4.
167. Hise ME, Kattelmann K, Parkhurst M. Evidence-based clinical practice: dispelling the myths. Nutr Clin Prac. 2005;20:294–302.
168. Morley JE. Pathophysiology of anorexia. Clin Geriat Med. 2002;18:661–73.

Metabolism in the Trauma Patient

5

Stephanie Gordy and Rosemary A. Kozar

The Metabolic Response to Trauma

Ebb and Flow

Severe injury and illness results in a complex cascade of metabolic responses that attempt to restore physiologic homeostasis in the injured organism. Sir David Cuthbertson is credited with the original recognition of the stress response in patients that suffered limb injuries. In 1942, he identified that there are two temporal physiologic categories and termed them the "ebb" and "flow" phases. The ebb phase is initiated immediately after the traumatic insult and persists for less than 24 h. This phase is characterized by decreased body temperature, decreased oxygen consumption (VO_2), as well as decreased basal metabolic rate and glucose tolerance [1]. The intended physiologic responses are aimed at reducing posttraumatic energy depletion but this initial response is short lived.

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Thereafter, the "flow" phase ensues. This phase is characterized by a hypercatabolic condition as evidenced by increased consumption of energy and oxygen. This results in elevations of cardiac output, body temperature, glucose production, and increased total body catabolism. Furthermore, mobilization and use of substrates such as glucose, fatty acids, and amino acids increase [2]. This process peaks several days after injury and may return to baseline in a few weeks. However, if homeostasis is not achieved, multiple organ failure develops. This is perhaps a simplified version of the cellular sequence of events that ultimately leads to a cascade of complex reactions, each inciting further autocrine and paracrine reactions.

A more contemporary perspective was recently suggested by Aller and colleagues. They proposed three classifications of phenotypes related to the injury response: the ischemia/reperfusion phenotype, the leukocytic phenotype, and the angiogenic phenotype [3]. The first phenotype represents the nervous system-related alteration in response to injury. Afferent nerve signals from the site of injury result in humoral and neuronal responses and edema. This phase regulates the metabolic supply to cells by diffusion. The leukocytic phenotype is characterized as an intermediate phase of the response to trauma. In this phenotype, leukocytes and bacteria infiltrate edematous, injured tissues. The anaerobic environment results in shock and hypercatabolism and hypermetabolism which leads to the hyperdynamic response including hyperthermia, increased oxygen consumption, glycogenolysis, lipolysis,

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proteolysis, and futile substrate cycling. The third angiogenic phenotype is the late phase and is characterized by a return of oxidative metabolism with resultant angiogenesis, tissue repair and regeneration. Though, this staging system is likely a superficial representation of these innumerable complex biochemical interactions [4].

Catabolic Response to Trauma

Traumatic injury induces inflammatory and hormonal responses that change metabolic processes and alter nutrition requirements. The stress response evolves temporally as the patient moves through the ebb and flow phases and into the rehabilitative period. Although initially beneficial, the exaggerated and prolonged inflammatory, metabolic and catabolic responses induce clinical complications, delay recovery, and increase morbidity. Nevertheless, these are part of a systemic reaction that encompasses a wide range of endocrine, immunologic, and hematologic effects. Surgery initiates changes in metabolism that can affect virtually all organs and tissues. The metabolic response results in hormone-mediated mobilization of endogenous substrates that leads to stress catabolism. Hypercatabolism has been associated with severe complications related to hyperglycemia, hypoproteinemia, and immunosuppression. Proper metabolic support is essential to restore homeostasis and ensure survival [5].

During this initial catabolic stage, metabolic changes are best understood as redistribution of macronutrients from labile reserves to more active tissues for host defense, visceral protein synthesis, and heat production. Hyperglycemia is due to increased hepatic glucose production and peripheral insulin resistance in skeletal muscle. Lipid metabolism increases and results in fatty acid recycling, hypertriglyceridemia, increased lipolysis, and hepatic steatosis. Skeletal and muscle catabolism results in depletion of lean body mass, as glutamine becomes the preferred energy substrate for enterocytes. Hepatic protein synthesis shifts to production of acute phase reactants [6].

Significant basal metabolic rate elevations occur in patients with over 30 % or more of total body surface area involved. Inflammatory, hormonal, and stress signaling mechanisms drive this hypermetabolic response including elevations of circulating catecholamines, glucocorticoids, and glucagon. This subsequently results in gluconeogenesis, glycogenolysis, and protein catabolism. Insulin resistance and peripheral lipolysis increase as well [6]. Patients with major injuries that do not receive adequate nutrition can develop cumulative caloric and protein deficits leading to increased incidence of infection and organ failure. Early enteral nutrition is recommended as prospective randomized controlled trials have clearly demonstrated the positive effect of early enteral nutrition regarding infection rates, duration of hospital stay, and improved overall outcome [7].

The net effect of these pathways is the liberation of peripherally stored substrates to meet the increased energy requirements due to the stress response. The fatty acids liberated provide an energy source for cardiac and skeletal muscle as well as the liver and additional tissues. The majority of amino acids are shuttled to synthesize acute phase proteins and act as substrates for thermogenesis and tissue repair. Once the cellular homeostasis is achieved, anabolism becomes the dominant phenomenon [8]. Hypercatabolism occurring after a burn, trauma, or septic events culminates in acute protein malnutrition, ultimately resulting in multiple organ failure. Nutritional support may prevent this cascade of events from leading to MOF and death.

Neuroendocrine Response to Trauma

Part of the initial response to injury is the stimulation of the hypothalamic–pituitary–adrenal axis. Immediately following injury, a cacophony of afferent neural signals are sent to the hypothalamus and the hypothalamus subsequently signals the pituitary to release hormones. Stimulation of the adenohypophysis results in increases of adrenocorticotropic hormone (ACTH) and growth hormone (GH). The ACTH released

circulates and stimulates the adrenal glands to release cortisol. Cortisol is a catabolic hormone that mobilizes energy stores to prepare the body for the "fight-or-flight" response. The normal feedback inhibitory mechanisms fail due to stress and an unregulated, hyper-response occurs. The release of cortisol results in hyperglycemia by stimulating the liver to increase gluconeogenesis. This leads to increased blood glucose levels. Hyperglycemia is detrimental and reduces the rate of wound healing, increases the incidence of infections and may contribute to sepsis, ischemia, and death. Additionally, the rate of protein breakdown exceeds that of protein synthesis and results in the net catabolism of muscle proteins to provide substrates for gluconeogenesis. Moreover, lipolysis provides further substrates for gluconeogenesis with the breakdown of triglycerides into fatty acids and glycerol [6].

The release of growth hormone from the pituitary results in propagation of the insulin-like growth factors. Signaling via these effectors regulates catabolism by increasing protein synthesis, reducing protein catabolism, and promoting lipolysis. Similar to cortisol, GH increases blood glucose levels by stimulating glycogenolysis. The anti-insulin effects of GH amplify the hyperglycemic effects [9].

Moreover, stimulation of the neurohypophysis results in the release of vasopressin. Its antidiuretic effects are due to stimulation of the aquaporin channels into the renal tubule. These channels result in the reabsorption of water from the renal tubule back in the systemic circulation and acts to conserve hydration and blood pressure in the setting of hypotension. Additionally, pain alone can stimulate the release and effects of vasopressin [10].

Trauma patients have an impaired capacity to oxidize glucose, and glucose infusion is less effective as a means of suppressing endogenous glucose production. Moreover, trauma patients have a high rate of consumption of host tissue for gluconeogenesis and the capacity to directly oxidize glucose increases. Injured patients are heavily reliant on fat as an energy substrate with an increased rate of fatty acid oxidation. Additionally, there is a net protein loss. Furthermore, the hormonal response to trauma results in increased plasma insulin and cortisol levels. The metabolic and hormonal response collectively results in trauma patients developing hyperglycemia. Although the direct oxidation of plasma glucose to CO_2 is lower in trauma patients, Cori cycling is enhanced and the net result is an inefficient use of carbohydrate. The liver has a limited ability to suppress glucose production which can result in hyperglycemia and glycosuria. Moreover, trauma patients are additionally relatively resistant to the action of insulin [11]. These combined occurrences contribute to hyperglycemia in the injured patient.

While hyperglycemia has been associated with poor outcomes in patients with critical illness, the ideal goal glucose level is hotly debated in the critical care literature. Hyperglycemia could reflect an adaptive, beneficial response to critical illness proportionately to the severity of illness, or alternatively, it could induce complications, as in diabetes mellitus, and therefore contribute to adverse outcomes. In 2001, Van Den Berghe et al. found that maintaining a blood glucose level at or below 110 mg/dl reduces mortality amount of critically ill patients in the surgical intensive care unit [12]. Subsequent studies revealed that this strict glucose control was associated with episodic hypoglycemia, which similarly negatively affected patient outcomes [13]. The NICE-SUGAR trial found that intensive glucose control increased mortality among adults in the intensive care unit (ICU). Furthermore, this study revealed that a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81–108 mg/dl [14]. Further randomized controlled trials to assess the impact of preventing and/or treating hyperglycemia as compared with tolerating hyperglycemia in severely injured patients are necessary.

In traumatic brain-injured patients, hyperglycemia is indicative of the severity of injury. In this subset of trauma patients, the mechanism for poor outcomes is associated with the conversion to anaerobic metabolism after acute injury. This results in a buildup of brain tissue lactic acid

which leads to secondary brain injury. Findings from a retrospective study by Liu-DeRyke et al. suggested that a glucose level ≥160 mg/dl within the first 24 h of admission following traumatic brain injury is associated with poor outcomes irrespective of severity of injury [14].

Additionally, numerous other studies have corroborated that hyperglycemia is associated with poor outcomes and that tighter glucose control may improve outcomes [15–19]. Prospective trials are necessary to determine the optimal level for glucose control in traumatic brain-injured patients.

The Cytokine Response to Trauma

Multiple organ failure is the leading cause of morbidity in the ICU following trauma. Injury and stress result in a constellation of signs and symptoms known as the systemic inflammatory response syndrome (SIRS). The term "SIRS" was established to differentiate sepsis from a noninfectious, inflammatory cause [20]. SIRS was defined as two or more of the following conditions: temperature >38 °C or <36 °C, heart rate greater than 90 beats/min, respiratory rate greater than 20 breaths per minute or $paCO_2$ lesser than 32 mm Hg, or white blood cell count > 12,000 or < 4,000, or > 10 % bands. SIRS could represent the symptoms from an infectious or noninfectious source. The pattern of changes seen in plasma proinflammatory and anti-inflammatory cytokine concentrations is similar for sepsis and trauma. The remarkably similar metabolic sequelae seen in critically ill patients following the onset of severe sepsis or major trauma may constitute a universal response to the induction of the systemic inflammatory response syndrome [21]. Multiple Organ Failure (MOF) is defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention and is the culmination of septic shock and multiple end-organ failure. Effectively, MOF is the end of a continuum that ranges from SIRS to severe organ dysfunction.

The subsequent balance between the proinflammatory (SIRS) and anti-inflammatory response has been referred to as the mixed antagonistic response syndrome or MARS [22]. If the balance of these two systems is disturbed, the inflammatory response becomes systemic and deregulated. The result is whole-body activation of the inflammatory response, with resultant disruption of normal cellular metabolism and microcirculatory perfusion. Both of these responses, if unchecked, can result in complications, the former leading to MOF and the later secondary infections. At the site of injury, endothelial cells and leukocytes coordinate the local release of mediators of the inflammatory response, including cytokines interleukins, interferons, leukotrienes, prostaglandins, nitric oxide, reactive oxygen species, and products of the classic inflammation pathway. It is this functional biologic response that becomes unregulated and leads to MOF [23, 24].

Genetic factors also play a role in determining the severity and progression of organ failure. Genetic variants, particularly single-nucleotide polymorphisms (SNPs), are critical determinants for individual differences in both inflammatory responses as well as clinical outcomes in trauma patients. Individuals who possess specific genetic polymorphisms in genes controlling the synthesis of cytokines or toll-like receptors (TLR) may be predisposed to excessive inflammatory response to sepsis which increases their risk for the development of MODS. For example, toll-like receptor 9 (TLR9) signaling plays an important role in the innate immune response. Trauma patients with SNPs of TLR9 have been found to have a greater responsiveness of their peripheral blood leukocytes as well as a higher risk of sepsis and multiple organ dysfunction. These functional polymorphisms involved in innate immunity predispose patients to severe infections and death [25].

Moore and colleagues demonstrated that MOF follows a bimodal distribution [26]. It may be initiated by trauma, burns, infection, or inflammation. Early MOF was defined as organ failure that developed within 72 h of the initial diagnosis of sepsis and late MOF as organ failure that developed after 72 h. Multiple theories exist regarding the cause for MOF and it is likely that these pathways overlap to cause initially organ insufficiency which, unless reverses, ultimately leads

to failure. Although there are multiple hypotheses to explain the cause of MOF, the cytokine hypothesis and the gut hypothesis are most relevant to trauma patients [27]. The "true" physiologic process is likely a combination of multiple hypotheses.

The Cytokine Hypothesis of MOF

In the cytokine hypothesis, the immune response to infection or inflammation results in excessive or prolonged activation or stimulation of mediators. These include interactions between polymorphonuclear neutrophils (PMNs), endothelial cells, and macrophages. PMN stimulation results in "priming" of the neutrophil and can lead to overzealous production, surface expression, and liberation of cytokines [28]. These mediators often have an exaggerated response and the products of these cascades exert damaging local and systemic effects. Cytokines predictive of MOF in trauma patients include inducible protein (IP)-10, macrophage inflammatory protein (MIP)-1B, interleukin (IL) IL-10, IL-6, IL-1Ra, and eotaxin [29]. Several lines of evidence support the central role of inflammatory cells in the pathogenesis of lung and systemic organ injury. Tumor necrosis factor (TNF) has been considered one of the most potent proinflammatory cytokines identified in SIRS and sepsis. Administration of TNF to experimental animals creates the hemodynamic and metabolic observations consistent with SIRS. Analysis of cytokine serum biomarkers has shown that patients with MOF show a biphasic elevation of IL-6 and significantly higher soluble TNF receptor (sTNF-R) concentrations [30]. Activation of leucocytes and their subsequent inappropriate sequestration in organs appears to additionally be one of the key events in the development of early MOF. Once activated, leukocytes have the capacity to release their cytotoxic factors including nitric oxide and lysosomal granules, which aid in polymicrobial killing. These factors can cause necrosis and inflammation of organs, such as the lung, despite a lack of an infectious stimulus. Additionally, PMN stimulation provokes endothelial and epithelial injury through up-regulation of adhesion molecules on these cells. This prompts changes in the cell wall leading to increased permeability and cell swelling that culminates in cellular dysfunction.

Gut Hypothesis of MOF

The gut is considered an immunologically active organ and a main barrier in the burden of infection-induced systemic inflammation. Gut barrier dysfunction can occur for a variety of reasons including trauma, shock, infection, and malnutrition. It is proposed that, as a result of the loss of the gut barrier function, intestinal bacteria and endotoxin cross the mucosal barrier and lead to exposure of the intestinal immune cells. The production of gut-derived toxins and inflammatory products reach the systemic circulation through the intestinal lymphatics, leading to SIRS and MOF [28]. These translocating bacteria are phagocytosed by intestinal immune cells and contribute to the intestinal inflammatory response. Some of these translocating bacteria or their toxic products are trapped in the intestinal lymph nodes, causing inflammatory reaction. This hypothesis is supported by the demonstration of circulating levels of endotoxin in the peripheral blood of critically ill patients with sepsis and SIRS. Reports of endotoxemia in these critically ill patients, even without clinical or microbiologic evidence of infection with Gram-negative organisms supports the potential role of translocation in the production of MOF [31]. The phenomenon of bacterial translocation however, is not sufficient to explain the development of MOF. The development of MOF in these high-risk patients is likely due to intestinal dysfunction and the resultant inflammatory cascade that reaches the systemic circulation via the intestinal lymphatics. The use of early enteral nutrition is known to reduce infectious complications after trauma and it thought to work by maintaining the gut barrier.

Nutrition in the Trauma Patient

Once an association between MOF and persistent hypermetabolism was realized, it was proposed that early administration of exogenous substrates to meet the increased metabolic demands would slow the development of acute protein malnutrition and improve patient outcomes. In the early 1970s, total enteral nutrition (TEN) was initially favored as it was inexpensive and readily available. However in the early 1980s, enteral nutrition was delayed until the gastrointestinal tract was clearly functioning and simultaneously, total parenteral nutrition (TPN) became more available and became the preferred route of nutrition administration in critically ill patients. In the late 1980s, it became clear that enterally delivered nutrition was better utilized and did not result in the hyperglycemia associated with TPN. Over the 1990s more data emerged supporting the relationship between nutritional support, gut function and MOF [32]. In addition to preventing acute protein malnutrition, TEN promotes normal gut function, and enhances systemic immune responsiveness, thereby preventing nosocomial infections [33]. A number of studies in the severely injured patient have substantiated the positive effect with regards to decreased infections, shorter hospital stays, and improved overall outcomes [34–36].

Estimating Nutritional Needs

The catabolic response to injury increases caloric requirements in the trauma patient due to increased metabolism and elevated nitrogen losses. These needs are increased over baseline by approximately 25 % in skeletal trauma, 50 % in sepsis, and 75–100 % in severe burns. Estimated needs range between 25 and 30 kcal/kg adjusted body weight and approximately 1.5 g protein/kg. However, predictive equations are less accurate in determining resting energy expenditure, especially in obese patients [37]. Indirect calorimetry remains the most accurate means for determining caloric requirements, though specific studies in trauma patients are lacking. Efforts should be made to provide approximately 85 % of goal calories by the enteral route over the first week of hospitalization.

Nutritional Assessment

Nutritional assessment in the ICU population should begin with a thorough history and physical exam focused on identifying clinical signs of malnutrition. A pre-injury history of recent weight loss or poor oral intake signals the need for early aggressive nutritional support. While provision of enteral nutrition is the preferred method of delivery, the overall hemodynamic status of the patient must be taken into consideration. The development of ischemic bowel is a rare but potentially fatal complication of enteral nutrition, occurring in <1 % of all patients [38]. Therefore intravascular volume depletion should be reversed prior to the initiation of enteral nutrition. This is especially true in patients that are receiving vasopressors [37].

Monitoring the Response to Nutritional Supplementation

Once nutritional support has been initiated, it is important to perform routine monitoring to assess the adequacy of the nutritional support that is being delivered and make modifications when necessary. Numerous diagnostic tests exist that can be utilized to assess nutritional adequacy. These include body measurement testing (weight change, anthropometric measures), body composition testing (determination of percent body fat, lean body mass, etc.), and laboratory testing (urine analysis, pre-albumin, etc.). In the setting of critical illness there can be short-term alterations in patient's fluid status, rendering the body composition testing inaccurate. Serum proteins are often measured to help assess for nutritional adequacy. Pre-albumin is commonly used due to its short half-life of 2–4 days. In the critically ill patient, it is important to note that the serum prealbumin level may be increased in patients with

renal failure or in patients receiving corticosteroids. On the other hand, with ongoing stress pre-albumin may be artificially low. The body reprioritizes hepatic protein synthesis away constitutive proteins such as pre-albumin to acute-phase reactants such as C-reactive protein (CRP). CRP is a sensitive acute phase reactant that increases from a normal level to 20–30 within 48 h of injury. Its elevation can be used as an indicator of the severity of injury or inflammation. When the levels begin to decline, the liver can again begin to synthesize constitutive proteins such as albumin, pre-albumin, and transferrin. Therefore, the use of serum pre-albumin to assess nutritional adequacy is of limited use until there is resolution of the acute phase response as documented by a drop in CRP. Lastly, pre-albumin levels may be decreased in patients with liver disease, those patients receiving hemodialysis, and patients with severe hyperglycemia.

Potential Modulators of Metabolism

Glutamine

Glutamine is a conditionally essential nutrient in states of serious illness or injury. It is the preferred fuel source for the enterocyte and the small intestine is the principal site for glutamine absorption. In addition to glutamine's gut protective effects, glutamine is also important in nucleotide synthesis; it is anti-catabolic, has antioxidant properties via metabolism to glutathione, and may enhance immune responsiveness [39].

There have been extensive studies on the effect of supplemental glutamine added to enteral formulas or as an isolated pharmaconutrient, though few specifically in trauma patients [40]. An updated meta-analysis examining the results of enteral glutamine supplementation in critically ill patients noted a modest treatment effect but with wide confidence intervals and the presence of heterogeneity across the studies [41, 42]. The largest effect on mortality was attributable to one study in burn patients [43], while the decrease in infectious complications was attributed to the study by Zhou et al. in burn patients and by Houdijk et al. in trauma patients [44, 45]. Recently, Heyland et al. in a blinded 2×2 factorial trial involving 40 international ICUs, randomized 1,223 critically ill, mechanically ventilated, adult patients with multiorgan failure to glutamine supplementation or no glutamine and antioxidants or no antioxidants [46]. There was increased harm associated with glutamine supplementation. The authors attribute this to two observations. First critical illness is not necessarily associated with a low plasma glutamine level as was believed. They actually reported supra-normal levels of plasma glutamine in 15 % of patients prior to any treatment. Secondly, previous studies reporting beneficial effects of glutamine were performed in less ill patients. Based on these results it is recommended that any patient in multiorgan failure in the ICU should not receive glutamine. For trauma and burn patients not in multiorgan failure, consideration can be given to providing enteral glutamine enterally [47].

Arginine

Arginine is a semi-essential amino acid obtained both from dietary sources and endogenous synthesis. Under nonstressed conditions, arginine contributes to adequate wound healing, an enhanced immune response, and stimulation of various anabolic hormones. L-arginine is also a unique substrate for the production of nitric oxide (NO). Sustained production of nitric oxide is thought to be a major contributor to the deleterious effects of post-injury inflammation and the reason for caution when utilizing arginine in patients with sepsis [39].

The metabolic fate of arginine is determined by nitric oxide synthase or arginase, depending on the immune state of the host and associated cytokine expression. In T-helper-1 immune states, such as sepsis, iNOS expression is preferentially expressed. In trauma, a T-helper 2 immune state predominates which increases arginase I expression. Ochoa et al. demonstrated that peripheral mononuclear cells of trauma patients have increased arginase-1 expression, corresponding to increased immune cell arginase

activity and decreased plasma arginine and citrulline levels [48]. Supplemental arginine may therefore be beneficial in trauma patients by altering metabolic pathways in immune cells that leads to reduced nitric oxide production in the post-injury period.

However, a recent update in criticalcarenutrition.org concluded that there was a lack of a treatment effect with respect to mortality and infections [41], similar to those in a recent meta-analysis of immunonutrition in ICU, trauma, and burn patients [49]. Therefore, given the possible harm in septic patients the use of arginine was not recommended in critically ill patients.

Nutritional Challenges in the Trauma Patient

There are a number of nutritional challenges posed by the trauma patient. These can include the institution of enteral feeds as well as the advancement and continuation of feeds. The institution of feeds may be delayed in patients undergoing prolonged resuscitation or damage control laparotomy. This is particularly true after a bowel resection with the bowel ends left in discontinuity. In general, these patients should return to the operating room in 24 h for reestablishment of gastrointestinal continuity and placement of a feeding tube. Feeds can then be instituted in the immediate postoperative period.

There have now been several studies examining the potential benefits of feeding patients with an open abdomen after a damage control laparotomy, though results are not consistent. Both fascial closure rates and ventilator-associated pneumonia rates have yielded conflicting results [50–52]. A recent study by Burlew et al. examined feeding practices in 597 patients who required an open abdomen after trauma, the vast majority of which were following a damage control operation [53]. Less than half the patients received EN initiated before abdominal closure, suggesting an opportunity for improvement. When comparing patients that received EN to those that were nil per os (NPO), logistic regression demonstrated no association between EN and complication rates but there was an association between EN and decreased mortality. In patients without a bowel injury, EN was associated with a higher fascial closure rate, decreased complication rates, and decreased mortality. EN for patients with bowel injuries did not affect outcomes in this retrospective study however this high risk subgroup of patients is now being studied prospectively by the same group.

For patients with a recent bowel anastomosis, evidence not only demonstrates safety of this practice but potential benefit as well, though there are no studies specific to trauma. A recent meta-analysis performed by Osland et al. reviewed 15 studies involving over 1,200 patients comparing surgical outcomes following the administration of nutrition proximal to a gastrointestinal anastomosis within 24 h of gastrointestinal surgery [54]. There was a significant reduction in total postoperative complications with no negative outcome on mortality, anastomotic dehiscence, or return of bowel function. It is our practice to initiate/resume enteral feeds in the immediate postoperative period following a gastrointestinal anastomosis.

Lastly, many trauma patients require frequent trips to the operating room for abdominal washouts and closure attempts, washout and debridement of open fractures and wounds, and post-injury complications. With few exceptions, feeding tubes should be considered at the time of take back in patients requiring damage control laparotomy. The use of guided placement of gastric or small bowel feeding tubes can provide prolonged access for even the most critically injured patient. The traditional use of NPO after midnight [55] in these patients poses a real risk of feeding inadequacy and malnutrition. Fear of aspiration or reflux in critically injured trauma patients has perpetuated this practice. Additionally, procedures are frequently delayed or postponed, leaving the patient without nutrition for extended periods of time. There are several potential ways to improve nutritional delivery in these patients. First, most anesthesia policies permit the use of enteral feeds until the time of operation if a post-pyloric feeding tube is in place. Second, recent data suggest that enteral feeds can similarly be

safely administered until the time of surgery in trauma patients receiving gastric feeds. Pousman et al. found a trend towards improved nutrition delivery with no increase in adverse outcomes including aspiration [56]. Enteral feeds have also been safely administered to burn patients during operative procedures without a significant increase in infective complications [57]. Even in the noncritically injured patient, the use of supplemental EN should be considered if frequent operating room trips are anticipated.

In summary, it is appropriate to attempt to provide judicious EN in patients with recent bowel anastomosis, open abdomens, and even through periods of ileus [50, 52, 58, 59]. Attention to early placement of feeding tubes and institution of enteral nutrition should be strongly considered in critically injured patients.

Nutritional Adequacy in the Critically Injured Trauma Patient

Despite the known benefits of early enteral nutrition in the critically ill, evidence clearly shows that ICU patients are significantly under fed [60]. For the trauma patient, this practice translates into reduced muscle mass and strength, reduced function, and prolonged recovery. Heyland et al. demonstrated in their large international nutrition survey involving 167 intensive care units (ICUs) in 2,772 mechanically ventilated patients that patients received an average of only 1,034 kcal/day and 47 g protein/day. Importantly, an increase of 1,000 cal/day was associated with reduced mortality and an increased number of ventilator-free days [61]. The effect of increased calories and protein was associated with lower mortality in patients with a body mass index of <25 and surprisingly ≥35. These findings formed the basis for the TOP UP (A Randomized Trial of Supplemental Parenteral Nutrition in Under and Over Weight Critically Ill Patients) study, which is an on-going prospective randomized study examining the use of supplemental parenteral nutrition in critically ill mechanically ventilated patients receiving enteral nutrition. Trauma patients with their risk factors for gut dysfunction and thus underfeeding are ideal for the study.

We recently examined feeding practices in critically injured trauma patients from an international database involving 355 ICUs and 8,838 critically ill adult patients mechanically ventilated within 48 h that remained in ICU for more than 72 h [62]. Patients admitted with a trauma diagnosis (10 % of the total population) were identified and nutritional practices and clinical outcomes were compared between trauma and nontrauma patients. More trauma patients received enteral feeding than non-trauma patients. The majority of patients were fed by the enteral route, 81 % in patients with traumatic injuries and 78 % in the non-trauma patients. Trauma patients were prescribed more calories and protein compared to non-trauma patients. However, nutritional adequacy, calculated daily as the percent of received/prescribed calories or protein, and was low in both trauma and non-trauma patients. Trauma patients had a cumulative deficit of 43.0 % in calories and 47.4 % in protein. Our highest risk trauma patients are receiving less than half of their estimated needs, suggesting that the benefits of early EN are being mitigated by our feeding practices.

The existence of malnutrition preoperatively or the deterioration of nutrition status through the perioperative period is a well-recognized factor increasing postoperative complications and hospital length of stay [63]. But unlike guidelines to optimize intraoperative conditions and reduced complications, little attention has been paid to standardizing nutrition management [64, 65]. In the elective surgical patients, there is a recent new appreciation of the role of perioperative nutrition therapy with an emphasis away from the prevention of malnutrition to attenuating oxidative stress, reducing inflammation, and modulating the metabolic response to planned surgical stress [66]. When feasible, it is recommended that malnourished patients forego elective surgical procedures and undergo a period of preoperative nutritional repletion. Unfortunately, in trauma, we do not have the ability to provide preoperative nutrition or base surgical procedures on nutritional risk. Therefore, we need to focus our attention and efforts to optimizing postoperative nutrition.

Critically Injured Elderly

Critically injured elderly patients and their metabolic requirements represent a unique set of problems. Malnutrition is more common among the elderly compared to younger patients and is associated with poor outcome. The reported incidence of malnutrition in the elderly ranges from 1 to 5 % in the community setting but up to 20 % in the hospitalized elderly [67–69]. Many elderly are presenting malnourished at the time of injury and are thus at higher risk than younger patients. Additionally, the elderly have lower muscle mass and are at risk for further loss after injury. Maintaining muscle mass is important for sustaining key metabolic processes such as glucose homeostasis and immune function. When differences between elderly and non-elderly trauma patients were examined using our international database [70], the elderly were found to have similar BMIs compared to younger patients. Interestingly, only 2 % of the elderly were underweight, similar to younger patients, while 54.4 % were overweight or obese. Despite similar BMIs, elderly trauma patients were prescribed fewer calories and protein than younger patients. Both groups had low nutritional adequacy.

Sarcopenia, or low muscle mass, is also associated with worse outcomes in critically ill surgical patients [71–73]. Importantly, sarcopenia increases with advanced age, as does the incidence of postoperative complications. A recent report by Sheetz et al. demonstrated that sarcopenia was associated with high payer costs and negative margins after major surgery [74]. A number of modalities have been used to calculate muscle mass, including X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). Although DXA may be ideal for whole-body composition analysis, the use of CT scanning is more applicable for the trauma patient as CT scans are frequently performed at the time of injury [75, 76]. Single slice CT images in the 3rd lumbar region can predict whole body muscle and adipose tissue volume in healthy [77] and disease [78] populations.

We conducted a study of severely injured elderly patients admitted to the ICU and found at the time of admission, 71 % were sarcopenic based on admission CT scans [79]. Importantly, patients identified as sarcopenic had significantly increased mortality and decreased ventilator-free and ICU-free days. Interestingly, despite the frequency of sarcopenia in our injured elderly population, 7 % of the patients were underweight, while 37 % were normal weight and 57 % were overweight/obese by body mass index. Neither BMI nor serum albumin on admission were predictive of survival, ventilator-free days, or ICU-free days. This study suggests that at risk patients may be overlooked using traditional indicators of nutritional status such as weight and body mass index. Muscularity therefore represents a potential new marker for risk of mortality and increased length of stay but more importantly may allow the early identification of patients who may benefit from aggressive nutritional and rehabilitative interventions.

Given the impact of ICU-acquired muscle weakness on clinical outcomes, recent research has focused on noninvasive methods to measuring muscle thickness. Although CT scanning is accurate and scans are typically available for trauma patients, calculation of muscle mass using CT scans is time consuming and not universally available. Additionally, a noninvasive tool to be able to follow critically injured and ill patients over time in the ICU could prove valuable. The use of ultrasound to measure the rectus femoris muscle thickness has been proposed [80, 81]. We recently examined the use of US in normal healthy volunteers and found excellent intra- and inter-reliability in the US measurements [82]. Further evaluation of this technique is required to evaluate the validity and clinical utility in critically ill patient and such studies are underway.

References

1. Hasenboehler E, Williams A, Leinhase I, et al. Metabolic changes after polytrauma: an imperative for early nutritional support. World J Emerg Surg. 2006;1:29. doi:10.1186/1749-7922-1-29.
2. Joseph B, Hadjizacharia P, Aziz H, et al. Continuous noninvasive hemoglobin monitor from pulse ox: ready for prime time? World J Surg. 2013;37(3):525–9. doi:10.1007/s00268-012-1871-y.

3. Stahel PF, Flierl MA, Moore EE. "Metabolic staging" after major trauma - a guide for clinical decision making? Scand J Trauma Resusc Emerg Med. 2010;18(1):34. doi:10.1186/1757-7241-18-34.
4. Blackburn GL. Metabolic considerations in management of surgical patients. Surg Clin North Am. 2011;91(3):467–80. doi:10.1016/j.suc.2011.03.001.
5. Cerra F, Blackburn G, Hirsch J, Mullen K, Luther W. The effect of stress level, amino acid formula, and nitrogen dose on nitrogen retention in traumatic and septic stress. Ann Surg. 1987;205(3):282–7.
6. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):21S–9S. doi:10.1177/0148607113496117.
7. Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. Crit Care Med. 2009;37(5):1757–61. doi:10.1097/CCM.0b013e3181a40116.
8. Block E, Lube M. Nutritional support of the injured. In: Trauma, contemporary principles and therapy, vol. 1. Philadelphia, PA: Lippincott Williams & Wilkins; 2008. p. 705–15.
9. Kozar R, Schwartz DA. Nutrition in the surgical patient. In: Common problems in acute care surgery, vol. 1. New York, NY: Springer; 2013. p. 119–29.
10. Shaw JH, Wolfe RR. An integrated analysis of glucose, fat, and protein metabolism in severely traumatized patients. Studies in the basal state and the response to total parenteral nutrition. Ann Surg. 1989;209(1):63.
11. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67. doi:10.1056/NEJMoa011300.
12. Vanhorebeek I, Langouche L, Van den Berghe G. Tight blood glucose control: what is the evidence? Crit Care Med. 2007;35(9 Suppl):S496–502. doi:10.1097/01.CCM.0000278051.48643.91.
13. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–1297. doi:10.1056/NEJMoa0810625.
14. Liu-DeRyke X, Collingridge DS, Orme J, Roller D, Zurasky J, Rhoney DH. Clinical impact of early hyperglycemia during acute phase of traumatic brain injury. Neurocrit Care. 2009;11(2):151–7. doi:10.1007/s12028-009-9228-6.
15. Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. J Neurosurg. 1991;75(4):545–51. doi:10.3171/jns.1991.75.4.0545.
16. Lee TH, Ryu SJ, Chen ST. The prognostic value of blood glucose in patients with acute stroke. J Formos Med Assoc Taiwan Yi Zhi. 1991;90(5):465–70.
17. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. J Trauma. 2005;58(1):47–50.
18. Levetan CS. Effect of hyperglycemia on stroke outcomes. Endocr Pr Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2004;10 Suppl 2:34–9.
19. Salim A, Hadjizacharia P, Dubose J, Hadjizacharia P, Dubose J, Brown C, et al. Persistent hyperglycemia in severe traumatic brain injury: an independent predictor of outcome. Am Surg. 2009;75(1):25–9.
20. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530–8. doi:10.1007/s00134-003-1662-x.
21. Plank LD, Hill GL. Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. World J Surg. 2000;24(6):630–8.
22. Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. Crit Care Clin. 2000;16(2):337–352, vii.
23. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–55.
24. Mundy LM, Doherty GM. Inflammation, infection, & antimicrobial therapy. In: Current diagnosis and treatment: surgery. 13th ed. New York, NY: McGraw-Hill; 2010.
25. Gordy S, Schreiber MA. Common problems in acute care surgery: multiple organ failure. Heidelberg: Springer; 2013.
26. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lesotte DC. Postinury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40(4):501–10.
27. Deitch EA. Multiple organ failure. Pathophysiology and potential future therapy. Ann Surg. 1992;216(2):117–34.
28. Deitch EA. Gut-origin sepsis: evolution of a concept. Surg J R Coll Surg Edinb Irel. 2012;10(6):350–6. doi:10.1016/j.surge.2012.03.003.
29. Jastrow KM 3rd, Gonzalez EA, McGuire MF, Suliburk JW, Kozar RA, Iyengar S, et al. Early cytokine production risk stratifies trauma patients for multiple organ failure. J Am Coll Surg. 2009;209(3):320–331. doi:10.1016/j.jamcollsurg.2009.05.002.
30. Maier B, Lefering R, Lehnert M, Lefering R, Lehnert M, Laurer HL, et al. Early versus late onset of multiple organ failure is associated with differing patterns of plasma cytokine biomarker expression and outcome after severe trauma. Shock Augusta Ga. 2007;28(6):668–74.
31. Balk RA. Severe sepsis and septic shock. Definitions, epidemiology, and clinical manifestations. Crit Care Clin. 2000;16(2):179–92.

32. Todd SR, Kozar RA, Moore FA. Nutrition support in adult trauma patients. Nutr Clin Pr Off Publ Am Soc Parenter Enter Nutr. 2006;21(5):421–9.
33. Kozar R, McQuiggan M. Nutritional support of trauma patients. In: Nutritional considerations in the intensive care unit. Dubuque, IA: Kendall Hunt; 2002. p. 229–44.
34. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma–a prospective, randomized study. J Trauma. 1986;26(10): 874–81.
35. Alexander JW, MacMillan BG, Stinnett JD, Ogle CK, Bozian RC, Fischer JE, et al. Beneficial effects of aggressive protein feeding in severely burned children. Ann Surg. 1980;192(4):505–17.
36. Doig GS, Heighes PT, Simpson F, Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. Injury. 2011;42(1):50–6. doi:10.1016/j.injury.2010.06.008.
37. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316.
38. McClave SA, Chang W-K. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? Nutr Clin Pr Off Publ Am Soc Parenter Enter Nutr. 2003;18(4):279–84.
39. Santora R, Kozar RA. Molecular mechanisms of pharmaconutrients. J Surg Res. 2010;161(2):288–94.
40. McQuigan M, Kozar RA, Moore FA. Enteral glutamine during active shock resuscitation is safe and enhances tolerance. JPEN J Parenter Enteral Nutr. 2008;32(1):28–35.
41. Clinical Evaluation Research Unit. Canadian Clinical Practice Guidelines updated in 2013. March 2013. http://criticalcarenutrition.com/index. Accessed October 11, 2013.
42. Novak F, Heyland DK, Avenell A, Novak F, Drover J, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med. 2002;30:2022–9.
43. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, D'Elia M, Bernier J. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit Care Med. 2003;31(10):2444–9.
44. Zhou YP, Jiang ZM, Sun YH, Wang XR, Ma EL, Wilmore D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. JPEN J Parenter Enteral Nutr. 2003; 27(4):241–5.
45. Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, Teerlink T, Meuwissen SG, Haarman HJ, Thijs LG, van Leeuwen PA. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet. 1998;352(9130):772–6.
46. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1487–95.
47. Heyland DK, Dhaliwal R. Role of glutamine supplementation in critical illness given the results of the REDOXS Study. JPEN J Parent and Enteral Nutr. 2013;37(4):442–3.
48. Ochoa JB, Bernard AC, O'Brien WE, Griffen MM, Griffen MM, Maley ME, Rockich AK, et al. Arginase 1 expression and activity in human mononuclear cells after injury. Ann Surg. 2001;233:393–9.
49. Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008;11:1980–90.
50. Dissanaike S, Pham T, Shalhub S, Warner K, Hennessy L, Moore EE, Maier RV, O'Keefe GE, Cuschieri J. Effect of immediate enteral feeding on trauma patients with an open abdomen: protection from nosocomial infections. J Am Coll Surg. 2008; 207:690–7.
51. Byrnes MC, Reicks P, Irwin E. Early enteral nutrition can be successfully implemented in trauma patients with an "open abdomen". Am J Surg. 2010;199: 359–62. discussion 363.
52. Collier B, Guillamondegui O, Cotton B, Donahue R, Conrad A, Groh K. Feeding the open abdomen. JPEN J Parenter Enteral Nutr. 2007;31:410–5.
53. Burlew CC, Moore EE, MD, Cuschieri J, Jurkovich GJ, Codner P, Nirula R, Millar D, Cohen MJ, Kutcher ME, Haan J, MacNew HJ, Ochsner G, Rowell SE, Truitt MS, Moore FO, Pieracci FM, Kaups KL, and the WTA Study Group. Who should we feed? A Western Trauma Association multi-institutional study of enteral nutrition in the open abdomen after injury. J Trauma Acute Care Surg 2012;73(6):1380–7.
54. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. JPEN J Parenter Enteral Nutr. 2011;35: 473–87.
55. American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. Anesthesiology. 1999;90: 896–905.
56. Pousman RM, Pepper C, Pandharipande P, Aers GD, Mills B, Diaz J, Collier B, Miller R, Jensen G. Feasibility of implementing a reduced fasting protocol for critically ill trauma patients undergoing operative and nonoperative procedures. JPEN J Parenter Enteral Nutr. 2009;33:176–80.

57. Jenkins ME, Gottschlich MM, Warden GD. Enteral feeding during operative procedures in thermal injuries. J Burn Care Rehabil. 1994;15:199–205.
58. Barlow R, Price P, Reid TD, Hunt S, Clark GW, Havard TJ, et al. Prospective multicentre randomized controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. Clin Nutr. 2011;30(5):560–6.
59. Caddell KA, Martindale R, McClave SA, Miller K. Can the intestinal dysmotility of critical illness be differentiated from postoperative ileus? Curr Gastroenterol Rep. 2011;13(4):358–67.
60. Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. Nutrition therapy in the critical care setting: what is "best achievable" practice? An international multicenter observational study. Crit Care Med. 2010;38(2):395–401.
61. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009;35:1728–37.
62. Wade CE, Kozar RA, Dyer CB, Bulger EM, Mourtzakis M, Heyland DK. Feeding the critically ill trauma patient: can we do better? JPEN J Parenter Enteral Nutr 2014 Feb 21.
63. Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and postoperative complications in patients with gastrointestinal cancer. J Hum Nutr Diet. 2010;23(4):393–401.
64. Windsor A, Braga M, Martindale R, et al. Fit for surgery: an expert panel review on optimising patients prior to surgery, with a particular focus on nutrition. Surgeon. 2004;2(6):315–9.
65. Delmore G. Assessment of nutritional status in cancer patients: widely neglected? Support Care Cancer. 1997;5(5):376–80.
66. McClave SA, Kozar R, Martindale RG, Heyland DK, Braga M, Carli F, Drover JW, Flum D, Gramlich L, Herndon DN, Ko C, Kudsk KA, Lawson CM, Miller KR, Taylor B, Wischmeyer PE. Summary points and consensus recommendations from the North American Surgical Nutrition Summit. JPEN J Parenter Enteral Nutr 2013;37(5 Suppl):99S–105S.
67. Feldblum I, German L, Castel H, Harman-Boehm I, Bilenko N, Eisinger M, et al. Characteristics of undernourished older medical patients and the identification of predictors for undernutrition status. Nutr J. 2007;6:37.
68. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med. 2002;18(4):737–57.
69. Saka B, Kaya O, Ozturk GB, Erten N, Karan MA. Malnutrition in the elderly and its relationship with other geriatric syndromes. Clin Nutr. 2010;29(6):745–8.
70. Kozar RA, Dyer C, Bulger E, Mourtzakis M, Wade CE, Heyland DK. Elderly trauma patients: highest risk, fewest calories. JPEN J Parenter Enteral Nutr. 2011;35:S26.
71. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211:271–8.
72. Lee JS, He K, Harbaugh CM, Schaubel DE, Sonnenday CJ, Wang SC, et al. Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. J Vasc Surg. 2011;53:912–7.
73. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107:931–6.
74. Sheetz KH, Waits SA, Terjimanian MN, Sullivan J, Campbell DA, Wang SC, Englesbe MJ. Cost of major surgery in the sarcopenic patient. J Am Coll Surg. 2013;217(5):813–8.
75. Di Sebastiano KM, Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. Appl Physiol Nutr Metab. 2012;37(5):811–21.
76. Ahmadinia K, Smucker JB, Nash CL, Vallier HA. Radiation exposure has increased in trauma patients over time. J Trauma Acute Care Surg. 2012;72:410–5.
77. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, Heymsfield SB, Heshka S. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97:2333–8.
78. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33:997–1006.
79. Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, Bulger E, Kozar RA. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Crit Care. 2013;17(5):R206.
80. Campbell IT, Watt T, Withers D, England R, Sukumar S, Keegan MA, Faragher B, Martin DF. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. Am J Clin Nutr. 1995;62(3):533–9.
81. Gruther W, Zorn BTC, Paternostro-Sluga T, Paternostro-Sluga T, Quittan M, Fialka-Moser V, et al. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. J Rehabil Med. 2008;40:185–9.
82. Tilquist M, Leung R, Kutsogiannis J, Wischmeyer P, Karvellas D, Preiser JC, Bird N, Kozar R, Heyland DK. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness in the critically ill. JPEN J Parenter Enteral Nutr. 2013;258(4):527–33.

Burns

6

Michael J. Mosier and Richard L. Gamelli

The Body's Response to Burn Injury

Severe burn injury continues to represent a significant public health problem worldwide. More than one million burn injuries occur annually in the USA. While most of these injuries are minor, approximately 10 % of patients with burn injury require hospital admission for treatment every year [1]. While there has been an approximate 50 % decline in burn-related deaths and hospital admissions over the last 20 years as a result of prevention strategies, advances in critical care and therapeutic strategies targeted toward resuscitation, wound coverage, infection control, inhalation injury, and the hypermetabolic response to injury, severe burns remain a devastating injury affecting nearly every organ system and leading to significant morbidity and mortality [1].

In burns 20 % total body surface area (TBSA) or greater, or with additional smoke inhalation injury or concomitant trauma, the local response to burn injury becomes systemic. Peripheral vasoconstriction occurs, with shunting of circulation away from the skin and viscera while a global capillary leak occurs, permitting loss of fluid and protein from the intravascular compartment into the extravascular compartment. Global perfusion is further impaired as cardiac output decreases with the initial cytokine response and associated increase in blood viscosity and decrease in blood volume.

Major burn injury is characterized by oxidative stress, a prolonged hypermetabolic, catabolic state, and immunosuppression. The systemic response to major burn injury is driven by a cascade of cytokines, catecholamines, and corticosteroids that are central to the hypermetabolic response. Serum levels of cytokines and catecholamines elevate 10- to 20-fold, with associated insulin resistance, increased gluconeogenesis, energy consumption, lipolysis, and proteolysis that may remain elevated for 12 months postinjury [2]. Resultantly, burn patients have increased cardiac work, increased myocardial oxygen consumption, tachycardia, lipolysis, liver dysfunction, severe muscle catabolism, increased protein degradation, insulin resistance, and growth retardation has been seen in children.

Thus, providing the right balance of macro- and micronutrients, antioxidants, and energy is essential to mitigate the hypermetabolic and hypercatabolic state that results. Nutritional support has long been and continues to be an important component of the management of severe burn injury.

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Historical Perspective to Nutrition and What Has Been Practiced

In the early 1970s, Curreri and Luterman recognized that patients with major thermal injury experience hypermetabolism, with an increased basal metabolic rate, increased oxygen consumption, negative nitrogen balance, and weight loss; hence, they concluded that these patients have exaggerated caloric requirements [3]. Furthermore providing inadequate caloric intake comes at a cost with delayed wound healing, decreased immune competence, and cellular dysfunction.

A patient with a large burn may lose as much as 30 g of nitrogen a day because of protein catabolism. Not only is urinary excretion of urea nitrogen increased, but also large amounts of nitrogen are lost from the wound itself. Therefore, total urea nitrogen levels do not accurately reflect all nitrogen losses in burn patients [4]. A patient with a small burn (<10 % TBSA) may lose nitrogen at a rate of 0.02 g/kg/day. A moderate burn (11–29 % TBSA) may be associated with nitrogen losses equaling 0.05 g/kg/day. A large burn (>30 % TBSA) may result in the loss of as much as 0.12 g/kg/day, which may be equivalent to daily losses of 190 g of protein or about 300 g of muscle. Thus, a highly catabolic patient with a large burn will typically require 2 g/kg/day of protein to maintain a positive nitrogen balance.

Catabolism generally continues until wounds have healed. However, once a patient becomes anabolic, pre-burn muscle takes three times as long to regain as it took to lose [5, 6]. Therefore, a patient in whom it takes 1 month for burn wounds and donor sites to heal may need 3 or more months to regain pre-burn weight and muscle mass. These statistics underscore the importance of accurately estimating each patient's caloric needs during hospitalization. Over the years, a number of equations have been developed to estimate caloric needs (97). Probably the most widely used formula is the Harris–Benedict equation, which estimates basal energy expenditure according to gender, age, height, and weight (Table 6.1).

Table 6.1 Equations used for estimating caloric requirements in burn patients

Harris–Benedict Formula
Basal energy expenditure (BEE) × activity factor = daily caloric requirement
Men: BEE = 66.5 + 13.8 (weight in kg) + 5.0 (height in cm) – 6.8 (age in years)
Women: BEE = 65.5 + 9.6 (weight in kg) + 1.8 (height in cm) – 4.7 (age in years)
For burns, the activity factor is 2 (which may overestimate caloric needs for patients with burns < 40 % TBSA). *TBSA* total body surface area
Curreri Formula
25 Kcal/kg + 40 Kcal/% TBSA burned = daily caloric requirement

Who Needs Nutritional Support

The innate response to significant burn injury increases metabolism to such a profound degree that severely burn-injured patients would succumb to the effects of protein calorie malnutrition without nutritional supplementation [7–11]. This post-burn hypermetabolism is associated with profound proteolysis resulting in lean body mass loss and muscle wasting. Appropriate monitoring for nutritional needs and deficiencies as well as provision of adequate caloric intake, nitrogen, micronutrients, and supplements is therefore critical to the success of burn care. With this in mind, it is our common practice to place a feeding tube and provide enteral nutrition to patients who are unable to meet their caloric requirements on their own. Typically, this includes intubated patients, patients with burns >15 % TBSA, and patients with concomitant trauma or malnutrition.

How Much to Feed and How Soon?

Burn patients rapidly accrue energy deficits and cumulative energy deficits during the first week following injury correlate with infectious complications and pressure sores [12–14]. Further, substantial loss of lean body mass impairs wound healing, which is critical in burn injury [15]. International nutrition support guidelines advocate that enteral feedings should begin early in critically ill patients who have a functioning gastrointestinal

tract, but there has been wide variation as to what is considered early [16–19]. The Canadian Clinical Practice Guidelines, the Eastern Association for the Surgery of Trauma, and the American Burn Association all advocate for initiation of enteral nutrition as soon as possible or within 24–48 h [16–19]. Additionally, enteral nutrition helps maintain immunity associated with the gut-associated lymphoid tissue; thus even low rates of enteral nutrition has theoretical benefits [20].

Recognizing the growing energy deficits, loss of lean body mass, and that delayed enteral nutrition results in a high rate of gastroparesis and ileus, it is our practice to place a nasogastric feeding tube and initiate enteral nutrition as soon as possible following admission and advancing to goal rate as tolerated. While reviews of other centers reveal that feeding tubes are commonly placed as late as 31 h post-admission with initiation of enteral nutrition as late as 48 h from admission [21], a recent review of our practice revealed that 80 % of patients with burns >20 % TBSA began enteral nutrition within 24 h of admission, and those fed within 24 h of admission had a shorter ICU length of stay and reduced wound infections [22]. This is consistent with the findings of others, specifically that children started on enteral nutrition within 48 h of admission had a shorter hospitalization and lower mortality rate than those with late initiation of enteral nutrition [23], and highlights the importance of starting nutrition early.

Total Parenteral Nutrition Versus Enteral Nutrition: When to Use What and Why

As early as 1976, the benefits of enteral nutrition over parenteral nutrition had already been identified for patients with functional gastrointestinal systems [24]. The problems of prolonged ileus and Curling stress ulcers in burn patients have been largely eliminated by early feeding [25]. Multiple studies have shown that patients with major thermal injury can receive adequate calories within 72 h after injury [26].

In addition to the question of when to start feeding, there is ongoing debate about where to feed and the benefits of gastric feeding versus duodenal feeding. Although feeding distal to the pylorus should pose less aspiration risk, one study found evidence of enteral formula in pulmonary secretions of 7 % of patients receiving gastric feeds compared with 13 % of patients receiving transpyloric feeding [27]. Hence, for burn patients with high caloric needs, the benefit of decreased aspiration with transpyloric feeds may only be theoretical and may be offset by the delay in feeding for confirmation of tube placement, though one center has published on the success of their nurse practitioner-driven protocol that has led to timely and economical placement of transpyloric feeding tubes [28].

Continuation of tube feedings during surgery in intubated patients who require multiple operations is a safe way to maximize caloric intake and decrease wound infections. There is no need to stop feedings for anesthesia induction and endotracheal intubation in the patient with a secure airway and communication with anesthesia providers may help facilitate perioperative feedings [29]; however, intraoperative positioning, especially if the patient will be prone during surgery, may necessitate stopping feedings preoperatively. Arguing that nutrition should be provided intraoperatively, Mayes and colleagues have presented data that support continuation of tube feedings in critically ill burn patients undergoing decompressive laparotomy [30].

While we much prefer enteral nutrition to parenteral nutrition for burn patients, there are times when patients are unable to tolerate or meet their needs with enteral nutrition. Encouragingly, parenteral nutrition has fewer complications than it once did and a recent pediatric trial found parenteral nutrition to be safe and effective in pediatric burn patients unable to achieve goal enteral nutrition during times such as hemodynamic instability or severe sepsis [31].

What Needs to Be Supplemented: Protein, Calories, Vitamins, and Minerals

Providing adequate amounts of carbohydrate is important for preserving lean body mass in the burn population as it spares protein from being

used as an energy source [2]. However, it is important (especially with parenteral nutrition) not to exceed the maximum rate at which glucose can be assimilated in the body (7 g/kg/day), providing glucose in excess of the rate at which it can be oxidized [32]. While different compositions of formulas have been provided, systematic review has shown that providing severely burned patients with a high-carbohydrate, high-protein, low-fat enteral diet can lower the incidence of catabolism and pneumonia, compared to a high-fat, high-protein, low-carbohydrate product [33].

Perhaps this should not be surprising, as there is a significant change in how fat is metabolized following burn injury and providing excess sources of fat can result in stress on the liver [2]. An increased breakdown of peripheral fat stores immediately after injury coupled with increased beta oxidation of fat to be used as fuel during the hypermetabolic phase leads to a potential for large accumulations of fat in the liver [34]. However, providing fat as part of the enteral diet is required to prevent essential fatty acid deficiencies, such that a minimum of 2–4 % of total calories provided needs to be from essential fatty acid [2].

Protein losses following significant burn injury are severe as protein stores are depleted for energy usage and muscle tissue is broken down at rates as high as 150–190 g/day [35]. This leads to detrimental muscle loss, and in children, a significant decline in growth trajectory for a year or longer post-burn, as well as decreased immune function and delayed wound healing [2]. Accordingly, long-established practices and studies have found that providing protein at 1.5–2.5 g/kg/day is typically sufficient for mitigating the hypermetabolic response in adults and 2.5–4.5 g/kg/day is typical for children.

Specialized nutritional formulas with purported effects on metabolic rate and immunologic status have garnered a great deal of interest as adjuncts in the management of critically ill and injured patients [36]. Unfortunately, much of the information on nutritional requirements for critically ill patients was derived from an animal burn model [37], and studies on the efficacy of specialized nutritional supplements in humans have generated contradictory data. As an example, a randomized trial of nutritional formulas that were intended to enhance immune status and included essential amino acids and omega-3 fatty acids showed no clinical advantage in burn patients [38]. However, the addition of glutamine supplementation to an enteral nutrition regimen has been shown to decrease hospital and ICU length of stay as well as mortality in adult burn patients [39].

Other nutritional or metabolically active supplements that have demonstrated promise in promoting anabolism in burn patients include insulin, recombinant human growth factor, the anabolic steroid oxandrolone, and propranolol [40]. Oxandrolone in particular has produced marked improvements in weight gain, return to function, and length of hospital stay [41]; however, its use should be cautioned in non-burn patients as surgical patients have not shown the same benefit [42]. Early administration of antioxidant supplementation with α-tocopherol and ascorbic acid has been shown to reduce the incidence of organ failure and shorten intensive care unit (ICU) length of stay in critically ill surgical patients [43]. Whether this is true for burn patients remains to be demonstrated, but the relatively low cost and the low risk of complications make this an attractive intervention for burn patients at risk for acute respiratory distress syndrome (ARDS).

While providing adequate calories and protein are the foundation of nutritional support, we believe it is also important to provide vitamins and minerals, also known as micronutrients. Depressed levels of vitamin C [44], vitamin D [45], selenium [46, 47], vitamin E [44, 48], zinc, and copper [46, 49–52] have been reported in burn patients and these losses occur mainly through the skin and urine [53]. Unfortunately, supplementation studies are scarce and have not provided guidance for appropriate micronutrient provision and there are no clear guidelines on how to assess micronutrient status. Benefits to providing micronutrients include mitigation of the negative effects of oxidative stress, which can contribute to the systemic inflammatory response syndrome (SIRS), inflammation, and organ failure, as well as contribute to wound healing, tissue repair, and immune system support.

Support for providing micronutrients can be found in a recent survey of 65 burn centers demonstrating 100 % of participants provide a multivitamin following burn injury and more than half provide vitamin C and Zinc supplementation [54]; as well as the recent guidelines from the Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition published in 2009, which recommended the antioxidant vitamins C and E and trace minerals (selenium, zinc, and copper) be provided to burn patients [55].

Modulation of the Stress Response to Burn Injury and Metabolically Altering Agents

Modulation of the stress response to significant burn injury has been attempted with pharmacologic and non-pharmacologic means. Non-pharmacologic means include early excision and grafting, thermoregulation of the environment, and enteral nutrition. Pharmacologic interventions include beta-blockade, anabolic agents, intensive insulin therapy (IIT), and supplementation of specific individual nutrients.

Non-Pharmacologic Means (Early Operative Intervention and Thermoregulation of the Environment)

Early Excision and Grafting

Surgical excision of burn wounds was not fully appreciated until the mid-1900s. Prior to that time, burn wounds were largely treated medically. While many different topical therapies were applied to the burn eschar, it was left intact over the wound surface and proteolytic enzymes produced by migrating neutrophils and bacteria within the contaminated eschar would cause a natural separation of the eschar from the wound bed. In partial thickness injuries, the burn wound could naturally heal from epidermal appendages by this process. With full-thickness injuries, the separation of the burn eschar left an open wound covered by well-vascularized granulation tissue that served as the first early bed for grafting. Unfortunately, this led to a long, painful process to achieve wound closure and hypertrophic scarring and contractures were common.

While early excision and grafting had been described and performed earlier, it was not until the Cocoanut Grove fire in 1942 that Cope and colleagues observed patients treated with early excision and grafting had better outcomes [56]. Other early efforts were discouraging, but Janzekovic's good results rekindled enthusiasm and as clinical experience with early excision and grafting grew, the benefits became clear [57]. Manafo and Burke introduced and expanded Janzekovic's concept of tangential excision of the burn wound to the USA and as experience grew, the advantages of more rapid healing, decreased blood loss, decreased hospital length of stay, and decreased hypertrophic scarring were realized [58–60]. Significantly, early total excision of full-thickness burns with immediate grafting led to a notable decrease in mortality of 24 % in 1974 to 7 % over 1979–1984 and what started as limited early excision of eschar rapidly progressed to staged, total excision of the burn wound [61].

Since that time, there have been many successive studies which have repeatedly verified favorable outcomes with early excision and grafting [62–67]. Improved understanding of the systemic inflammatory response syndrome (SIRS) has suggested that immediate removal of dead and severely damaged tissue can interrupt and attenuate SIRS and normalize immune function [68–70].

Temperature Regulation

Because the burn patient has lost the barrier function of the skin, temperature regulation is an important goal of successful management. Keeping a patient warm and dry is a major goal during resuscitation, especially during the pre-burn center transport of patients. This includes maintaining a warm ambient temperature. Large evaporative losses combined with administration of large volumes of intravenous fluids that are at room temperature or colder may accentuate the hypovolemia, which will complicate the patient's

overall course and may lead to disseminated intravascular coagulopathy [71]. Mild hyperthermia may occur in the first 24 h as a result of pyrogen release or increased metabolic rate and may cause tachycardia that misleadingly suggests hypovolemia [72]. Because infection is unlikely early on, especially within the first 72 h after injury, elevated temperatures should be treated with antipyrogens to control the energy expenditure associated with increased catabolism [73]. About 72 h after injury, patients with thermal injuries commonly develop a hyperdynamic state, the systemic inflammatory response syndrome (SIRS), which is characterized by tachycardia, hypotension, and hyperthermia; classic signs of sepsis that in this case do not have an infectious source.

Although patients with burns are likely to have elevated temperatures and may even have elevated white blood cell counts, fevers in burn patients are not reliable indicators of infections [74, 75]. At least one study has demonstrated that in pediatric burn patients, physical examination is the most reliable tool for evaluating the source of fever [74].

Pharmacologic Means (Beta-blockade, Oxandrolone, Insulin, Glutamine, Erythropoietin, and Iron)

Beta-blockade

As catecholamines are the main drivers of the hypermetabolic response to burn injury [76], with levels increasing tenfold following injury [76, 77], efforts to dampen this response hold a certain attraction. As catecholamines increase cardiac work, drive lipolysis, enhance glycogenolysis, and impair glucose clearance by altering insulin response [78], blocking the catecholamine surge could improve multiple aspects of post-burn hypermetabolism. Efforts to prove this hypothesis by treating patients with propranolol have demonstrated suppression of lipolysis, decreased resting energy expenditure, preservation of lean body mass, and decreased hospital length of stay [79–84].

Propranolol significantly decreases fatty infiltration of the liver, inhibits the release of free fatty acids from adipose tissue, and decreases the rates of fatty acid oxidation and triacylglycerol secretion while increasing the efficiency of the liver to excrete fatty acids, thereby decreasing hepatic steatosis [85–88]. Propranolol has also been shown to increase lean body mass, through decreased skeletal muscle wasting, and doses titrated to target a 20 % heart rate reduction from admission heart rate have been shown to increase the efficiency of muscle protein synthesis [82].

Oxandrolone

Oxandrolone is a synthetic analog of testosterone with minimal virilizing activity and hepatotoxicity compared to testosterone [89]. In skeletal muscle, oxandrolone binds to the androgen receptor and migrates to the cell nucleus, stimulating protein synthesis and anabolism. Additionally, oxandrolone exerts anabolic effects by counteracting the catabolic effects of cortisol through competitive inhibition of glucocorticoid receptors [90].

The hypermetabolic state following burn injury leads to protein–calorie malnutrition, muscle wasting, deconditioning, and delayed wound healing. These complications are accompanied by prolonged hospital length of stay, increased hospital costs, and need for extensive and long-lasting rehabilitation. Modulation of the post-burn hypermetabolism with oxandrolone can potentially improve these consequences [5, 84, 91–95]. Patients with severe burn injury treated with oxandrolone have been found to have a shorter hospital and ICU length of stay accounting for severity of illness, TBSA burn, and age [96].

Oxandrolone has been given in many varied ways to burn patients. It has been given within the first few days of admission, a week after admission, during burn rehabilitation following the acute hospitalization, or for as long as a year after injury. While each of these groups has been evaluated, no group has been as extensively studied as that of the massively burned child. Physiologic evaluation and long-term follow up of children with >30 % TBSA burns treated with

oxandrolone for 1 year revealed that oxandrolone substantially decreased resting energy expenditure (REE) and increased insulin-like growth factor-1 secretion during the first year after burn injury, and when combined with exercise, considerably increased lean body mass and muscle strength [97]. When given early, within the first week of admission, the American Burn Association Multicenter Trials Group found that patients treated with oxandrolone had a shorter length of stay [94], and our work with the Glue Grant demonstrated an improved mortality [98]. Just how oxandrolone improves outcomes such as mortality and length of stay remains to be better understood, but we are encouraged by results showing an improved length of stay and lean body mass when given a week after injury [84], as well as during acute rehabilitation, where body weight and lean mass lost from injury can be restored more effectively than with nutrition alone [41, 99]. Based on these results, it is our practice to treat severe burns with oxandrolone over their acute hospitalization, with initiation following burn resuscitation.

Insulin

Both hyperglycemia and hypoglycemia are associated with increased mortality and morbidity in critically ill patients. While hyperglycemia has been believed to be an adaptive stress response, it has been associated with worse outcomes and glucose variability has been found to be a predictor of mortality following burn injury [100–102]. The association of poor glucose control with bacteremia, reduced graft take, and higher mortality in pediatric burn patients has further supported this practice [102]. Improved survival in surgical ICU patients maintained with tight blood glucose control of 80–110 mg/dL led to the widely practiced policy of tight glycemic control [103].

Since Van den Berghe's landmark study in 2001 [103], there have been many randomized controlled trials and meta-analyses that have reported conflicting results or found that only surgical ICU patients, and not medical ICU patients, benefited from strict glucose control [100, 104]. More recently, the large multicenter Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial demonstrated that an intermediate glucose target (140–180 mg/dL) was ideal for most patients, and resulted in lower mortality than stricter control (80–110 mg/dL) [105]. Based on the current literature, it is our policy to maintain blood glucose levels as close to normal as possible, without evoking unacceptable glucose fluctuations, hypoglycemia, or hypokalemia, and therefore aim for a range of 100–180 mg/dL.

Glutamine

Glutamine plays an important role in many metabolic processes and has a high turnover of approximately 1 g of glutamine per kilogram per day [106]. As this is nearly ten times the normal dietary intake, the body relies upon endogenous sources. In a critically ill patient, the demand for glutamine increases (secondary to immune system activation and damage repair efforts), while production is decreased (secondary to immobility and insulin resistance), making glutamine conditionally essential and leading to a functional deficiency. It is not surprising therefore, that a low plasma glutamine level has been independently associated with worse outcomes in critical illness [107], and some single center studies have shown improved outcomes related to dose and duration [108, 109]. Unfortunately, a randomized trial of nutritional formulas that were intended to enhance immune status and included essential amino acids and omega-3 fatty acids showed no clinical advantage in burn patients [38], the addition of glutamine supplementation to an enteral nutrition regimen has been shown to decrease hospital and ICU length of stay as well as mortality in adult burn patients.

These findings could potentially be explained by glutamine's role in reducing oxidative stress through its function as a precursor to glutathione, as well as serving as a fuel for macrophages, fibroblasts, and lymphocytes, and aiding in preventing bacterial translocation through preservation of gut integrity by serving as a source for enterocytes [39]. Confirmatory support for the

immune-enhancing effects of glutamine can be found in a recent meta-analysis of four randomized controlled trials, involving 155 patients, which found glutamine supplementation to be associated with a decrease in the number of patients with Gram-negative bacteremia as well as hospital mortality [110].

Glutamine has many valuable functions that may be beneficial to burn patients and studies have reported advantages to glutamine, perhaps explained by its trophic influence on intestinal epithelium and on maintenance of gut integrity [39]. Studies in adult burn patients have shown enteral glutamine supplementation to preserve gut integrity [111, 112] while decreasing infectious complications [39, 111], mortality [39], and length of stay [111, 112]. Unfortunately, these studies have had small sample sizes and different dosing methods and glutamine supplementation has not been well studied in children, leaving unanswered questions about the potential benefits of glutamine supplementation. Future studies will need to take into account the nutritional status of patients, the degree of glutamine deficiency, and duration of use rather than using a single standard dose for a short duration and being surprised by a lack of effect. Similarly, less ill patients with less of a glutamine deficiency may not benefit from additional supplementation.

Erythropoietin

While patients with large burns will often have a long hospitalization, a longer period of critical illness than many other ICU patients, and many operative interventions that can all lead to blood loss and anemia, there is no definitive study on the use of erythropoietin in the burn population. One interesting and positive study encouraging the use of erythropoietin in the ICU was performed by the EPO Critical Care Trials Group and reported in JAMA in 2002. This prospective, randomized, double-blind, placebo-controlled, multicenter trial was performed over 2.5 years and involved 1,302 mixed medical and surgical ICU patients randomized to receive recombinant human erythropoietin (EPO) or placebo on ICU day 3 and then weekly for 3 doses. Interestingly, they found patients receiving EPO to be less likely to undergo transfusion, experiencing a 19 % reduction in total units of red blood cells (RBCs) transfused, reduction in RBC units transfused per day alive, and increase in hemoglobin from baseline to study end, with no difference in mortality or adverse clinical events [113].

While we await definitive studies investigating the use of erythropoietin in burned humans, a recent study in burned rats demonstrated preservation of microcirculatory perfusion within endangered areas in a dose-dependent manner, leading to quicker healing with less contracture formation, as well as an increase in hematocrit [114]. Recognizing that there are differences between the human and rat response to burn injury, and that human studies are needed, remembering that erythropoietin is not just a renal hormone responsible for maintaining erythrocytes, but also involved in the acute and subacute response to tissue damage, attenuating injury and facilitating healing and restoration of function [115], may prove an opportunity to further improve future burn care.

Iron

While iron is known to play a role in wound healing, iron deficiency has not been associated with poor wound healing outcomes and iron has not been thoroughly studied in burn patients [116]. Similar to vitamin C, iron contributes to collagen synthesis as a cofactor for hydroxylation of proline and lysine as well as plays a role in oxygen transport to tissues [116, 117]. While iron levels are known to decrease after burn injury, they typically increase back to normal levels without supplementation [118, 119], and the combination of necessary blood transfusions and iron supplementation may lead to excessive levels.

Measuring Effectiveness of Nutritional Support

As post-burn hypermetabolism is associated with profound proteolysis resulting in lean body mass loss and muscle wasting, appropriate monitoring for nutritional needs and deficiencies as well as provision of adequate caloric intake, nitrogen,

micronutrients, and supplements is critical. Yet, providing carbohydrate, protein, and fat in excessive amounts can result in complications. Excess carbohydrate can lead to fat deposition in the liver and increased fat synthesis, as well as difficulties in weaning from mechanical ventilation secondary to elevated respiratory quotients and increased carbon dioxide production. While available tools for monitoring nutritional status following a burn injury are not consistently utilized among the burn community, and there is no agreed upon standard for assessing effectiveness of nutritional support, trending visceral protein measurements combined with acute phase reactants is a common practice in burn units.

Highlighting the lack of good evidence, two studies including 121 burn patients suggest that C-reactive protein and prealbumin (transferrin) predicts morbidity and mortality [120, 121], while two smaller studies question the reliability of these markers [122, 123]. Further questioning the value of this practice, another more recent study, concluded that serum transthyretin levels measured weekly over a hospitalization were reflective of the severity of illness rather than nutritional status, and lower levels correlated with those who were more severely injured [124].

In addition to low visceral protein levels, burn patients characteristically have hypoalbuminemia that persists until wounds are healed and the rehabilitation phase of recovery has begun. In fact, one study found patients with large burns have serum albumin levels that average 1.7 g/dL and never exceed 2.5 g/dL [125]. Suggesting that low albumin levels may be similar to low prealbumin levels, a recent collaborative study between centers in Spain and the USA found that serum albumin level 3–7 days after burn injury is reflective of the severity of injury rather than nutritional status and was predictive of hospital length of stay [126].

However, while the albumin level may be reflective of the severity of illness, similar to anemia, there has been question about what to do about the often significant hypoalbuminemia. Thus, management of hypoalbuminemia is controversial, but there is general agreement that once burn resuscitation is complete, infusion of exogenous albumin to serum levels above 1.5 g/dL does not affect burn patient length of stay, complication rate, or mortality [127, 128].

Perhaps just as important as whether or not to trend visceral proteins is critically following differences between what nutritional supplementation is ordered and what is received or absorbed. Delayed initiation of enteral nutrition, slow advancement of infusion rate, and underprescription, as well as holding tube feeds for operations, tests such as CT scans, mechanical problems such as inadvertently pulled or clogged feeding tubes, or high residuals, all contributes to a receipt of inadequate nutrition. Correspondingly, a recent review of enteral nutrition practices in critical care identified that only about half of critically ill enterally fed patients receive their energy requirements [129]. Thus, when patients fall behind in what they have received for nutritional support, it may be necessary to increase the rate of enteral nutrition and critically assess obstacles to achieving desired support in an effort to catch up on missing calories until the deficit is replaced. Use of enteral feeding protocols increases the overall percentage of goal calories provided and can minimize some of these obstacles [55].

Special Considerations (Children, Elderly, Morbidly Obese)

Children

Much of what is currently practiced for nutritional support of the severely burned patient comes from lessons learned from the severely burned child. With a greater ability to survive otherwise devastating injuries and often better follow up over time, children have provided a resource for long-term follow up. In addition to the research on propranolol and oxandrolone, which started in children, there continues to be research on the long-term effects of what nutritional support is provided during acute hospitalization and chronic deficiencies or effects. One such lesson comes from a study of nearly 1,000 children with >40 % TBSA burns who were randomized to either a low-fat/high-carbohydrate

diet or a high-fat diet. While demographics and caloric intake were similar, those fed the low-fat/high-carbohydrate diet had shorter ICU stays, a lower incidence of sepsis, and lived significantly longer until death than those in the high-fat diet. While there was no difference in overall mortality between groups, there was less hepatic steatosis and less kidney and spleen enlargement [130]. Thus, it is important to not only look at the caloric needs of patients, but the composition of the nutritional support as well.

In addition to the content of nutritional support, providing appropriate support early seems to be a universal theme across all patient populations (adult [22], pediatric [23], and obese [133]) as well. A recent randomized, prospective pediatric study demonstrated that burned children who received enteral nutrition within 3–6 h following the burn had a shorter hospitalization and lower mortality than children who had enteral nutrition initiated 48 h after burn injury [23].

Elderly

The elderly burn patient often has many comorbidities, including chronic organ dysfunction such as chronic kidney disease or congestive organ failure, as well as an already compromised immune system and decreased basal metabolic requirements [131]. Additionally, many elderly patients also have socioeconomic challenges that increase the likelihood of preexisting protein energy malnutrition prior to their burn injury and further compromises their health status, impedes wound healing, and their overall recovery, with resultant poor outcomes if not properly addressed [131]. Similarly, the elderly are more likely to live in a nursing home or be discharged to a nursing home following burn injury. This has another impact on nutritional status, as a recent systematic review of nutritional status of residents in nursing homes revealed a wide range of prevalence of low body mass index, poor appetite, malnutrition, and eating disability in nursing home residents [132]. The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient do not specifically address the geriatric population [55], so we believe assessments of nutritional deficiencies and need for support should be assessed by a nutritionist upon admission to the hospital, and with understanding of the above obstacles to adequate nutritional status in the elderly, it is our practice to follow adult guidelines as described above.

Morbidly Obese

Obesity has become increasingly prevalent in the USA and resultantly in the critical care population as well, with recent demographic trends suggesting that the prevalence of obesity will only continue to grow. Unfortunately, little is known about the nutritional needs of obese burn patients. A multidisciplinary survey sent to US burn centers found that obesity was commonly defined as a BMI > 30 and the Harris–Benedict equation was the most frequently used equation to calculate the caloric needs of obese burn patients at 32 %, most commonly altering the calculations by using adjusted body weight. Hypocaloric formulas were not commonly used (21 %) and enteral nutrition was initiated within 24 h in most centers [133]. These results are consistent with our clinical practice as well; however, there is likely an opportunity for improvement as the perception is that obese patients have a longer length of stay, poor wound healing, poor graft take, and prolonged need for mechanical ventilation relative to the non-obese population.

Recognizing there may be important differences between the obese burn population and other obese ICU populations, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommends that while the basic principles of critical care nutrition apply to the obese ICU patient, a high-protein, hypocaloric regimen should be provided to reduce fat mass, improve insulin sensitivity, and preserve lean body mass [134]. They conclude that the ideal enteral formula should have a low non-protein calorie to nitrogen ratio and have a variety of pharmaconutrient agents

added to modulate immune responses and reduce inflammation [134].

While additional research is necessary, specifically in the obese burn population there are many recognized obstacles to adequate nutritional support in the obese population. One such obstacle is misperceptions about obesity. For example, while greater fat mass in the obese patient may represent an energy reservoir, problems with futile cycling, insulin resistance, and poor fuel utilization may actually predispose the patient to greater losses of lean body mass and delays in feeding reduce the value and impact of enteral nutrition for the critically ill obese patient [135, 136]. Additionally, the obese patient has a greater incidence of associated comorbidities and greater likelihood of metabolic derangements that affect fuel utilization, such as insulin resistance, impaired glucose tolerance, increased fatty acid mobilization, and hyperlipidemia [136]. Finally, bariatric surgery may lead to development of nutrition complications and micronutrient deficiencies such as iron, folate, B12, copper, thiamine, and vitamin D which can uniquely complicate management of critical illness [137, 138].

Conclusions

Severe burn injury continues to represent a significant public health problem worldwide. Major burn injury is characterized by oxidative stress, a prolonged hypermetabolic, catabolic state, and immunosuppression. Resultantly, burn patients have increased cardiac work, increased myocardial oxygen consumption, tachycardia, lipolysis, liver dysfunction, severe muscle catabolism, increased protein degradation, insulin resistance, and growth retardation has been seen in children. Thus, providing the right balance of macro- and micronutrients, antioxidants, and energy is essential to mitigate the hypermetabolic and hypercatabolic state that results. Nutritional support has therefore long been and continues to be an important component of the management of severe burn injury. Some nutritional or metabolically active supplements have demonstrated promise in promoting anabolism in burn patients, including insulin, the anabolic steroid oxandrolone, and propranolol; however, ongoing and future research is necessary to better understand modulation of the hypermetabolic response to severe burn injury and continue to improve burn outcomes.

References

1. Bessey PQ, Lentz CW, Edelman LS, Faraklas I, Finocchiarro MA, Kemalyna KA, et al. National Burn Repository 2013 Report. Chicago: American Burn Association; National Burn Repository; 2013 [cited 2013 Sep 30]. Available at http://ameriburn.org/2013NBRAnnualReport.pdf. Accessed March 3, 2014.
2. Rodriguez NA, Jeschke MG, Williams FN, Kamolz LP, Herndon DN. Nutrition in burns: Galveston contributions. JPEN J Parenter Enteral Nutr. 2011;35:704–14.
3. Curreri PW, Luterman A. Nutritional support of the burned patient. Surg Clin North Am. 1978;58:1151.
4. Waxman K, Rebello T, Pinderski L, O'Neal K, Khan N, Tourangeau S, Himes E, Cordill K. Protein loss across burn wounds. J Trauma. 1987;27:136–40.
5. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. J Crit Care. 2000;15:12–7.
6. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, Ferrando AA, Wolfe RR, Herndon DN. Persistence of muscle catabolism after severe burn. Surgery. 2000;128:312–9.
7. Hart DW, Wolf SE, Chinkes DL, Gore DC, Micak RP, Beauford RB, et al. Determinants of skeletal muscle catabolism after severe burn. Ann Surg. 2000;232:455–65.
8. Jeschke MG, Norbury WB, Finnerty CC, Branski LK, Herndon DN. Propranolol does not increase inflammation, sepsis, or infectious episodes in severely burned children. J Trauma. 2007;62:676–81.
9. Keleman 3rd JJ, Cioffi Jr WG, Mason Jr AD, Mozingo DW, McManus WF, Pruitt Jr BA. Effect of ambient temperature on metabolic rate after thermal injury. Ann Surg. 1996;223:406–12.
10. Matsuda T, Clark N, Hariyani GD, Bryant RS, Hanumadass ML, Kagan RJ. The effect of burn wound size on resting energy expenditure. J Trauma. 1987;27:115–8.
11. Mlcak RP, Jeschke MG, Barrow RE, Herndon DN. The influence of age and gender on resting energy expenditure in severely burned children. Ann Surg. 2006;244:121–30.
12. Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr. 2006;25:37–44.
13. Faisy C, Candela Llerena M, Savalle M, Savalle M, Mainardi JL, Fagon JY. Early ICU energy deficit is a

risk factor for Staphylococcus aureus ventilator-associated pneumonia. Chest. 2011;140:1254–60.
14. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeax RNMC, Delarue J, Berger MM. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24:502–9.
15. Moran L, Custer P, Murphy G. Nutritional assessment of lean body mass. JPEN J Parenter Enteral Nutr. 1980;4:595.
16. Kreymann K, Berger M, Deutz N, Hiesmayr M, Jolliet P, Kazandjiev G. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25:210–23.
17. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27:355–73.
18. Jacobs DG, Jacobs DO, Kudsk KA, et al. EAST Practice Management Guidelines Workgroup. Practice management guidelines for nutritional support of the trauma patient. J Trauma. 2004;57:660–78.
19. Evidence-Based Guidelines Group ABA. Practice guidelines for burn care. J Burn Care Rehabil. 2001;22:59–65S.
20. Alverdy J, Chi HS, Sheldon GF. The effect of parenteral nutrition on gastrointestinal immunity. The importance of enteral stimulation. Ann Surg. 1985;202:681.
21. Holt B, Graves C, Faraklas I, Cochran A. Compliance with nutrition support guidelines in acutely burned patients. Burns. 2012;38(5):645–9.
22. Mosier MJ, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL, Tompkins RG, Herndon DN. Early enteral nutrition in burns: compliance with guidelines and associated outcomes in a multicenter study. J Burn Care Res. 2011;32:104–9.
23. Khorasani EN, Mansouri F. Effect of early enteral nutrition on morbidity and mortality in children with burns. Burns. 2010;36:1067–71.
24. Blackburn GL, Bistrian BR. Nutritional care of the injured and/or septic patient. Surg Clin North Am. 1976;56:1195.
25. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. Burns. 1997;23:313.
26. Raff T, Hartmann B, Germann G. Early intragastric feeding of seriously burned and long-term ventilated patients: a review of 55 patients. Burns. 1997;23:19.
27. Esparza J, Boivin MA, Hartshorne MF, Boivin MA, Hartshorne MF, Levy H. Equal aspiration rates in gastrically and transpylorically fed critically ill patients. Intensive Care Med. 2001;27:660–4.
28. Hauschild TB, Fu KY, Hipwell RC, Baraghoshi G, Mone MC, Nirula MC, Nirula R, Kimball EJ, Barton RG. Safe, timely, convenient, and cost-effective: a single-center experience with bedside placement of enteral feeding tubes by midlevel providers using fluoroscopic guidance. Am J Surg. 2012;204(6):958–62.
29. Jenkins ME, Gottschlich MM, Warden GD. Enteral feeding during operative procedures in thermal injuries. J Burn Care Rehabil. 1994;15:199.
30. Mayes T, Gottschlich MM, Warden GD. Nutrition intervention in pediatric patients with thermal injuries who require laparotomy. J Burn Care Rehabil. 2000;21:451.
31. Dylewksi ML, Baker M, Prelack K, Weber JM, Hursey D, Lydon M, Fagan SP, Sheridan RL. The safety and efficacy of parenteral nutrition among pediatric patients with burn injuries. Pediatr Crit Care Med. 2013;14(3):e120–5.
32. Wolfe RR, Allsop JR, Burke JF. Glucose metabolism in man: responses to intravenous glucose infusion. Metabolism. 1979;28:210–20.
33. Masters B, Aarabi S, Sidhwa F, Wood F. High-carbohydrate, high-protein, low-fat versus low-carbohydrate, high-protein, high-fat enteral feeds for burns. Cochrane Database Syst Rev 2012; 1. doi:10.1002/14651858.CD006122.pub3.
34. Consensus recommendations from the U.S. summit on immune-enhancing enteral therapy. JPEN J Parenter Enteral Nutr 2001;25:S61–2.
35. Patterson E, Wall R, Fitzgerald GF, Ross RP, Stanton C. Health implications of high dietary omega-6 polyunsaturated fatty acids. J Nutr Metab. 2012. doi:10.1155/2012/539426.
36. Gottschlich MM, Jenkins M, Warden GD, Baumer T, Havens P, Snook JT, Alexander JW. Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. JPEN J Parenter Enteral Nutr. 1990;14:225–36.
37. Saito H, Trocki O, Alexander JW, Kopcha R, Heyd T, Joffe SN. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion, and gut mucosal integrity after burn injury. JPEN J Parenter Enteral Nutr. 1987;11:1–7.
38. Saffle J, Wiebke G, Jennings K, Morris SE, Barton RG. Randomized trial of immune-enhancing enteral nutrition in burn patients. J Trauma. 1997;42:793–800.
39. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, D'Elia M, Bernier J. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit Care Med. 2003;31:2444–9.
40. Herndon DN. Nutritional and pharmacological support of the metabolic response to injury. Minerva Anestesiol. 2003;69:264.
41. Demling RH, DeSanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. Burns. 2003;29:793–7.
42. Bulger EM, Jurkovich GJ, Farver CL, Klotz P, Maier RV. Oxandrolone does not improve outcome of ventilator dependent surgical patients. Ann Surg. 2004;240:472–80.

43. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg. 2002;236:814–22.
44. Rock CL, Dechert RE, Khilnani R, Parker RS, Rodriguez JL. Carotenoids and antioxidant vitamins in patients after burn injury. J Burn Care Rehabil. 1997;18:269–78.
45. Gottschlich MM, Mayes T, Choury J, Warden GD. Hypovitaminosis D in acutely injured pediatric burn patients. J Am Diet Assoc. 2004;104:931–41.
46. Berger MM, Cavadini C, Bart A, Mansourian R, Guinchard S, Bartholdi I, et al. Cutaneous copper and zinc losses in burns. Burns. 1992;18:373–80.
47. Dylewski ML, Bender JC, Smith AM, Prelack K, Lydon M, Weber JM, Sheridan RL. The selenium status of pediatric patients with burn injuries. J Trauma. 2010;69:584–8.
48. Traber MG, Leonard SW, Traber DL, Traber LD, Gallagher J, Bobe G, et al. Alpha tocopherol adipose tissue stores are depleted after burn injury in pediatric patients. Am J Clin Nutr. 2010;92:1378–84.
49. Cunningham J, Leffell M, Harmatz P. Burn severity, copper dose, and plasma ceruloplasmin in burned children during total parenteral nutrition. Nutrition. 1993;9:329–32.
50. Gosling P, Rothe HM, Sheehan TM, Hubbard LD. Serum copper and zinc concentrations in patients with burns in relation to burn surface area. J Burn Care Rehabil. 1995;16:481–6.
51. Khorasani G, Hosseinimehr SJ, Kaghazi Z. The alteration of plasma's zinc and copper levels in patients with burn injuries and the relationship to the time after burn injuries. Singapore Med J. 2008;49: 627–30.
52. Voruganti VS, Klein GL, Lu HX, et al. Impaired zinc and copper status in children with burn injuries: need to reassess nutritional requirements. Burns. 2005;31: 711–6.
53. Berger MM. Antioxidant micronutrients in major trauma and burns: evidence and practice. Nutr Clin Pract. 2006;21:438–49.
54. Graves C, Saffle J, Cochran A. Actual burn nutrition care practices: an update. J Burn Care Res. 2009;30: 77–82.
55. McClave SA, Martindale RG, Vanek VW, et al. A.S.P.E.N. Board of Directors; American College of Critical Care Medicine; Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33:277–316.
56. Cope O, Langohr J, Moore F, Webster RC. Expeditious care of full-thickness burn wounds by surgical excision and grafting. Ann Surg. 1947; 125:1–22.
57. Janzekovic Z. A new concept in the early excision and immediate grafting of burns. J Trauma. 1970;10: 1103–8.
58. Manafo W, Auelenbacher C, Papplardo C. Early tangential excision of the eschars of major burns. Arch Surg. 1972;104:503–7.
59. Burke J, Bondoc C, Quinby W. Primary burn excision and immediate grafting: a method for shortening illness. J Trauma. 1974;14:389–95.
60. Burke J, Quinby W, Bondoc C. Primary excision and prompt grafting as routine therapy for the treatment of thermal burns in children. Surg Clin North Am. 1976;56:447–94.
61. Thompkins RG, Burke J, Schoenfeld DA, Bondoc CC, Quinby Jr WC, Behringer GC, Ackroyd FW. Prompt eschar excision: a treatment system contributing to reduced burn mortality. Ann Surg. 1986;204:272–81.
62. Thompkins RG, Remensnyder JP, Burke JF, Tompkins DM, Hilton JF, Schoenfeld DA, et al. Significant reductions in mortality for children with burn injuries through the use of prompt eschar excision. Ann Surg. 1988;208:577–85.
63. Deitch E, Clothier J. Burns in the elderly: an early surgical approach. J Trauma. 1983;23:891–4.
64. Demling R. Effect of early burn excision and grafting on pulmonary function. J Trauma. 1984;24:830–4.
65. Gray D, Pine R, Harner T, Marvin JA, Engrav LH, Heimbach DM. Early surgical excision versus conventional therapy in patients with 20 to 40 percent burns: a comparative study. Am J Surg. 1982;144: 76–80.
66. Chicarilli ZN, Cuono CB, Heinrich JJ, Fichandler BC, Barese S. Selective aggressive burn excision for high mortality subgroups. J Trauma. 1986;26:18–25.
67. Herndon D, Parks D. Comparison of serial debridement and autografting and early massive excision with cadaver skin overlay in the treatment of large burns in children. J Trauma. 1986;26:149–52.
68. Yamamoto H, Silthram S, deSerres S, Hultman CS, Meyer AA. Immediate burn wound excision restores antibody synthesis to bacterial antigen. J Surg Res. 1996;63:157–62.
69. Demling R, Lalonde C. Early burn excision attenuates the postburn lung and systemic response to endotoxin. Surgery. 1990;108:28–35.
70. Drost A, Burleson D, Cioffi W, Jordan BS, Mason Jr AD, Pruitt Jr BA. Plasma cytokines following thermal injury and their relationship with patient mortality, burn size, and time postburn. J Trauma. 1993;35: 335–9.
71. Salisbury R, Carnes R, Enterline D. Biological dressings and evaporative water loss from burn wounds. Ann Plast Surg. 1980;5:270.
72. Childs C, Little RA. Acute changes in oxygen consumption and body temperature after burn injury. Arch Dis Child. 1994;71:31.
73. Gore DC, Chinkes D, Sanford A, Hart DW, Wolf SE, Herndon DN. Influence of fever on the hypermetabolic response in burn-injured children. Arch Surg. 2003;138:169.
74. Parish RA, Novack AH, Heimbach DM, Engrav LR. Fever as a predictor of infection in burned children. J Trauma. 1987;27:69.

75. Greenhalgh DG, Saffle JR, Holmes 4th JH, Gamelli RL, Palmieri TL, Horton JW, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. 2007;28(6): 776–90.
76. Wilmore DW, Long JM, Mason Jr AD, Skreen RW, Pruitt Jr BA. Catecholamines: mediator of the 270 hypermetabolic response to thermal injury. Ann Surg. 1974;180:653–69.
77. Goodall M, Stone C, Haynes Jr BW. Urinary output of adrenaline and noradrenaline in severe 272 thermal burns. Ann Surg. 1957;145:479–87.
78. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. AACN Clin Iss. 2004;15: 45–62.
79. Wolfe RR, Herndon DN, Peters EJ, Peters EJ, Jahoor F, Desai MH, Holland OB. Regulation of lipolysis in severely burned children. Ann Surg. 1987;206: 214–21.
80. Arbabi S, Ahrns KS, Wahl WL, Hemmila MR, Wang SC, Brandt MM, Taheri PA. Beta-blocker use is associated with improved outcomes in adult burn patients. J Trauma. 2004;56:265–9.
81. Herndon DN, Barrow RE, Rutan TC, Minifee P, Jahoor F, Wolfe RR. Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. Ann Surg. 1988;208:484–92.
82. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. N Engl J Med. 2001;345(17): 1223–9.
83. Herndon DN, Nguyen TT, Wolfe RR, Maggi SP, Biolo G, Muller M, Barrow RE. Lipolysis in burned patients is stimulated by the beta 2-receptor for catecholamines. Arch Surg. 1994;129:1301–4.
84. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, Herndon DN. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. Ann Surg. 2007;246:351–60.
85. Aarsland A, Chinkes D, Wolfe RR, Barrow RE, Nelson SO, Pierre E, Herndon DN. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone: rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. Ann Surg. 1996;223(6):777–89.
86. Barret JP, Jeschke MG, Herndon DN. Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. J Trauma. 2001;51(4):736–9.
87. Gore DC, Honeycutt D, Jahoor F, et al. Propranolol diminishing extremity blood flow in burned patients. Ann Surg. 1991;213(6):568–74.
88. Morio B, Irtun O, Herndon DN, Wolfe RR. Propranolol decreases splanchnic triacylglycerol storage in burn patients receiving a high-carbohydrate diet. Ann Surg. 2002;236(2):218–25.
89. Karim A, Ranney RE, Zagarella J, Maibach HI. Oxandrolone disposition and metabolism in man. Clin Pharmacol Ther. 1973;14:862–9.
90. Orr R, Fiatarone SM. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. Drugs. 2004;64:725–50.
91. Barrow RE, Dasu MR, Ferrando AA, Spies M, Thomas SJ, Perez-Polo JR, Herndon DN. Gene expression patterns in skeletal muscle of thermally injured children treated with oxandrolone. Ann Surg. 2003;237:422–8.
92. Demling RH. Comparison of the anabolic effects and complications of human growth hormone and the testosterone analog, oxandrolone, after severe burn injury. Burns. 1999;25:215–21.
93. Hart DW, Wolf SE, Ramzy PI, Chinkes DL, Beauford RB, Ferrando AA, et al. Anabolic effects of oxandrolone after severe burn. Ann Surg. 2001;233:556–64.
94. Wolf SE, Edelman LS, Kemalyan N, Donison L, Cross J, Underwood M, et al. Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial. J Burn Care Res. 2006;27:131–9.
95. Wolf SE, Thomas SJ, Dasu MR, Ferrando AA, Chinkes DL, Wolfe R, Herndon DN. Improved net protein balance, lean mass, and gene expression changes with oxandrolone treatment in the severely burned. Ann Surg. 2003;237:801–10.
96. Cochran A, Thuet W, Holt B, Faraklas I, Smout RJ, Horn SD. The impact of oxandrolone on length of stay following major burn injury: a clinical practice evaluation. Burns. 2013;39(7):1374–9.
97. Porro LJ, Herndon DN, Rodriguez NA, Jennings K, Klein GL, Mlcak RP, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg. 2012;214:489–504.
98. Pham TN, Klein MB, Gibran NS, Arnoldo BN, Gamelli RL, Silver GM. Impact of oxandrolone treatment on acute outcomes after severe burn injury. J Burn Care Res. 2008;29:902–6.
99. Demling RH, DeSanti L. The rate of restoration of body weight after burn injury, using the anabolic agent oxandrolone, is not age dependent. Burns. 2001;17:46–51.
100. Van den Berghe G, Schetz M, Vlasselaers D, Hermans G, Wilmer A, Bouillon R, Mesotten D. Clinical Review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? J Clin Endocrinol Metab. 2009;94:3163.
101. Pidcoke HF, Wanek SM, Rohleder LS. Glucose variability is associated with high mortality after severe burn. J Trauma. 2009;67:990.
102. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M. Association of hyperglycemia with increased mortality after severe burn injury. J Trauma. 2001;51:540.
103. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359.
104. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A. Intensive insulin therapy and mortality among critically ill patients: a

meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180:821.
105. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283.
106. Biolo G, Zorat F, Antonione R, Ciocchio B. Muscle glutamine depletion in the intensive care unit. Int J Biochem Cell Biol. 2005;37:2169–79.
107. Oudemans-van Straaten HM, Bosman RJ, Treskas M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive Care Med. 2001;27:84–90.
108. Griffiths RD, Jones C, Palmer TEA. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition. 1997; 4:296–302.
109. Griffiths RD, Allen KD, Andrews FJ, Jones C. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. Nutrition. 2002;18:546–52.
110. Lin JJ, Chung XJ, Yang CY, Lau HL. A meta-analysis of trials using the intention to treat principle for glutamine supplementation in critically ill patients with burn. Burns. 2013;39:565–70.
111. Zhou YP, Jiang ZM, Sun YH, Wang XR, Ma EL, Wilmore D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. JPEN J Parenter Enteral Nutr. 2003;27:241–5.
112. Peng X, Yan H, You Z, Wang S. Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. Burns. 2004;30:135–9.
113. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, et al. Efficacy of recombinant human erythropoietin in critically ill patients a randomized controlled trial. JAMA. 2002;288:2827–35.
114. Tobalem M, Harder Y, Rezaeian F, Wettstein R. Secondary burn progression decreased by erythropoietin. Crit Care Med. 2013;41:963–71.
115. Kamolz LP, Smolle-Juettner F, Parvizi D. The use of erythropoietin in burns: sometimes good, sometimes not? Crit Care Med. 2013;41:1138–9.
116. Sherman AR, Barkley M. Nutrition and wound healing. J Wound Care. 2011;20(357–8):360,362–367.
117. Stechmiller JK. Understanding the role of nutrition and wound healing. Nutr Clin Pract. 2010;25:61–8.
118. Sanchez-Agreda M, Cimorra GA, Mariona M, Garcia-Jolón. Trace elements in burned patients: studies of zinc, copper and iron contents in serum. Burns. 1977;4:28–31.
119. Belmonte JA, Ibanez L, Ras MR, Aulesa C, Vinzo J, Iglesias J, Carol J. Iron metabolism in burned children. Eur J Pediatr. 1999;158:556–9.
120. Cynober L, Prugnaud O, Lioret N, Duchemin C, Saizy R, Giboudeau J. Serum transthyretin levels in patients with burn injury. Surgery. 1991;109:640–4.
121. Gottschlich MM, Baumer T, Jenkins M, Khoury J, Warden GD. The prognostic value of nutritional and inflammatory indices in patients with burns. J Burn Care Rehabil. 1992;13:105–13.
122. Carlson DE, Cioffi Jr WG, Mason Jr AD, McManus WF, Pruitt Jr BA. Evaluation of serum visceral protein levels as indicators of nitrogen balance in thermally injured patients. JPEN J Parenter Enteral Nutr. 1991;15:440–4.
123. Rettmer RL, Williamson JC, Labbe RF, Heimbach DM. Laboratory monitoring of nutritional status in burn patients. Clin Chem. 1992;38:334–7.
124. Yang HT, Yim J, Cho YS, Kim D, Hur J, Kim JH, et al. Serum transthyretin level is associated with clinical severity rather than nutritional status in massively burned patients. JPEN J Parenter Enteral Nutr. 2013. doi:10.1177/0148607113499588.
125. Sheridan RL, Prelack K, Cunningham JJ. Physiologic hypoalbuminemia is well tolerated by severely burned children. J Trauma. 1997;43:448.
126. Perez-Guisado J, de Haro-Padilla JM, Rioja LF, Derosier LC, de la Torre JI. Serum albumin levels in burn people are associated to the total body surface burned and the length of hospital stay but not to the initiation of the oral/enteral nutrition. Int J Burn Trauma. 2013;3(3):159–63.
127. Greenhalgh DG, Housinger TA, Kagan RJ, Rieman M, James L, Novak S, et al. Maintenance of serum albumin levels in pediatric burn patients: a prospective, randomized trial. J Trauma. 1995;39:67.
128. Cartotto R, Callum J. A review of the use of human albumin in burn patients. J Burn Care Res. 2012;33(6):702–17.
129. Kim H, Stotts NA, Froelicher ES, Engler MM, Porter C. Why patients in critical care do not receive adequate enteral nutrition? A review of the literature. J Crit Care. 2012;27(6):702–13.
130. Lee JO, Gauglitz GC, Herndon DN, Hawkins HK, Halder SC, Jeschke MG. Association between dietary fat content and outcomes in pediatric burn patients. J Surg Res. 2011;166(1):e83–90.
131. Demling RH. The incidence and impact of preexisting protein energy malnutrition on outcome in the elderly burn patient population. J Burn Care Rehabil. 2005;26:94.
132. Bell CL, Tamura BK, Masaki KH, Amella EJ. Prevalence and measures of nutritional compromise among nursing home patients: weight loss, low body mass index, malnutrition, and feeding dependency, a systematic review of the literature. J Am Med Dir Assoc. 2013;14(2):94–100.
133. Coen JR, Carpenter AM, Shupp JW, Matt SE, Shaw JD, Flanagan KE, et al. The results of a national survey regarding nutritional care of obese burn patients. J Burn Care Res. 2011;32:561–5.
134. McClave SA, Kushner R, Van Way CW, Cave M, DeLegge M, Dibaise J, et al. Nutrition therapy of the severely obese, critically ill patient: summation of conclusions and recommendations. JPEN J Parenter Enteral Nutr. 2011;35:88S–96S.

135. Joffe A, Wood K. Obesity in critical care. Curr Opin Anaesthesiol. 2007;20(2):113–8.
136. Port AM, Apovian C. Metabolic support of the obese intensive care unit patient: a current perspective. Curr Opin Clin Nutr Metab Care. 2010;13:184–91.
137. Schweiger C, Weiss R, Berry E, Kaidar A. Nutritional deficiencies in bariatric surgery candidates. Obes Surg. 2010;20(2):193–7.
138. Kazemi A, Frazier T, Crave M. Micronutrient-related neurologic complications following bariatric surgery. Curr Gastroenterol Rep. 2010;12(4):288–95.

Obesity

7

Roland N. Dickerson

The obesity epidemic in the United States is staggering with recent data from 2009 to 2010 indicating 36 % of adult men and women have a body mass index (BMI) of ≥30 kg/m^2 [1]. Four and eight percent of men and women in the U.S. suffer from class III obesity (BMI ≥ 40 kg/m^2), respectively [1]. The prevalence of obesity is also increasing worldwide [2]. It has been estimated that as much as 25 % [2] to 31 % [3] of patients in the intensive care unit (ICU) are obese. Despite this universal healthcare issue, the amount of literature is very limited regarding the best means for optimizing nutrition therapy for hospitalized patients with obesity. Despite the paucity of data, the author intends to provide an evidence-based approach to the metabolic management of these complex patients.

Impact of Obesity upon Clinical Outcome

The diagnosis of obesity is currently based on body mass index (BMI) and is organized into classes of obesity (Table 7.1). However, it has been questioned whether BMI alone is sufficient for assessing obesity and its associated risk in clinical outcomes. Clinical outcomes for patients with obesity may be influenced by the presence of comorbid conditions including diabetes, hyperglycemia, hypoventilation syndrome, other associated metabolic perturbations, and any modifications made to their clinical care because of their obesity including nutrition therapy.

Studies regarding clinical outcomes for obese versus nonobese patients are conflicting. Some studies indicate patients with obesity have worse outcomes, others show no difference, whereas some even suggest improved outcomes. Many of these studies have limitations and are often fraught by retrospective study design and an inadequate number of patients [4]. A limitation with the large datasets is that multivariate analysis has been employed to "control" for variables such as diabetes, hyperglycemia, cardiovascular disease, and other comorbidities associated with obesity. By negating these factors, the data may be biased to omit those obese patients with an unfavorable metabolic profile [3]. For example, in a study evaluating 1,334 trauma patients with Class III (BMI ≥ 40 kg/m^2) obesity, overall mortality was 7.8 % compared to 4.6 % for those with less severe (Class I and II) obesity [5]. Hyperglycemia was discovered to be an independent predictor of outcome. The investigators concluded that when controlling the dataset for hyperglycemia, there was no effect of obesity upon survival. However, the etiology for hyperglycemia during critical illness is often multifactorial and obese patients are at higher risk for

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Table 7.1 Classification of obesity based on body mass index (BMI) for adults

Classification	BMI (kg/m^2) range
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25–29.9
Class I obesity	30–34.9
Class II obesity	35–39.9
Class III obesity	≥40

hyperglycemia due to a greater incidence of insulin resistance, diabetes, and a preexisting inflammatory state due to obesity itself. By controlling for the detrimental effect of hyperglycemia upon outcome, the investigators may have negated the impact and role of obesity upon hyperglycemia which may have contributed to their overall poorer outcome.

Another consideration in the evaluation of the hospitalized patient with obesity is patient acuity. There may be a marked difference in the level of stress among patients. The surgical or trauma patient is admitted to the ICU as a result of an acute stress event, whereas the medical ICU patient may have an exacerbation of a chronic disease. Depending on the patient, the intensity and life-threatening nature for their admission and subsequent events such as multiple operative procedures likely dictates their propensity towards adverse clinical outcomes including mortality, length of stay in the ICU, ventilator days, etc. Table 7.2 depicts studies that have examined the effect of obesity upon clinical outcomes for those admitted to a trauma or surgical ICU. The majority of the studies indicated greater mortality for those with morbid obesity (BMI ≥ 40 kg/m^2) [6–10, 12], although some studies are conflicting [5, 11]. Nasraway et al.'s data indicated an exponential increase in ICU mortality relative to an increase in BMI for surgical patients whose BMI was 40 kg/m^2 or greater for those with an extended stay in the ICU [9]. ICU mortality increased from ~12 % to 15 % for patients with a BMI of about 40 kg/m^2 to 50 % for those with a BMI of ~60 kg/m^2. Mortality increased to over 90 % for those with a BMI above 70 kg/m^2 [9]. Further study to confirm the potential impact of morbid obesity upon survival is warranted.

Because of difficulty in ambulation, the obese patient would be considered at risk for increased morbidity such as pneumonia, venous thromboembolism, and decubitus ulcer formation. The odds ratio was twice to three times higher towards developing these complications for trauma patients with obesity compared to nonobese trauma patients in one study [8]. Conversely, studies examining outcomes of obese versus nonobese patients admitted to the medical ICU or a "mixed population" ICU are divergent. Some suggest an increase in mortality [1], no difference in mortality [13–16], and/or a reduction in mortality [17]. These divergent findings are likely due to heterogeneity in the study populations including the etiology for admission to the intensive care unit, presence of single versus multisystem organ failure [18], adjustment for confounders that may be attributed to or augmented by the presence of obesity [5], duration of stay in the ICU [13], and duration of ventilator dependency [6, 8, 14, 16]. Studies from a "mixed" type of ICU population may also be uninterpretable for evaluating certain subsets (e.g., surgical versus trauma versus medical) of patients.

Another factor, often not addressed in studies regarding clinical outcomes for hospitalized patients with obesity, is the presence of sarcopenia. Sarcopenic obesity is the presence of excessive body fat and reduced lean tissue mass with impaired physical function [19]. ICU patients with this body composition abnormality may have substantial influence upon clinical outcomes and requires further study. A final consideration, often not addressed in these large studies, is the nutrition therapy given to the patients. Early initiation of nutrition therapy decreases infectious morbidity for critically ill surgical and trauma patients [20]. Provision of higher amounts of protein has been associated with improved survival during critical illness [21, 22]. Preliminary evidence indicates excessive caloric intake worsens morbidity for critically ill obese patients [23]. Thus, early or delayed nutrition therapy, as well as the composition and amount of nutrition therapy, may have influenced clinical outcomes.

Table 7.2 Impact of obesity upon clinical outcomes for critically ill surgical and trauma patients

Author, year	Patient care setting	Population characteristics, No. of patients	Results
Hoffman, 2012 [6]	Trauma ICU	ISS > 16 BMI < 20, *n* = 269 BMI 20–24.9, *n* = 2,617 BMI 25–29.9, *n* = 2,120 BMI ≥ 30, *n* = 760	Obese patients had an increased risk for hospital mortality (OR 1.6, *P* = 0.01). Obese patients had greater multiple organ failures (30 % vs. 23 %; *P* = 0.03), hospital LOS (31 vs. 27 days; *P* = 0.001), ICU LOS (13 vs. 11 days; *P* = 0.001); ventilator days (8 vs. 6 days; *P* = 0.001) than those with a normal BMI, respectively.
Hutagalung, 2011 [7]	Surgical ICU	BMI < 18.5, *n* = 186 BMI 18.5–24.9, *n* = 2,633 BMI 25–29.9, *n* = 4,093 BMI 30–39.9, *n* = 2,066 BMI ≥ 40, *n* = 179	Patients with Class I and II obesity had lower 60 days mortality than patients with normal BMI (HR 0.86, *P* = 0.047). Morbidly obese patients had greater 60 days mortality than those with normal BMI especially after neurosurgical procedures (HR 0.3, *P* = 0.039).
Newell, 2007 [8]	Trauma ICU	ISS > 16, blunt trauma BMI < 18.5, *n* = 61 BMI 18.5–24.9, *n* = 554 BMI 25–29.9, *n* = 529 BMI 30–39.9, *n* = 271 BMI ≥ 40, *n* = 93	Obese and morbidly obese patients were more likely to develop ARDS (OR 1.2, 3.6; *P* = 0.03), acute respiratory failure (OR 1.8, 2.8; *P* = 0.001), acute renal failure (OR 4.4, 13.5; *P* = 0.01) or multisystem organ failure (OR 1.4, 2.6; *P* = 0.03), pneumonia (OR 1.7, 2.5; *P* = 0.001), DVT (OR 2.2, 4.1; *P* = 0.014), or a decubitus ulcer (OR 1.6, 2.8; *P* = 0.001) than those with normal BMI.
Nasraway, 2006 [9]	Surgical ICU	ICU Stay ≥ 4 days BMI < 18.5, *n* = 26 BMI 18.5–24.9, *n* = 164 BMI 25–29.9, *n* = 118 BMI 30–39.9, *n* = 74 BMI > 40, *n* = 24	ICU and Hospital mortality (%) increased from 19 % and 23 % for those with a normal BMI to 33 % (*P* = 0.009) and 33 % (*P* = 0.045), respectively.
Bochicchio, 2006 [10]	Trauma ICU	BMI < 30, *n* = 1,105 BMI ≥ 30, *n* = 62	No difference in mortality between groups. Obese patients had a greater hospital LOS (25 vs. 15 days, *P* = 0.001), ICU LOS (19 vs. 12 days; *P* = 0.001), and infections (61 % vs. 34 %; *P* = 0.001)
Ciesla, 2006 [11]	Surgical ICU (trauma patients)	ISS > 15; excluded patients with isolated TBI and those who died within 48 h of admission BMI < 25, *n* = 286 BMI 25–29.9, *n* = 278 BMI > 30, *n* = 152	No difference in mortality for obese vs. nonobese. Obesity was associated with increased multiple organ failure (37 % vs. 22 %; OR 1.8). ICU LOS and hospital LOS were longer for obese patients (21 vs. 16 days; *P* = 0.001) and (25 vs. 20 days, *P* = 0.001).
Brown, 2005 [12]	Trauma ICU	BMI < 30, *n* = 870 BMI ≥ 30, *n* = 283	Increased risk for mortality associated with obesity (OR 1.6, *P* = 0.03). More obese patients developed multisystem organ failure (19 % vs. 11 %, *P* = 0.001), ARDS (11 % vs. 6 %, *P* = 0.002), and required dialysis (8 % vs. 4 %, *P* = 0.01). ICU LOS and hospital LOS were longer for obese patients (13 vs. 10 days, *P* = 0.005) and 24 vs. 19 days, *P* = 0.01.

ARDS Acute respiratory distress syndrome, *BMI* Body mass index, *HR* Hazard ratio, *ICU* Intensive care unit, *ISS* Injury severity score, *LOS* Length of stay, *OR* Odds ratio, *TBI* Traumatic brain injury

The Obesity Paradox

Recent data have challenged the prevailing theme that increased mortality is associated with an increased BMI above normal but an inverse J-shaped curve may be present when relating BMI to survival [1, 7, 17, 24]. Malnourished patients with a low BMI have the worst survival rate followed by those with severe Class III obesity (BMI ≥ 40). Surprisingly, overweight and mild-to-moderate obese patients have similar or even improved survival rates compared to those with a normal BMI [1, 7, 17, 24]. Since these data appear incongruent of what would be expected, the term "obesity paradox" has been used to describe this phenomenon.

Etiologies for this presumed paradox are not clear. Emerging research indicates that adipose cells may mediate a range of short-term beneficial functions in response to sepsis or stress. Adipose tissue is a functional organ capable of altering metabolism and secreting immune-modulating chemokines and not just a passive depot for excess energy. Leptin, secreted from adipose tissue, augmented the immune response and improved bacterial clearance in animals [25]. In one study, critically ill patients who survived from sepsis had threefold higher plasma concentrations of leptin compared with those who died [26]. Lipoproteins, apoproteins, and eicosanoid-derived resolvins and protectins have been shown to neutralize lipopolysaccharide, stimulate clearance of inflammatory debris, and exert direct anti-inflammatory actions [27].

It has been argued that the obesity paradox is not a real phenomenon, but rather reflective of selection bias in study design without adequately adjusting for confounding factors that may have influenced clinical outcomes. It has also been suggested that reverse causation may explain the apparent benefits of being overweight or having mild obesity for critically ill patients [28]. Reverse causation could potentially explain the apparent benefits of overweight and mild-to-moderate obesity if the nonobese group suffered from diseases causing weight loss (to the extent of achieving a normal or low BMI) prior to ICU admission [28]. One significant omission by the studies examining the obesity paradox is lack of consideration regarding the impact of parenteral or enteral nutrition therapy. Based on the current state of evidence, critically ill patients who are malnourished (BMI < 18.5 kg/m^2) or have Class III obesity (BMI ≥ 40 kg/m^2) are at greater risk for increased morbidity and mortality. However, further studies assessing the impact of obesity upon clinical outcomes for critically ill patients are needed to conclusively determine whether the obesity paradox is real or not.

Metabolic and Physiologic Consequences of Obesity that Compound Critical Illness and Nutrition Therapy

In developing a nutritional regimen for the critically ill obese patient, it is often necessary to modify the regimen based on obesity-associated comorbidities (Table 7.3). The greatest concern is to not overfeed the obese patient as complications from overfeeding extend beyond just a simple amplification in preexisting abundant caloric reserves. The nutritional regimen may need to be modified for hyperglycemia, hyperlipidemia, hypercapnia, congestive heart failure, or nonalcoholic fatty liver disease. Modification of the nutritional regimen is often complicated since many critically ill patients with obesity may experience multiple concurrent comorbidities.

Patients with even mild degrees of obesity may be insulin-resistant, but it becomes more common in the morbidly obese patient [29].

Table 7.3 Metabolic and physiologic effects of obesity that compound the metabolic response to critical illness and the adverse effects of overfeeding

1.	Insulin resistance and increased incidence of diabetes mellitus
2.	Increased incidence of hypertriglyceridemia
3.	Hypoventilation syndrome, difficulty with ventilator weaning
4.	Decreased left ventricular contractility and ejection fraction, fluid overload
5.	Nonalcoholic fatty liver disease and steatosis

Critically ill patients with sepsis or traumatic injuries experience a post-receptor insulin resistance with increased counter-regulatory hormone production resulting in substantial hyperglycemia [30]. Thus, when obesity, critical illness, and nutrition therapy are compounded together, hyperglycemia is a prevalent complication that requires vigilant management. Given the recent data over the past decade that trauma [31–33], cardio-thoracic surgery [34], thermally-injured [35], and potentially other surgical patients benefit from tighter glycemic control (e.g., blood glucose concentrations less than 140–150 mg/dL) than that required of other populations (e.g., medical ICU patients) [36], glycemic control can be challenging for the critically ill, surgical patient with obesity. We found that our critically ill trauma patients with obesity-related diabetes mellitus who required a continuous intravenous insulin infusion experienced a greater hyperglycemic index, greater blood glucose concentration variability, and spent less average time in the target blood glucose concentration (e.g., 70–149 mg/dL) than nondiabetics [37].

Hyperlipidemia, particularly hypertriglyceridemia, is also more prevalent in patients with obesity versus the nonobese. This is particularly problematic for patients given intravenous lipid emulsion as part of the parenteral nutrition therapy or propofol (10 % lipid emulsion is used as the drug carrier solution) as triglyceride clearance may be impaired. Severe hypertriglyceridemia from impaired lipid emulsion clearance may impair immune function, reticuloendothelial system clearance, cause hepatic fat accumulation, as well as potentially induce acute pancreatitis. For those with hypertriglyceridemia associated with insulin-dependent diabetes mellitus, improvement in glycemic control with insulin therapy will often result in near normalization of serum triglyceride concentration [38] allowing for the use of intravenous lipid emulsion. For patients with non-insulin-dependent diabetes mellitus, hypertriglyceridemia may not be fully corrected with appropriate glycemic control [38] and lipid emulsion clearance may potentially remain impaired.

It is well established that patients with morbid obesity have a prolonged duration of mechanical ventilation compared to their nonobese counterparts [6, 8, 12, 16]. Obesity hypoventilation syndrome is characterized by hypercapnic respiratory failure and alveolar hypoventilation resulting in a progressive requirement for a higher minute ventilation [39]. Aggressive nutrition therapy with higher amounts of total calories, resulting in overfeeding, can significantly worsen hypercapnia [40, 41]. Talpers and associates demonstrated increased carbon dioxide production from parenteral nutrition therapy when total energy intake exceeded 1.3 times the predicted energy expenditure based on the Harris-Benedict equations [42] for nonobese patients [40, 41]. Thus, caution regarding the amount of calories given to ventilator-dependent patients with chronic obstructive pulmonary disease or obesity hypoventilation syndrome is pivotal when planning their nutritional regimen.

Because of extreme body mass and the requirement for an increased circulating blood volume, patients with morbid obesity can develop myocardial hypertrophy and decreased compliance in addition to hypertension. These cardiovascular alterations may eventually lead to congestive heart failure, total body fluid overload, higher risk for arrhythmias, and sudden death [39]. In severe cases of obesity hypoventilation syndrome, extreme pulmonary failure may lead to right heart failure with pulmonary edema [39]. Provision of nutrition therapy may be problematic due to their requirement for fluid restriction.

The critically ill surgical patient with morbid obesity is also at risk for nonalcoholic fatty liver disease (NAFLD) and hepatic steatosis. The prevalence of NAFLD ranges from 57 % of overweight subjects to 98 % of nondiabetic obese patients [43]. About one third of patients with obesity exhibit hepatic steatosis. Older patients with obesity tend to be at greater risk for NFALD likely due to their prolonged duration of hypertension, obesity, hyperlipidemia, and diabetes [43]. Overfeeding has long been established as a common complication of parenteral nutrition therapy resulting in fatty infiltration of the liver and hepatic steatosis. Evidence of fatty infiltration of the liver and hepatic dysfunction has been demonstrated as early as 10–14 days of caloric overfeeding with

parenteral nutrition [44]. Therefore, it is essential that the critically ill patient with obesity not be overfed with excessive calories.

Defining Calorie and Protein Requirements for Surgical Patients with Obesity

Defining caloric requirements for the hospitalized obese surgical or trauma patient with obesity is problematic due to the wide variability in resting energy expenditure and the lack of precision in predicting their resting energy expenditure [45]. Historically, many methods have attempted to predict energy expenditure for critically ill obese patients, but most have been found to be unsuccessful. This inaccuracy in predicting resting energy expenditure is due to the wide variability in muscle mass among obese patients as well as the myriad of diseases and conditions that can variably increase or decrease energy expenditure. Within the past decade, better methods of predicting resting energy expenditure for critically ill obese patients have been developed. Frankenfield and coworkers have developed two equations (one for older patients ≥ 60 years of age and the other for adults < 60 years of age) which have been validated for critically ill, ventilator-dependent obese patients (Table 7.4) [46, 47, 50]. These equations tend to accurately estimate resting energy expenditure (+10 %) of critically ill, ventilator patients 70 % of the time, but the remaining patients will be significantly under or overestimated [47, 50]. For less sick, nonmechanically ventilated, hospitalized patients with obesity, some clinicians have favored the use of the Mifflin equations to estimate resting energy expenditure (Table 7.4). Unfortunately, the Mifflin equations were developed in "unstressed, healthy obese subjects" and its use has not been validated in the hospitalized, non-ventilator-dependent obese population. Because of the high risk for overfeeding complications in hospitalized patients with obesity and the uncertainty of accurately estimating resting energy expenditure, we have adopted the use of a hypocaloric, high-protein nutritional regimens for these patients. To understand the rationale for this type of therapy, it is necessary to review the impact of calories and protein upon nitrogen balance as well as its overall effect on changes in body composition.

Table 7.4 Predictive methods for estimating resting energy expenditure (REE) for hospitalized patients with obesity

Ventilator-dependent, critically ill patients with obesity < 60 years of age [46, 47]: REE (kcal/day) = (Mifflin REE × 0.96) + (T_{max} × 167) + (Ve × 31) − 6212 whereas T_{max} is maximum temperature for the day (°C) and Ve is minute ventilation (L/min)
Ventilator-dependent, critically ill patients with obesity ≥ 60 years of age [48]: REE (kcal/day) = (Mifflin REE × 0.71) + (T_{max} × 85) + (Ve × 64) − 3085 whereas T_{max} is maximum temperature for the day (°C) and Ve is minute ventilation (L/min)
Mifflin-St. Jeor Equation [49] (Mifflin REE): Men: REE (kcal/day) = (Weight × 10) + (Height × 6.25) − (Age × 5) + 5 Female: REE (kcal/day) = (Weight × 10) + (Height × 6.25) − (Age × 5) − 161 whereas weight is in kg, height is in cm, and age is in years

Interpreting Nitrogen Balance

Despite its limitations, the most common clinical tool to assess adequacy of a nutritional regimen in terms of net protein anabolism is nitrogen balance. Nitrogen balance is simply the difference between the amount of nitrogen given to the patient and the amount of nitrogen lost. If more nitrogen is given to the patient than lost, the patient is considered to be anabolic or "in positive nitrogen balance." If more nitrogen is lost than given, the patient is considered to be catabolic or "in negative nitrogen balance." A nitrogen balance within −4 g/day to +4 g/day is usually considered as "nitrogen equilibrium." To determine nitrogen balance, a 24 h urine collection for urea nitrogen excretion is conducted and protein intake from the parenteral or enteral nutrition from that same 24 h period is ascertained. An appropriate

nitrogen balance (NB) equation for critically ill surgical and trauma patients [51] is as follows:

$$\text{NB (g/day)} = \text{Protein intake (g/day)}/6.25 - \text{Urine Urea Nitrogen (g/day)}/0.85 - 2^{1}$$

This NB formula is more accurate for critically ill surgical and trauma patients than the classic NB formula (NB = Protein intake/6.25 – Urine Urea Nitrogen – 4). The "fudge factor" of 4 g assumes 2 g for non-urea nitrogen in the urine and 2 g for estimation of stool and insensible losses. Catabolic, critically ill patients often experience high urinary urea nitrogen excretion rates and the amount of urinary non-urea nitrogen excretion is often greater than the assumed 2 g and sometimes as much as 4–6 g/day [51]. We found that an estimation of ~15 % of total urinary nitrogen better predicted actual urinary non-urea nitrogen excretion in our critically ill trauma patients [51]. Ideally, the goal should be to achieve positive nitrogen balance. Unfortunately, a positive nitrogen balance may not be possible during the acute phase post-injury or during sepsis as total body protein catabolism will exceed total body protein anabolism despite the provision of parenteral or enteral nutrition [52, 53]. We have generally accepted a nitrogen balance of about −5 or −6 g/day or better during an aggressive protein intake (e.g., within ~2 to 3 g/kg/day) as successful in such patients until the stress abates [54].

Given the increased risk for metabolic complications from overfeeding for obese patients, it is necessary to be conservative with caloric intake to avoid these complications, yet provide an effective regimen whereby patients can achieve net protein anabolism, provide an effective immune response, heal wounds, and exhibit positive clinical outcomes. As a result, clinician researchers have pursued techniques to provide a calorie-reduced, high-protein regimen in an effort to meet these desired outcomes. To understand the rationale for hypocaloric, high-protein regimens for hospitalized and critically ill patients with obesity, it is necessary to describe the relationship between calories and protein and their effect on net protein anabolism and body composition.

Relationship Between Calories and Protein and Its Influence on Nitrogen Balance and Body Composition

The relationship between calorie and protein intake upon nitrogen balance for unstressed nutritionally depleted patients is depicted in Fig. 7.1 [55, 56]. At a fixed protein intake, nitrogen balance increases rapidly as calories are increased until a caloric intake of about 60–70 % of total energy expenditure is achieved. When the caloric intake exceeds 60–70 % of energy expenditure, nitrogen balance continues to improve but at a much slower rate. Points A and B in Fig. 7.1 illustrate achievement of nitrogen equilibrium at caloric intakes less than energy expenditure when given a greater protein intake. Point C indicates nitrogen equilibrium with a lesser protein intake but with a greater caloric intake than that given at points A and B. Point D reflects nitrogen equilibrium with a low protein intake but with marked overfeeding of calories. Thus, the same nitrogen balance (slightly positive or nitrogen equilibrium) can be achieved by different macronutrient prescriptions (a very low calorie/very high-protein regimen, a low-calorie/high-protein regimen, a moderate protein and moderate calorie regimen, or a low protein, very high calorie regimen). However, despite a similar nitrogen balance, each of these regimens will result in different body composition changes. The low-calorie, high-protein regimens (points A and B) given to the unstressed protein-depleted patient will likely result in lean body mass gain and body fat loss, whereas the moderate calorie and protein

[1] Whereas the divisor of 6.25 assumes good quality protein with a nitrogen content of about 16 %. The divisor of 0.85 for urine urea nitrogen indicates 15 % of total nitrogen excretion is from non-urea nitrogen sources such as ammonia, creatinine, and amino acids. The final 2 g is an estimation of stool/integumentary and insensible losses for a patient without diarrhea.

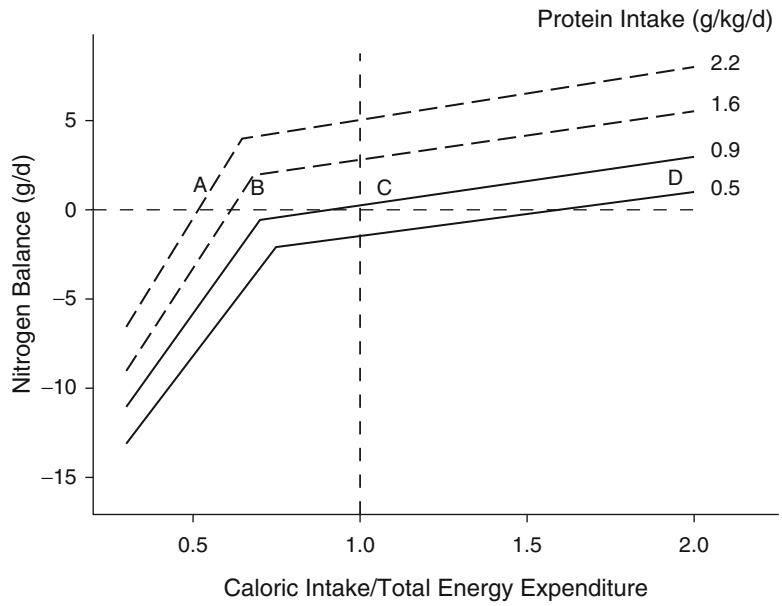

Fig. 7.1 Potential relationship between calorie and protein intake on nitrogen balance [55]. The *dashed lines* represent protein intakes that could achieve net protein anabolism during hypocaloric nutrition therapy. Points A and B illustrate achievement of nitrogen equilibrium at caloric intakes less than energy expenditure when given higher protein intakes, whereas point C indicates nitrogen equilibrium with a lesser protein intake with a greater caloric intake, and point D reflects nitrogen equilibrium with a low protein intake but with a markedly increased caloric intake

regimen (point C) will result in lean body and body fat maintenance (possibly some minor gain in both compartments). The high-calorie, low-protein regimen (point D) will result in marked body fat mass gain with minimal change or even loss of lean body mass [57]. These inferred changes in body composition are derived from the series of studies from Hill and associates that examined varying caloric and protein intakes and their influence upon changes in body protein, fat, and water compartments for surgical and gastroenterological patients requiring parenteral nutrition [57–59].

However, during critical illness, the impact of calories and protein upon nitrogen balance and body composition is different than that previously described for the unstressed, nutritionally depleted patient. Isotope amino acid studies indicate that the marked increase in whole body catabolism cannot be overcome by an increase in whole body synthesis from nutrition therapy, until the stress of trauma or sepsis begins to resolve [52, 53]. Although total body protein content declines during critical illness despite nutrition therapy [60], the rate of net protein catabolism is substantially reduced when compared to when not given nutrition therapy [52, 53]. An aggressive protein intake of 2–2.5 g/kg/day will achieve nitrogen equilibrium in only about half of critically ill patients during the first 14 days post-admission to the trauma ICU [54]. To ascertain if increases in caloric intake will improve nitrogen balance and decrease skeletal muscle catabolism (urinary 3-methylhistidine excretion) in critically ill trauma patients, Frankenfield randomized 30 patients to receive a total caloric intake of either 1.5, 1.2, or 0.8 times the measured resting energy expenditure while keeping protein intake constant at 1.7 g/kg/day [61]. Nitrogen balance was similar among the three groups at approximately −8 g/day. No significant difference in urinary 3-methylhistidine excretion (a marker of muscle proteolysis) among the different caloric intake groups was also noted. Increasing caloric delivery to critically ill, thermally injured patients resulted in a significant

increase in total body fat especially when caloric intake exceeded 1.2 times the measured resting energy expenditure [62]. Additionally, increasing caloric intake had no significant effect on lean body mass as it remained essentially unchanged [62]. Taken together, these data suggest that protein has a more profound effect than calorie intake on net protein catabolism, nitrogen balance, and loss of body protein mass during critical illness. Increases in caloric intake may be potentially detrimental for the obese patient who is already calorically abundant and who is susceptible to overfeeding complications.

These data serve as the premise for providing hypocaloric, high-protein nutrition therapy for hospitalized patients with obesity. By providing a conservative caloric intake, complications associated with overfeeding such as worsening hyperglycemia, hypercapnia, and hepatic fat accumulation would likely be reduced. A conservative caloric intake may also result in increased lipolysis and net fat oxidation with weight loss [63] which would be a welcome secondary benefit. However, in order to compensate for the conservative caloric intake, an increase in protein supplementation is essential in an effort to achieve net protein anabolism as illustrated in Fig. 7.1.

Evidence for the Efficacy of Hypocaloric, High-Protein Nutrition Therapy for the Hospitalized Surgical Patient with Obesity

Prior to discussing the evidence for the use of hypocaloric high-protein nutrition therapy, it is essential that permissive underfeeding be differentiated from hypocaloric, high-protein feeding as the literature sometimes refers to these two terminologies interchangeably or even concurrently (e.g., permissive hypocaloric, high-protein feeding). Permissive underfeeding indicates that the patient is intentionally allowed to receive less than what is considered "goal intake" for BOTH calories and protein, whereas the intent of a hypocaloric, high-protein regimen is to provide only a calorie deficit while ensuring adequate protein intake. However, it is important to recognize that a significant amount of the permissive underfeeding data was created in nonobese populations whereby attention to feeding intolerance or avoidance of overfeeding complications may not have been well managed. The permissive underfeeding studies were usually noninterventional or observational in design and may not have controlled for factors such as duration of feeding or length of stay in the ICU that may have influenced interpretation of their data [64–66].

An often cited permissive underfeeding study indicated that patients who received the highest average amount of nutrition (highest tertile) had the worse outcomes [64]. Thoughtful interpretation of their data may lead to a different conclusion. Less sick patients who were discharged from the medical ICU in a just few days are less likely to have received full nutrition therapy for a prolonged time since feedings are generally advanced daily over 2–4 days until the goal feeding rate is achieved. Therefore, their average caloric intake may be considered as "low." Conversely, sicker patients with a prolonged ICU stay were more likely to have received a greater average caloric intake since the goal rate may have been provided for a more prolonged time period. Thus, clinical outcomes may have been more reflective of duration of ICU stay and the reasons for the patients' prolonged stay, as opposed to the amount of nutrition the patient received.

Finally, and probably most importantly, protein intake was usually inadequate for the critically ill patient [54, 67–69] in many of the permissive underfeeding studies. The impact of inadequate protein intake is evident from a large, observational cohort study of international nutrition practices that indicated patients with Class II obesity (BMI 35–39.9 kg/m^2) who received a hypocaloric diet combined with a low protein intake (average intake of 1,000 kcal/day or 9 kcal/kg/day and 46 g of protein/day or 0.4 g/kg/day, respectively) experienced a worsened 60 day mortality rate [70]. In summary, we recommend that intentional permissive underfeeding with inadequate protein intake be avoided for the seriously ill surgical or trauma patient with obesity.

Table 7.5 summarizes the current literature on hypocaloric, high-protein nutrition therapy for surgical and trauma patients with obesity. The first case series documenting the use of

Table 7.5 Summary of clinical studies with hypocaloric, high-protein therapy in hospitalized obese surgical and trauma patients

Author, year	Population characteristics No. of patients	Protein intake (g/kg/day)	Caloric intake (kcal/kg/day)	Nutritional outcome	Clinical outcome
Dickerson, 1986 [63]	Surgical, PN $n=13$	2.1 IBW	25 IBW	NB: +2.4 g/day; increased serum albumin and TIBC	Healed wounds, closed fistulae
Burge, 1994 [71]	Surgical, PN				
	$n=9$	2.0 IBW	22 IBW	NB: +1.3 g/day	
	$n=7$	2.2 IBW	42 IBW	NB: +2.8 g/day	
Choban, 1997 [72]	Surgical, SICU, PN				Less insulin therapy, no difference in mortality
	$n=16$	2.0 IBW	22 IBW	NB: +4.0 g/day	
	$n=14$	2.0 IBW	36 IBW	NB: +3.6 g/day	
Liu, 2000 [80]	Surgical, PN				No difference in morbidity or mortality
	<60 yo, $n=18$	1.8 IBW	18 CBW	NB: +3.4 g/day	
	≥ 60 yo, $n=12$	1.9 IBW	18 CBW	NB: +0.2 g/day	
Dickerson, 2002 [23]	Trauma ICU, EN				Decreased ICU stay, decreased antibiotic days, trending decrease in ventilator days
	$n=28$	1.5 IBW	22 IBW	NB: −1.4 g/day, improved PA	
	$n=12$	1.9 IBW	30 IBW	NB: −2.7 g/day, improved PA	
Choban and Dickerson, 2005 [29]	Surgical, SICU, Trauma ICU, PN, EN BMI 30–39.9 $n=48$ BMI ≥ 40 $n=22$	Regression analysis for determination of protein requirements to achieve nitrogen equilibrium from 2 sites		ICU patients: BMI 30–39.9: 2 g/kg IBW/day BMI > 40: 2.5 g/kg IBW/day Non ICU patients: BMI 30–39.9: 1.7 g/kg IBW/day BMI > 40: 1.8 g/kg IBW/day	
Hamilton, 2011 [87]	Post-bariatric surgery with fistula/anastomotic leak, PN $n=23$	1.2 CBW	14 CBW	7 % decrease in BMI in 1.5 months Increase in serum albumin	21 out of 23 transitioned to EN or oral diet; 1 lost to follow-up
Dickerson, 2013 [67]	Trauma ICU, EN, PN				No difference in ICU LOS, ventilator days, hospital LOS
	<60 yo, $n=41$	1.9 IBW	18 IBW	NB: −4.9 g/day @ 2.3 g/kg IBW	
	≥60 yo, $n=33$	2.1 IBW	21 IBW	NB:−3.2 g/day @ 2.3 g/kg IBW Similar changes in PA; higher SUN for older patients	

BMI Body mass index (kg/m^2), *CBW* Current body weight, *EN* Enteral nutrition, *IBW* Ideal body weight, *ICU* Intensive care, *LOS* Length of stay, *n* Number of patients, *NB* Nitrogen balance, *PA* Serum prealbumin concentration, *PN* Parenteral nutrition, *SICU* Surgery intensive care unit, *TIBC* Total iron binding capacity, *yo* Years old

hypocaloric, high-protein nutrition therapy for mild to moderately stressed, obese surgical patients evaluated 13 adult patients with obesity (208 ± 114 % ideal body weight) and postoperative complications of sepsis with anastomotic leaks, abscesses, fistulae, or wound dehiscence were administered hypocaloric, high-protein parenteral nutrition. [63] Patients received 52 % of measured resting energy expenditure as nonprotein calories (or ~70 % of measured

resting energy expenditure as total calories) and 2.1 ± 0.6 g/kg ideal body weight/day of protein for 48 ± 31 days. Positive nitrogen balance or nitrogen equilibrium and an increased serum protein response were achieved. Fifty to sixty-eight percent of nonprotein energy expenditure was derived from endogenous net fat oxidation and a 2.3 ± 2.7 kg/week average weight loss occurred. All patients demonstrated complete healing, as evidenced by closed fistulae, resolution of abscess cavities, and wound closure.

This case series was followed by two prospective, randomized, controlled trials from Choban and the Ohio State University Hospital group comparing hypocaloric with a higher calorie parenteral nutrition regimen [71, 72]. In their first study, 16 hospitalized obese (>130 % ideal body weight) patients received hypocaloric (50 % of measured energy expenditure as nonprotein calories or 14 total kcal/kg actual weight/day) or eucaloric (100 % of measured energy expenditure or 25 total kcal/kg actual weight/day) parenteral nutrition therapy [71]. Protein intake was similar at 2.0 ± 0.6 g/kg ideal body weight/day and 2.2 ± 0.4 g/kg ideal body weight/day, respectively. The length of time patients received the study formula was limited to 2 weeks. No significant difference in nitrogen balance was observed between feeding groups (1.3 ± 3.6 g/day versus 2.8 ± 6.9 g/day). In their second study [72], calorie dosing was weight-based rather than titrated to measured resting energy expenditure. Thirty obese (average BMI, 35 kg/m^2) patients (13 of which were ICU patients) were given either 22 kcal/kg ideal body weight/day (14 kcal/kg actual weight/day) or 30 kcal/kg ideal body weight/day (23 kcal/kg actual weight/day). Protein intake was 2.0 g/kg ideal body weight/day for both groups. Duration of therapy was 11 ± 3 days. Nitrogen balance was similar at 4.0 ± 4.2 g/day vs. 3.6 ± 4.1 g/day for the hypocaloric and eucaloric groups, respectively. Patients who received the greater caloric intake tended to have higher serum glucose concentrations and increased insulin requirements; however, these differences were not statistically significant. Length of hospital stay and mortality were not different between groups.

In 2002, Dickerson and colleagues retrospectively examined the impact of hypocaloric vs. eucaloric enteral feeding in critically ill trauma patients with obesity. This study was different from the previously published work in that patients were enterally fed as opposed to parenterally fed. Additionally, all patients were critically ill, ICU patients [23]. Twenty-eight patients (average BMI, 41 kg/m^2) received hypocaloric feeding (<25 kcal/kg ideal body weight/day) and twelve (average BMI, 36 kg/m^2) received eucaloric feeding (25–30 kcal/kg ideal body weight/day). Protein goals were 2 g/kg ideal body weight/day for both groups. Mean nitrogen balance was not different between groups (−1.4 ± 5.8 g/day vs. −2.7 ± 5.9 g/day, respectively). In contrast to the previous studies, a modest mean negative nitrogen balance was observed due to the hypercatabolic state of the critically ill patients [54]. Serum prealbumin concentrations significantly increased for both groups. Unlike the previous studies that indicated no difference in clinical outcomes between hypocaloric and eucaloric feeding groups, enteral hypocaloric feeding (with an isonitrogenous protein intake to eucaloric feeding) was associated with improved clinical outcomes. The hypocaloric feeding group had a statistically significant shorter duration of ICU stay (19 ± 10 days vs. 29 ± 16 days), decreased antibiotic days (17 ± 12 days vs. 27 ± 17 days), and a trending decrease in days of mechanical ventilation (16 ± 11 days vs. 24 ± 17 days) [23]. Since this small, retrospective study is the only study to date to indicate improved clinical outcomes with hypocaloric, high-protein feeding for obese critically ill patients, confirmation of these data by a large prospective, randomized controlled trial is warranted.

Despite the paucity of published studies, the use of hypocaloric, high-protein nutrition therapy for the critically ill obese patient has been gaining momentum. Expert opinions from the 2013 American Society for Parenteral and Enteral Nutrition clinical guidelines on nutrition support of hospitalized patients with obesity [4], 2009 American Society for Parenteral and Enteral Nutrition and Society for Critical Care Medicine guidelines for the provision and assessment of

nutrition support therapy in the adult critically ill patient [73], and 2011 summit report on nutrition therapy of the severely obese, critically ill patient [74] recommend this mode of therapy for hospitalized patients with obesity.

Evaluation of Unique Patient Populations and Specialized Considerations for Hypocaloric, High-Protein Nutrition Therapy

To ascertain if patients with severe obesity (BMI ≥ 40 kg/m^2) respond differently to nutrition therapy than less obese patients, Choban and Dickerson [29] combined their databases from their previous studies examining hypocaloric high-protein feeding [23, 71, 72]. Forty-eight patients with Class I and II obesity were compared to 22 patients with severe Class III obesity. Regression analysis examining the effect of protein intake upon nitrogen demonstrated achievement of nitrogen equilibrium at ~1.8 g/kg ideal body weight/day for those with Class III obesity compared to ~1.7 g/kg ideal body weight/day for those with less severe obesity. For patients in the ICU, those with Class III obesity required a protein intake of ~2.5 g/kg ideal body weight/day to achieve nitrogen equilibrium compared to ~2 g/kg ideal body weight/day for those with Class I and II obesity. Thus, the severity of obesity, as well as severity of illness, may mandate different initial protein goals when dosing protein based on ideal body weight.

Patients with Class III obesity tended to experience higher blood glucose concentrations compared to those with less severe obesity despite receiving a similar caloric intake. This phenomenon appeared more evident at higher caloric intakes. These data would imply that clinicians should have a heightened awareness towards overfeeding complications in those with severe obesity.

Patients with significant renal or hepatic disease may not be optimal candidates for hypocaloric, high-protein nutrition therapy as they may not be able to tolerate a large protein load due to impending uremia or worsening of encephalopathy. Our empiric approach for these populations is to liberalize caloric intake by providing more calories and reduce protein intake while closely monitoring for azotemia, uremia, or worsening encephalopathy. The Penn State equations [46, 47, 50] (Table 7.4) are used to estimate resting energy expenditure and a caloric intake designed to match (or slightly less than) the predicted resting energy expenditure is empirically given. Patients are closely monitored for evidence of overfeeding complications such as hyperglycemia and hypercapnia and the calories are decreased (even in the face of reduced protein intake) if necessary. For patients who are not in the ICU, we empirically use the Mifflin-St. Jeor equation (Table 7.4) in the same manner as the Penn State equation to estimate resting energy expenditure. Protein intake is adjusted based on patient response (e.g., change in serum urea nitrogen concentration) and the frequency and type of dialysis (e.g., hemodialysis, continuous renal replacement therapy) for both critically ill and non-critically ill patients with obesity.

It has been questioned whether older or elderly hospitalized patients with obesity should receive hypocaloric, high-protein nutrition therapy. Decreased sensitivity of muscle to anabolic stimuli, including amino acids, occurs during aging and has been associated with muscle mass loss [75, 76]. As a result, older patients generally need more protein to achieve the same nitrogen balance as younger patients. A concern of providing high protein intakes, as required for hypocaloric, high-protein nutrition therapy, to older patients is the insidious decline in renal function that cannot be detected by serum creatinine concentration alone. This is because the older patients have less muscle mass (the source of creatinine appearance in the serum). Thus, a serum creatinine concentration in the "normal range" for an elderly person may be equivalent to a greater serum creatinine concentration for a young person [77]. Although the decrease in glomerular filtration rate that occurs with aging is much less than necessary to elicit symptoms of renal failure [78], concern is often expressed by clinicians about prescribing aggressive protein intakes to older patients due to anticipation of a decreased renal functional reserve [79] resulting

in an increase in serum urea nitrogen (SUN) concentration.

To evaluate hypocaloric, high-protein nutrition therapy in older vs. younger patients with obesity, Liu retrospectively compared the anabolic response to parenteral nutrition in 18 patients younger than 60 years of age to 12 patients 60 years of age or older [80]. Patients were given 1.5–2 g/kg adjusted body weight/day of protein and 60–75 % of their estimated caloric requirements (based on the Harris-Benedict equations [42] using an adjusted body weight). Despite similar protein and calorie intakes between age groups, nitrogen balance was lower for the older patient group (0.2 ± 5.0 vs. 3.4 ± 3.9 g/day, respectively) [80]. However, it is possible that inadequate protein intake was given to the patients as recent studies in healthy older subjects and critically ill older patients indicated that provision of greater amounts of protein can overcome this "anabolic resistance" [67, 81, 82]. Dickerson and colleagues examined nitrogen balance and clinical outcomes to hypocaloric, high-protein nutrition therapy in 33 older (>59 years of age) vs. 41 younger (<60 years of age) critically ill trauma patients with obesity [67]. When given an isonitrogenous regimen (2.3 g/kg ideal body weight/day), nitrogen balance was similar between older and younger age groups (−3.2 + 5.7 g/day vs. −4.9 + 9.0 g/day). Clinical outcomes of survival, duration of ICU stay, hospital length of stay, and duration of mechanical ventilation were similar between age groups. It was concluded that older patients exhibited an equivalent net protein response as younger patients during hypocaloric, high-protein nutrition therapy. However, older patients experienced a greater mean serum urea nitrogen concentration than the younger patients (30 ± 14 mg/dL vs. 20 ± 9 mg/dL) during hypocaloric high-protein nutrition therapy and are at greater risk for developing azotemia. Close monitoring for worsening azotemia when using hypocaloric, high-protein diets in older patients with obesity is warranted.

Because hyperglycemia is so prevalent in critically ill obese patients, clinicians often opt for use of a mixed fuel-based parenteral nutrition prescription whereby lipids are partially substituted for carbohydrate intake. However, some patients with obesity experience hyperlipidemia with hypertriglyceridemia that does not improve when the hyperglycemia is resolved. During hypercaloric, fat-free, continuous parenteral nutrition, biochemical evidence for the development of essential fatty acid deficiency occurs in 30 %, 66 %, 83 %, and 100 % of patients after 1, 2, 3, and 4 weeks, respectively [83]. The explanation for their results was that due to the hypercaloric amount of dextrose calories provided to the patients, lipolysis was suppressed which prevented the availability of endogenous essential fatty acids. During hypocaloric feeding, even with a glucose-based parenteral nutrition solution, lipolysis would be expected to occur for energy and also provide a source for essential fatty acids. The respiratory quotient data from the case series of Dickerson et al. [63] indicated that 68 ± 19 % of nonprotein energy originated from net fat oxidation. Since the parenteral nutrition solutions did not contain lipid emulsion, endogenous fat oxidation occurred [63]. Parnes and coworkers examined fatty acid profiles in 15 overweight cancer patients who were hypocalorically fed continuous, fat-free, parenteral nutrition for 2–5 weeks [84]. None of the patients experienced biochemical or clinical evidence for essential fatty acid deficiency. Despite these data, availability of endogenous fat post-injury in obese patients is not without debate [85]. Jeevanadam and colleagues studied 7 obese patients and 10 nonobese, ventilator-dependent patients with multiple traumatic injuries two to four days after injury, but before the provision of nutrition therapy [85]. Glycerol turnover (a marker of lipolysis) and net fat oxidation (from indirect calorimetry measurements) were reduced in the obese group compared to the nonobese control patients. The investigators concluded that the critically ill obese patient could not effectively use their most abundant fat fuel sources [85]. Taking the results of Parnes [84], Dickerson [63], and Jeevanandam [85] studies together, these data might imply that obese patients may exhibit a transient impairment in fat metabolism that occurs early after the stress event, but resolves quickly during the patients' hospital course.

Metabolic Considerations Following Bariatric Surgery

It is recognized that bariatric surgery is the only treatment for morbid obesity that consistently achieves and maintains substantial weight loss, decreases obesity-related comorbidities, and improves quality of life and survival [86]. Two case series demonstrate the effectiveness of hypocaloric, high-protein parenteral nutrition therapy in achieving net protein anabolism and weight loss while facilitating wound healing for patients who experience postoperative surgical complications from obesity surgery [63, 87].

The clinical impact of surgical procedures that shorten small bowel absorptive capacity resulting in malabsorption of both macronutrients and micronutrients are evident [4, 88–92]. The most common vitamin and mineral deficiencies include iron, folate, vitamin B12, calcium, thiamine, and vitamins A, D, and K. In addition to a physical exam and patient interview for signs and symptoms of various nutrition deficiencies, laboratory evaluation is also necessary as part of the patient's long-term care. For patients with a microcytic anemia, determination of serum ferritin concentration is necessary for evaluation of potential iron deficiency. Although less common, some post-bariatric surgery patients develop microcytic anemia as a result of copper deficiency rather than iron deficiency [89]. Patients with a macrocytic anemia should be evaluated for folate or vitamin B12 deficiency using serum methylmalonic acid and homocysteine concentrations rather than folate or vitamin B12 concentrations as the former are more sensitive markers for folate or vitamin B12 depletion [93]. Although it may take 4–5 years for depletion of vitamin B12 stores, it is necessary that the clinician routinely evaluate the patient for vitamin B12 depletion as neurologic sequelae from vitamin B12 deficiency may not necessarily be completely reversible. Metabolic bone disease and secondary hyperparathyroidism, attributed to calcium and vitamin D deficiency, may also occur post-bariatric surgery [94].

In 2008, Aasheim recently summarized 104 reported cases of Wernicke encephalopathy from thiamine depletion following bariatric surgery [90]. Admissions to the hospital occurred within 6 months after surgery in 94 % of the cases. Intravenous glucose administration without thiamine supplementation was a risk factor in 18 % of the patients. Unfortunately, an incomplete clinical recovery was observed in about half of the patients who developed Wernicke's encephalopathy. Thiamine-depleted patients can also develop beriberi (presenting either as a lactic acidosis or congestive cardiomyopathy) which also may not be completely reversible. Therefore, analogous to the patient with alcoholism, it is recommended that patients who have previously undergone bariatric surgery who are admitted to the hospital receive parenteral thiamine supplementation prior to administration of intravenous dextrose solutions [89].

The American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic and Bariatric Surgery guidelines recommend that post-bariatric surgery patients with compromised intestinal absorption receive two multivitamins plus minerals capsules daily, calcium citrate 1,200–1,500 mg/day, ≥3,000 units of vitamin D daily (titrate to serum vitamin D concentration of >30 ng/mL), and vitamin B12 (sufficient to maintain normal concentrations) [88]. Additional vitamin A, thiamine, copper, zinc, and selenium may be necessary for some patients. It is recommended that routine vitamin and mineral laboratory monitoring be performed every 3–6 months and a bone density evaluation be performed at 2 years following bariatric surgery [88].

Technical Issues of Providing a Parenteral or Enteral Hypocaloric, High-Protein Nutrition Regimen

There are some technical and logistic issues with providing a hypocaloric, high-protein parenteral or enteral nutrition regimen. Parenteral nutrition has the advantage over enteral nutrition

in that each macronutrient can be independently prescribed. The primary limitation with prescribing a hypocaloric high-protein parenteral nutrition regimen relates to the initial concentrations of macronutrient ingredients available in the pharmacy prior to admixture into the final parenteral nutrition solution. A wide range of concentrations of dextrose, amino acids, and lipids are commercially available. It is sometimes necessary that the formula be compounded using the most concentrated, commercially available, macronutrient ingredients for those patients with fluid volume overload: dextrose 70 % in water, 15 % or 20 % amino acid solution, and 30 % lipid emulsion. However, due to cost considerations, hospital formulary management, and perception of need, not all hospital pharmacies have the most concentrated macronutrient solutions.

Providing a hypocaloric, high-protein enteral regimen is technically more difficult than when given via parenteral nutrition. The primary limitation with enteral nutrition is, unlike parenteral nutrition solutions whereby macronutrients are available in individual components, enteral formulas are only commercially available in fixed macronutrient concentrations (e.g., 1 kcal/mL, 62 g protein/L, etc.). As a result, use of protein supplements, along with a reduction in enteral formula feeding rate, may be necessary to achieve the intended goals. It is not recommended that protein powder be added to the enteral formulation at the patient bedside as there is an increased chance for microbial contamination and inadequate mixing of the powder resulting in clumping and potential tube clogging. If this administration technique is chosen, it is preferred that the protein powder be admixed with the feeding under aseptic or clean conditions in the pharmacy and blenderized to reduce clumping. Given the wide use of ready to hang enteral products, a better alternative would be protein boluses via the feeding tube in addition to the continuous enteral feeding. Use of liquid protein solutions, as opposed to reconstitution of protein powder, may be less likely to cause tube clogging when patients are fed via a small bore feeding tube. Use of liquid protein solution may also reduce nursing workload. However, we have found that due to the viscosity of the liquid protein solution, administration via a small bore feeding tube requires that a 50:50 dilution with water is necessary for ease in administration [95]. Since the hypocaloric high-protein technique often requires a low enteral formula feeding rate (because of the calories being provided by the protein supplementation), daily liquid multivitamin supplementation may also be necessary to meet the daily Dietary Reference Intakes for vitamins. An easier alternative to intermittent protein doses, but also more expensive, is the use of a new commercially available enteral product in the U.S. which is designed to provide a hypocaloric, high-protein regimen for obese patients. The formula contains 1 kcal/mL and 93 g protein/L. Dosing of the enteral formula based on a goal protein intake of about 2 g/kg ideal body weight/day will usually result in a regimen that is also within the intended calorie target range (e.g., 20–25 kcal/kg ideal body weight/day). For critically ill patients with a BMI ≥ 40 kg/m^2 [29], or those whose nitrogen balance is still markedly negative despite a protein intake of ~2 g/kg ideal body weight/day, a protein intake within 2.5–3 g/kg ideal body weight/day may be required. Intermittent administration of protein supplements along with the specialized bariatric formula may be required when attempting to achieve a high-protein intake of ≥ 2.5 g/kg ideal body weight/day while limiting total caloric intake to about 25 kcal/kg ideal body weight/day.

Metabolic Monitoring of the Critically Ill Surgical Patient with Obesity

Monitoring is designed to insure efficacy of the prescribed regimen as well as prevention of complications associated with overfeeding or aggressive feeding [96]. In the ICU, despite its limitations, the best marker in routine clinical practice for objectively assessing the efficacy of the nutrition regimen is nitrogen balance.

During the acute phase of illness post-trauma or surgery, if nitrogen equilibrium (e.g., about −4 g/day to +4 g/day) can be achieved, we consider the regimen successful. If the nitrogen balance is markedly negative at goal protein intake, we will escalate the protein dosage. We have empirically set our maximum protein dose at 3 g/kg ideal body weight/day [54, 67]. If the patient is still in substantial negative nitrogen balance near our ceiling protein dose, we continue our current therapy and wait for the catabolic stress to diminish. Nitrogen balance determinations are performed weekly while the patient is in the ICU at our institution. Serum prealbumin concentration for assessing protein recovery is also monitored weekly. However, changes in serum prealbumin concentrations are limited in that its concentration is decreased by the presence of stress, infection, or inflammation. Resultantly, we also obtain concurrent C-reactive protein concentrations with weekly serum prealbumin concentrations to serve as a point of reference towards interpreting changes in serum prealbumin concentrations.

We do not use body weight or loss of weight as a marker of efficacy for multiple reasons. The difficulty of accurately determining weight in the ICU for the critically ill, surgical, or trauma patient with obesity often limits its interpretation. Weight is a poor marker of nutritional status due to fluid perturbations following resuscitation and throughout their course of stay in the ICU. Finally, weight loss is not necessarily a primary clinical outcome or goal for patients receiving hypocaloric, high-protein nutrition therapy while in the ICU. Our primary intent is to avoid overfeeding complications in this highly susceptible patient population. Fat weight loss is considered as a welcome secondary benefit.

Our primary short-term goals for metabolic support of the hospitalized patient with obesity are achievement of net protein anabolism and avoidance of complications associated with nutritional overfeeding (Table 7.6). Use of hypocaloric, high-protein therapy is primarily directed at avoiding hyperglycemia, hypercapnia, and worsening of nonalcoholic fatty liver disease. The critically ill surgical, thermally injured, and trauma patient appears to benefit from tighter glycemic control than that of other populations [31–35]; however, the impact of obesity upon insulin sensitivity and a higher incidence of diabetes mellitus makes glycemic control more complex. Despite hypocaloric feeding with low carbohydrate intakes, use of our graduated continuous intravenous regular human insulin infusion algorithm or our tightened sliding scale coverage is often warranted to maintain blood glucose concentrations within a desirable target range (e.g., 70–149 mg/dL while the patient is in the ICU) [37, 97]. Arterial blood gases are closely monitored for rises in pCO_2 concentrations not attributable to other causes [41]. Daily fluid volume intake and output, along with physical examination of the patient (with radiological evidence or hemodynamic measurements when available), are monitored for evidence of fluid overload. The presence of nonalcoholic fatty liver disease is often associated with increased serum concentrations of liver function tests, particularly the aminotransferases. Because a slow rate of weight loss may improve hepatomegaly and decrease serum ALT concentration associated with nonalcoholic fatty liver disease [98], it would be important to avoid overfeeding hospitalized obese patients. Unfortunately, it is unclear whether routine monitoring of liver function tests would be of any significant value as the presence of sepsis or inflammation confounds interpretation of these tests [99].

Table 7.6 Recommended nutrient intakes for the hospitalized patient with obesity

Total caloric intake[a]	11–14 kcal/kg actual body weight/day or 22–25 kcal/kg ideal body weight/day
Protein intake (ICU patients)	
BMI 30–39.9 kg/m^2:	2–2.5 g/kg ideal body weight/day
BMI >40 kg/m^2:	≥2.5 g/kg ideal body weight/day (maximum 3 g/kg ideal body weight/day)
Protein intake (non-ICU patients)	2–2.5 g/kg ideal body weight/day

[a]Caloric intake should comprise at least 130–150 g/day of glucose for obligatory glucose requirements for unstressed patients without surgical wounds or thermal injury; 200–250 g/day of glucose is recommended for patients with surgical wounds or thermal injury

Older patients or those with a modestly compromised renal function may exhibit azotemia during hypocaloric, high-protein therapy due to the high protein doses required for this mode of nutrition therapy. Patients who received hypocaloric, high-protein nutrition therapy and were older than 60 years of age demonstrated a mean serum urea nitrogen concentration of 30 ± 14 mg/dL versus 20 ± 9 mg/dL when compared to those who were younger, respectively [67]. However, four patients (13 % of the older patient population) had a maximum serum urea nitrogen concentration that exceeded 59 mg/dL [67]. Therefore, serial serum urea nitrogen concentrations should also be closely monitored.

Conclusions

Metabolic management of the critically ill surgical patient with obesity presents with numerous challenges. Implementation of nutrition therapy for this population requires unique considerations towards avoiding metabolic complications of overfeeding while attempting to achieve net protein anabolism. Implementation of hypocaloric, high-protein nutrition support can sometimes be arduous in its implementation given the current limitations for enteral and parenteral nutrition therapy. However, this mode of therapy appears beneficial for achieving nutritional goals and positive clinical outcomes for the hospitalized and critically ill surgical patient with obesity. Close monitoring and individualization of the regimen based on clinical response is warranted.

References

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012;307:491–7.
2. Winfield RD, Bochicchio GV. The critically injured obese patient: a review and a look ahead. J Am Coll Surg. 2013;216:1193–206.
3. Kiraly L, Hurt RT, Van Way 3rd CW. The outcomes of obese patients in critical care. JPEN J Parenter Enteral Nutr. 2011;35:29S–35.
4. Choban P, Dickerson R, Malone A, Worthington P, Compher C; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. Clinical Guidelines: nutrition support of hospitalized adult patients with obesity. JPEN J Parenter Enteral Nutr. 2013;37(6):714–44.
5. Diaz Jr JJ, Norris PR, Collier BR, Berkes MB, Ozdas A, May AK, et al. Morbid obesity is not a risk factor for mortality in critically ill trauma patients. J Trauma. 2009;66:226–31.
6. Hoffmann M, Lefering R, Gruber-Rathmann M, Rueger JM, Lehmann W, Trauma Registry of the German Society for Trauma Surgery. The impact of BMI on polytrauma outcome. Injury. 2012;43:184–8.
7. Hutagalung R, Marques J, Kobylka K, Zeidan M, Kabisch B, Brunkhorst F, et al. The obesity paradox in surgical intensive care unit patients. Intensive Care Med. 2011;37:1793–9.
8. Newell MA, Bard MR, Goettler CE, Toschlog EA, Schenarts PJ, Sagraves SG, et al. Body mass index and outcomes in critically injured blunt trauma patients: weighing the impact. J Am Coll Surg. 2007;204:1056–62.
9. Nasraway Jr SA, Albert M, Donnelly AM, Ruthazer R, Shikora SA, Saltzman E. Morbid obesity is an independent determinant of death among surgical critically ill patients. Crit Care Med. 2006;34:964–71.
10. Bochicchio GV, Joshi M, Bochicchio K, Nehman S, Tracy JK, Scalea TM. Impact of obesity in the critically ill trauma patient: a prospective study. J Am Coll Surg. 2006;203:533–8.
11. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. Obesity increases risk of organ failure after severe trauma. J Am Coll Surg. 2006;203:539–45.
12. Brown CV, Neville AL, Rhee P, Salim A, Velmahos GC, Demetriades D. The impact of obesity on the outcomes of 1,153 critically injured blunt trauma patients. J Trauma. 2005;59:1048–51.
13. Ray DE, Matchett SC, Baker K, Wasser T, Young MJ. The effect of body mass index on patient outcomes in a medical ICU. Chest. 2005;127:2125–31.
14. Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. Crit Care Med. 2008;36:151–8.
15. Sakr Y, Madl C, Filipescu D, Moreno R, Groeneveld J, Artigas A, et al. Obesity is associated with increased morbidity but not mortality in critically ill patients. Intensive Care Med. 2008;34:1999–2009.
16. Martino JL, Stapleton RD, Wang M, Day AG, Cahill NE, Dixon AE, et al. Extreme obesity and outcomes in critically ill patients. Chest. 2011;140:1198–206.
17. Hogue Jr CW, Stearns JD, Colantuoni E, Robinson KA, Stierer T, Mitter N, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. Intensive Care Med. 2009;35:1152–70.
18. Kumar G, Majumdar T, Jacobs ER, Danesh V, Dagar G, Deshmukh A, et al. Outcomes of morbidly obese patients receiving invasive mechanical ventilation: a nationwide analysis. Chest. 2013;144:48–54.

19. Gallagher D, DeLegge M. Body composition (sarcopenia) in obese patients: implications for care in the intensive care unit. JPEN J Parenter Enteral Nutr. 2011;35:21S–8.
20. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264–70.
21. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr. 2012;31:462–8.
22. Weijs PJ, Stapel SN, de Groot SD, Driessen RH, de Jong E, Girbes AR, et al. Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr. 2012;36:60–8.
23. Dickerson RN, Boschert KJ, Kudsk KA, Brown RO. Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition. 2002;18:241–6.
24. Pickkers P, de Keizer N, Dusseljee J, Weerheijm D, van der Hoeven JG, Peek N. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. Crit Care Med. 2013; 41:1878–83.
25. Druml W. ICU patients: fatter is better? Intensive Care Med. 2008;34:1961–3.
26. Bornstein SR, Licinio J, Tauchnitz R, Engelmann L, Negrão AB, Gold P, Chrousos GP. Plasma leptin levels are increased in survivors of acute sepsis: associated loss of diurnal rhythm, in cortisol and leptin secretion. J Clin Endocrinol Metab. 1998;83:280–3.
27. Wendel M, Paul R, Heller AR. Lipoproteins in inflammation and sepsis. II. Clinical aspects. Intensive Care Med. 2007;33:25–35.
28. Oliveros H, Villamor E. Obesity and mortality in critically ill adults: a systematic review and meta-analysis. Obesity. 2008;16:515–21.
29. Choban PS, Dickerson RN. Morbid obesity and nutrition support: is bigger different? Nutr Clin Pract. 2005;20:480–7.
30. Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW. Mechanisms of insulin resistance following injury. Ann Surg. 1982;196:420–35.
31. Collier B, Diaz Jr J, Forbes R, Morris Jr J, May A, Guy J, et al. The impact of a normoglycemic management protocol on clinical outcomes in the trauma intensive care unit. JPEN J Parenter Enteral Nutr. 2005;29:353–9.
32. Scalea TM, Bochicchio GV, Bochicchio KM, Johnson SB, Joshi M, Pyle A. Tight glycemic control in critically injured trauma patients. Ann Surg. 2007;246: 605–12.
33. Bochicchio GV, Joshi M, Bochicchio KM, Pyle A, Johnson SB, Meyer W, et al. Early hyperglycemic control is important in critically injured trauma patients. J Trauma. 2007;63:1353–9.
34. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359–67.
35. Jeschke MG. Clinical Review: Glucose control in severely burned patients - current best practice. Crit Care. 2013;17:232.
36. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
37. Dickerson RN, Swiggart CE, Morgan LM, Maish III GO, Croce MA, Minard G, Brown RO. Safety and efficacy of a graduated intravenous insulin infusion protocol in critically ill trauma patients receiving specialized nutritional support. Nutrition. 2008;24: 536–45.
38. Goldberg IJ. Clinical review 124: Diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab. 2001;86:965–71.
39. Brown CV, Velmahos GC. The consequences of obesity on trauma, emergency surgery, and surgical critical care. World J Emerg Surg. 2006;1:27.
40. Askanazi J, Carpentier YA, Elwyn DH, Nordenström J, Jeevanandam M, Rosenbaum SH, et al. Influence of total parenteral nutrition on fuel utilization in injury and sepsis. Ann Surg. 1980;191:40–6.
41. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. Excess total calories vs. high proportion of carbohydrate calories. Chest. 1992;102:551–5.
42. Harris JA, Benedict FG. Biometric studies of basal metabolism in man. Washington, D.C.: Carnegie Institute of Washington; 1919. Publication no. 297.
43. Vernon G, Baranova A, Younossi ZM. Systematic Review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34: 274–85.
44. Sheldon GF, Peterson SR, Sanders R. Hepatic dysfunction during hyperalimentation. Arch Surg. 1978;113:504–8.
45. Feurer ID, Crosby LO, Buzby GP, Rosato EF, Mullen JL. Resting energy expenditure in morbid obesity. Ann Surg. 1983;197:17–21.
46. Frankenfield DC, Ashcraft CM, Galvan DA. Prediction of resting metabolic rate in critically ill patients at the extremes of body mass index. JPEN J Parenter Enteral Nutr. 2013;37:361–7.
47. Frankenfield DC, Coleman A, Alam S, Cooney RN. Analysis of estimation methods for resting metabolic rate in critically ill adults. JPEN J Parenter Enteral Nutr. 2009;33:27–36.
48. Frankenfield DC, Rowe WA, Smith JS, Cooney RN. Validation of several established equations for resting metabolic rate in obese and nonobese people. J Am Diet Assoc. 2003;103:1152–9.
49. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51:241–7.
50. Frankenfield D. Validation of an equation for resting metabolic rate in older obese, critically ill patients. JPEN J Parenter Enteral Nutr. 2011;35:264–9.

51. Dickerson RN, Tidwell AC, Minard G, Croce MA, Brown RO. Predicting total urinary nitrogen excretion from urinary urea nitrogen excretion in multiple-trauma patients receiving specialized nutritional support. Nutrition. 2005;21:332–8.
52. Shaw JH, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. The response to glucose infusion and total parenteral nutrition. Ann Surg. 1987;205:288–94.
53. Shaw JH, Wolfe RR. An integrated analysis of glucose, fat, and protein metabolism in severely traumatized patients. Studies in the basal state and the response to total parenteral nutrition. Ann Surg. 1989;209:63–72.
54. Dickerson RN, Pitts SL, Maish 3rd GO, Schroeppel TJ, Magnotti LJ, Croce MA, Minard G, Brown RO. A reappraisal of nitrogen requirements for patients with critical illness and trauma. J Trauma Acute Care Surg. 2012;73:549–57.
55. Elwyn DH. Nutritional requirements of adult surgical patients. Crit Care Med. 1980;8:9–20.
56. Elwyn DH, Gump FE, Munro HN, Iles M, Kinney JM. Changes in nitrogen balance of depleted patients with increasing infusions of glucose. Am J Clin Nutr. 1979;32:1597–611.
57. Hill GL, Church J. Energy and protein requirements of general surgical patients requiring intravenous nutrition. Brit J Surg. 1984;71:1–9.
58. Macfie J, Smith RC, Hill GL. Glucose or fat as a non-protein energy source? A controlled clinical trial in gastroenterological patients requiring intravenous nutrition. Gastroenterology. 1981;80:103–7.
59. Smith RC, Burkinshaw L, Hill GL. Optimal energy and nitrogen intake for gastroenterological patients requiring intravenous nutrition. Gastroenterology. 1982;82:445–52.
60. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma. 1987;27:262–6.
61. Frankenfield DC, Smith JS, Cooney RN. Accelerated nitrogen loss after traumatic injury is not attenuated by achievement of energy balance. JPEN J Parenter Enteral Nutr. 1997;21:324–9.
62. Hart DW, Wolf SE, Herndon DN, Chinkes DL, Lal SO, Obeng MK, Beauford RB, Mlcak RTRP. Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. Ann Surg. 2002;235:152–61.
63. Dickerson RN, Rosato EF, Mullen JL. Net protein anabolism with hypocaloric parenteral nutrition in obese stressed patients. Am J Clin Nutr. 1986;44:747–55.
64. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest. 2003;124:297–305.
65. Ibrahim EH, Mehringer L, Prentice D, Sherman G, Shaiff R, Fraser V, Kollef MH. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. JPEN J Parenter Enteral Nutr. 2002;26:174–81.
66. Dickerson RN. Optimal caloric intake for critically ill patients: first, do no harm. Nutr Clin Pract. 2011;26:48–54.
67. Dickerson RN, Medling TL, Smith AC, Maish III GO, Croce MA, Minard G, Brown RO. Hypocaloric, high-protein nutrition therapy in older vs. younger critically ill patients with obesity. JPEN J Parenter Enteral Nutr. 2013;37:342–51.
68. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr. 2012;96:591–600.
69. Hoffer LJ, Bistrian BR. Why critically ill patients are protein deprived. JPEN J Parenter Enteral Nutr. 2013;37:300–9.
70. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009;35:1728–37.
71. Burge JC, Goon A, Choban PS, Flancbaum L. Efficacy of hypocaloric total parenteral nutrition in hospitalized obese patients: a prospective, double-blind randomized trial. JPEN J Parenter Enteral Nutr. 1994;18:203–7.
72. Choban PS, Burge JC, Scales D, Flancbaum L. Hypoenergetic nutrition support in hospitalized obese patients: a simplified method for clinical application. Am J Clin Nutr. 1997;66:546–50.
73. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33:277–316.
74. McClave SA, Kushner R, Van Way 3rd CW, Cave M, DeLegge M, Dibaise J, et al. Nutrition therapy of the severely obese, critically ill patient: summation of conclusions and recommendations. JPEN J Parenteral Enteral Nutr. 2011;35:88S–96.
75. Guillet C, Prod'homme M, Balage M, Gachon P, Giraudet C, Morin L, Grizard J, Biorie Y. Impaired anabolic response of muscle protein synthesis is associated with S6K1 dysregulation in elderly humans. FASEB J. 2004;18:1586–7.
76. Volpi E, Mittendorfer B, Rasmussen BB, Wolfe RR. The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. J Clin Endocrinol Metab. 2000;85:4481–90.
77. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
78. Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. Clin Nutr. 2008;27:675–84.
79. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. J Am Soc Nephrol. 1993;3:1371–7.
80. Liu KJ, Cho MJ, Atten MJ, Panizales E, Walter R, Hawkins D, Donahue PA. Hypocaloric parenteral

nutrition support in elderly obese patients. Am Surg. 2000;66:394–400.
81. Dickerson RN, Maish 3rd GO, Croce MA, Minard G, Brown RO. Influence of aging on nitrogen accretion during critical illness. JPEN J Parenter Enteral Nutr. 2014.
82. Guillet C, Zangarelli A, Gachon P, Morio B, Giraudet C, Rousset P, Biorie Y. Whole body protein breakdown is less inhibited by insulin, but still responsive to amino acid, in nondiabetic elderly subjects. J Clin Endocrinol Metab. 2004;89:6017–24.
83. Goodgame JT, Lowry SF, Brennan MF. Essential fatty acid deficiency in total parenteral nutrition: time course of development and suggestions for therapy. Surgery. 1978;84:271–7.
84. Parnes HL, Mascioli EA, LaCivita CL, Gutierrez PL, Friedman J, Lopes SM, Bistrian BR. Parenteral nutrition in overweight patients: are intravenous lipids necessary to prevent essential fatty acid deficiency? J Nutr Biochem. 1994;5:243–7.
85. Jeevanandam M, Young DH, Schiller WR. Obesity and the metabolic response to severe multiple trauma in man. J Clin Invest. 1991;87:262–9.
86. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004;351:2683–93.
87. Hamilton C, Dasari V, Shatnawei A, Lopez R, Steiger E, Seidner D. Hypocaloric home parenteral nutrition and nutrition parameters in patients following bariatric surgery. Nutr Clin Pract. 2011;26:577–82.
88. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient–2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity. 2013;21 Suppl 1:S1–27.
89. Fujioka K, DiBaise JK, Martindale RG. Nutrition and metabolic complications after bariatric surgery and their treatment. JPEN J Parenter Enteral Nutr. 2011;35:52S–9.
90. Aasheim ET. Wernicke encephalopathy after bariatric surgery: a systematic review. Ann Surg. 2008;248:714–20.
91. Aasheim ET, Bjorkman S, Sovik TT, Engström M, Hanvold SE, Mala T, Olberts T, Bøhmer T. Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch. Am J Clin Nutr. 2009;90:15–22.
92. Malone M. Recommended nutritional supplements for bariatric surgery patients. Ann Pharm. 2008;42:1851–8.
93. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Int Med. 1999;159:1289–98.
94. Slater GH, Ren CJ, Siegel N, Williams T, Barr D, Wolfe B, Dolan K, Fielding GA. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. J Gastrointest Surg. 2004;8:48–55. discussion 54–5.
95. Dickerson RN, Harris SL. Difficulty in administration of liquid protein solution via an enteral feeding tube. Am J Health Syst Pharm. 2009;66:796–7.
96. Dickerson RN, Drover JW. Monitoring nutrition therapy in the critically ill patient with obesity. JPEN J Parenter Enteral Nutr. 2011;35:44S–51.
97. Dickerson RN, Wilson VC, Maish 3rd GO, Croce MA, Minard G, Brown RO. Transitional NPH insulin therapy for critically ill patients receiving continuous enteral nutrition and intravenous regular human insulin. JPEN J Parenter Enteral Nutr. 2013;37:506–16.
98. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:1221–31.
99. Sikuler E, Guetta V, Keynan A, Neumann L, Schlaeffer F. Abnormalities in bilirubin and liver enzyme levels in adult patients with bacteremia. A prospective study. Arch Int Med. 1989;149:2246–8.

Malignancy

8

Laleh G. Melstrom, Vadim Koshenkov, and David A. August

The Consequences of Nutrition in Cancer

Cancer is a major public health problem in the United States, and worldwide. There will be an estimated 1.66 million cases of "serious minded" (that is, potentially life-threatening) cancer in the United States in 2013, and approximately 580,000 people are projected to die from cancer in 2013 [1]. Cancer is a disease that also has an enormous impact worldwide [2]. In addition to a human toll, cancer exacts a significant toll on healthcare expenditures. In the United States, cancer treatment costs over $200 billion annually and has a major impact on Medicare expenditures [3]. Nutrition and diet play a major role in cancer. Dietary factors are a significant component of the identifiable attributable risks of cancer. Cancer-related malnutrition and cancer cachexia are prominent elements that cause signs and symptoms of cancer and are major contributors to patient distress. When people refer to wasting disease currently, they are much more likely to be referring to cancer than to tuberculosis ("consumption") or even AIDS (acquired immunodeficiency syndrome). Furthermore, malnutrition and weight loss often contribute to the death of cancer patients [4–7]. More recently, the role of overnutrition in cancer pathogenesis and prognosis has also been emphasized. While progress has been made, heightened awareness and clinical research have yet to solve these pressing problems.

The term attributable risk refers to the proportion of cancers in which a factor plays an etiologic role. It was estimated in 1981 that 35 % of all cancers in the United States could be prevented by changes in diet [8]. This avoidable risk estimate was subsequently updated and affirmed, with a confidence interval of approximately 20–42 % [9]. This most recent analysis was performed in 1995. In light of recent insights into the obesity epidemic, and into the relationship between obesity and cancer risk, an updated estimate would likely be higher [10]. Especially strong associations are observed between diet and cancer risk for colorectal cancer, breast cancer, prostate cancer, pancreas cancer, endometrial cancer, and gall bladder cancer [9]. Of additional concern is that more patients are surviving cancer, and therefore may be at increased risk for the development of a second cancer because of their dietary behaviors and obesity. Fortunately, these patients also represent an opportunity for health improvement [11, 12].

Undernutrition

Malnutrition is a hallmark of cancer. An estimated 40 % of cancer patients present with

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weight loss; the devastating consequences of cancer cachexia may be present in as many as 80 % of those with advanced malignancies [13, 14]. The extent of weight loss at the time of diagnosis is prognostic for survival. More than 10 % loss of usual body weight appears to be especially problematic as is a rate of weight loss of greater that 2.75 % per month [14, 15]. Weight loss in cancer patients can also cause symptom distress, including fatigue, depression, and social withdrawal [16–18]. The impact of malnutrition on operative morbidity and mortality is well described in cancer patients [4]. This association was reported more than 75 years ago and continues to be observed [19, 20]. Despite the critical role of surgery in curing cancer, there are some patients who are not candidates for curative surgery because of the risk of life-threatening complications that their malnutrition confers.

Quality of Life

Malnutrition is also a significant factor that affects the quality of life (QoL) in cancer patients. In 2012, Vashi et al. systematically reviewed the literature on the role of nutrition status in predicting QoL in cancer [21]. They identified 26 studies, with 6 investigating head and neck cancer, 8 gastrointestinal, 1 lung, 1 gynecologic, and 10 heterogeneous cancers. Of these studies, 24 concluded that better nutrition status was associated with better QoL. There was only one study that concluded that there was no association. They concluded that correcting malnutrition may improve QoL in cancer patients, and this is likely an important outcome of interest to cancer patients, their caregivers, and families.

Overnutrition

Although cancer is often characterized as a wasting disease, overnutrition (overweight, body mass index greater than 25 kg/m^2 and obese, body mass index greater than 30 kg/m^2) is being seen more frequently in cancer patients as a result of the rising incidence of being overweight and obesity in the United States. In the authors' experience, it is not uncommon to perform major gastrointestinal cancer operations in people who weigh more than 125 or even 150 kg. Obesity is associated with a higher risk of death from a variety of cancers, including cancers traditionally associated with wasting such as liver cancer, pancreas cancer, gastric cancer, and esophageal cancer. Obesity may be an avoidable cause of more than 15 % of cancer deaths in the United States, particularly in women. Strong associations between cancer death and overnutrition in women are seen in uterine cancer, cervix cancer, and breast cancer [22]. The pathophysiology of the link between cancer mortality and obesity is unclear, but there are a number of plausible hypotheses [23]. In many animal models, severe caloric restriction increases longevity and prevents cancer. Obesity may interfere with cancer detection, as physical exam findings may be masked. The precision of cancer therapy, including surgery, radiation therapy, and chemotherapy, is compromised in obese patients, resulting in increased treatment-associated morbidity and decreased efficacy. Weight gain and decreased physical activity can modulate hormonal mediators such as estrogens and may also affect the cytokine milieu in ways that adversely alter host inflammatory activation and homeostasis.

The Metabolic Milieu in Malignancy-Cancer Cachexia

Cancer cachexia is a syndrome that is frequently encountered in cancer patients and is associated with a poor prognosis. Clinically, it is characterized by progressive weight loss from both fat and skeletal muscle tissues, anorexia, fatigue, and anergy. The underlying etiologies include anatomic, physiologic, and metabolic derangements that result in a state of undernutrition [24] (Table 8.1). Cancer cachexia can be seen in the early stages of tumor growth, but more commonly presents in advanced stages of the disease. The extent of undernutrition parallels the type of

Table 8.1 Causes of cancer-associated weight loss and cachexia

- Gastrointestinal dysfunction
  - Malabsorption
  - Dysmotility
  - Obstruction
- Side effects of therapy
- Pain-preprandial or postprandial
- Cytokine, peptide, and hormonal changes
- Depression and psychosocial factors

Table 8.2 The incidence of weight loss or malnutrition in adult cancer patients by primary tumor site

Site of primary	Incidence of weight loss or malnutrition (%)
Acute non-lymphocytic leukemia	39
Breast	36–39
Bronchial carcinoma	66
Colorectal	54–60
Diffuse lymphoma	55
Esophagus	79–100
Gastric	44–87
Head and neck (including larynx)	40–72
Lung (all types)	36–61
Neuroblastoma	56
Non-Hodgkins lymphoma	31

neoplasm, with more severe malnutrition observed with upper gastrointestinal and pancreatic cancers, and less severe malnutrition with lymphomas, breast cancers, and sarcomas [14] (Table 8.2). Multiple factors contribute to undernutrition and their interplay is variable among different patients.

Energetics

One of the potential etiologies of cancer cachexia is a change in the metabolic rate. Resting energy expenditure (REE) has been studied extensively in relation to cancer cachexia, but the findings of the published literature have been inconsistent. While many studies have reported an increase in REE of cancer patients [25–30], other reports have indicated that REE may be decreased or remain unchanged [31–34]. This has led some investigators to postulate that the metabolic response to cancer is highly variable and may be dependent on the type of a malignancy and the host response [27, 29]. It has been shown that patients with lung cancer and gastric cancer are usually hypermetabolic [35–37], while those with hepatobiliary tumors are predominantly hypometabolic [38]. With respect to esophageal, pancreatic, and colorectal neoplasms, the metabolic rates are more evenly distributed [37]. However, different responses of REE for patients with the same type of cancer have also been observed [39].

Resting energy expenditure has also been postulated to be affected by the aggressiveness and the duration of the disease. Although two recent reports by Ravasco et al. and Cao et al. showed that REE was significantly higher in patients with advanced cancer [29, 30], findings from other reports suggest that tumor stage does not play a role in REE [32]. Moderately or poorly differentiated histology, increased acute phase proteins, and a prolonged duration of illness have all been associated with elevated REE [27, 29–31, 33].

In order to understand these conflicting results, a thorough understanding of factors that affect REE is required. Age, gender, height, and weight are major determinants of REE [31]. Women have a propensity to become hypometabolic with cancer. With respect to height and weight, an elevated metabolic rate is found in taller and heavier individuals [40]. Additionally, it is important to note that cancer patients losing weight tend to initially lose fat mass. Lean body mass (LBM) or the fat-free mass (FFM) contributes more to REE. Consequently, any calculation that does not account for a different body composition of a weight-losing individual will yield erroneous data. Unfortunately, the most commonly used formulas to predict REE, such as the Kleiber formula and the Harris Benedict formula, do not account for the changes in body composition that are frequently seen in cancer patients [41, 42]. As a result, earlier studies looking at metabolism in cancer patients did not measure FFM, and erroneously suggested an elevated REE. Since then, attempts have been made to adjust the formulas for certain illnesses known to increase the

metabolic rate, such as surgery, sepsis, and burns, by adding a stress factor to the equation [43, 44]. Despite these efforts, overestimation of REE because of a stress factor and the general nonuniformity of LBM have been reported, posing further difficulties to the accuracy of metabolic rate calculation in cancer patients [28, 33, 45].

It seems safe to conclude that there is great variability of REE in response to cancer. It seems that the energy requirements of cancer patients do not follow a Gaussian distribution. Moreover, cancer patients do not adjust food intake to changes in metabolic rate appropriately, leading their intake to be chronically below energy expenditure [24]. Consequently, the assessment of nutritional requirements is challenging and can impair clinicians' abilities to appropriately replete patients nutritionally.

Intermediary Metabolism

Cellular metabolism of lipids, proteins, and carbohydrates is significantly altered in cancer cachexia. Much of the weight loss associated with cancer cachexia is a result of the depletion of fat stores. Total body fat can be decreased by as much as 85 % secondary to augmented lipolysis by adipocytes [46]. This has been demonstrated recently by comparing weight-losing cancer patients with weight-stable cancer patients and weight-losing noncancer patients [47]. Adipocytic lipolysis is more sensitive to a variety of stimuli in weight losing as opposed to weight-stable cancer patients, and hormone-sensitive lipase (HSL), the rate-limiting enzyme for lipolysis, is integral to the process [46]. Hormone-sensitive lipase appears to be regulated by lipid-mobilizing factor (LMP) [48]. Fat cell lipolysis, not reduced lipogenesis, is considered the primary mechanism of fat loss in cancer cachexia [49]. Interestingly, glucose infusion did not suppress lipolysis in a study of cachectic cancer patients, who were shown to have impaired capacity to oxidize endogenous-free fatty acid and infused lipid [50]. The most likely explanation for this lies in the overexpression of adipocyte-specific gene cell death-inducing DNA fragmentation factor α-like effector A (CIDEA). The function of CIDEA favors the breakdown of fatty acids to acetyl coenzyme A (CoA) over glucose [51]. The alteration of lipid metabolism is frequently accompanied by a change in the serum lipid profile, creating a lipid profile similar to type IV hyperlipidemia [52]. Although increased serum levels of lipids may aid host substrate utilization, tumor cells may also derive benefit from the elevated lipid levels because of their high requirement for polyunsaturated fatty acids [53].

The dramatic diminution of fat stores that occurs in cancer cachexia is accompanied by a significant depletion of skeletal muscle mass. While the muscle protein component may be reduced by as much as 75 %, the nonmuscle visceral protein compartment remains largely unchanged [46]. Muscle wasting results in weakness, fatigue, and respiratory complications that are observed in weight-losing patients with advanced cancer. Respiratory failure and pneumonia are responsible for the deaths of a significant percentage of cancer patients [54]. This severe muscle atrophy is a consequence of an unfavorable combination of depressed protein synthesis and increased protein degradation. Protein catabolism occurs primarily through increased activity of the ubiquitin-proteasome proteolytic pathway, which is triggered by activation of the transcription factor nuclear factor-κB (NF-κB) [55]. Proteolysis-inducing factor (PIF) is a catabolic factor for skeletal muscle and initiates a cascade of processes that lead to the activation of NF-κB [49]. Akin to the insensitivity of lipolysis to the infusion of glucose, the increased protein turnover observed in cancer cachexia does not respond to administration of exogenous nitrogen [56, 57]. The problem of muscle atrophy is further compounded by a decrease in muscle protein synthesis [58]. Simultaneously, protein synthesis by the liver is preserved and may even be elevated [59, 60].

The metabolism of carbohydrates is frequently deranged in cancer cachexia. Much of the alteration stems from the fact that most cancer cells use glycolysis as their main source for energy generation. The Warburg effect refers to the observation that cancer cells derive most of their

adenosine triphosphate (ATP) from the sustained conversion of glucose into lactate, while mitochondrial oxidation is suppressed [61]. As the result of tumor cells' reliance on glycolysis, an energy-inefficient process, gluconeogenesis is significantly increased to provide the necessary fuel. The Cori cycle is activated in response to the excessive production of lactic acid [62, 63].

Increased hepatic gluconeogenesis occurs for several reasons. First, an abundance of lactic acid from widespread glycolysis is resynthesized into glucose. Second, elevated concentrations of peripherally released alanine and glycerol are converted into glucose [64, 65]. Third, insulin resistance is commonly encountered in patients with cancer cachexia [66, 67]. There is evidence to suggest that insulin resistance develops because of decreased levels of leptin, an adipocyte-derived hormone that plays a role in appetite regulation [68]. The end result of these changes is that normal tissues may be energy-starved from the increased rate of hepatic gluconeogenesis, as this is an energy-consuming process, and this likely has clinical significance for patients.

The metabolic changes described above that are observed in patients with cancer cachexia result in an overall state of "metabolic churning." Net rates of carbohydrate, protein, and lipid turnover are increased without any apparent metabolic benefit.

Cytokine Milieu

The primary driver of cancer cachexia is the alteration in cytokine milieu observed in many cancer patients (Table 8.3). Cytokines are polypeptides that provide short-range signaling between cells in multiple physiologic processes. Tumor necrosis factor-α (TNF) is believed to play a central role in the body's response to a variety of immunologic challenges [69]. Other cytokines, such as interferon (INF)-γ, interleukin-1(IL-1), and interleukin-6 (IL-6), mediate various pro-inflammatory biologic functions. Both tumor cell production and host immune response to tumor contribute to the generation of pro-inflammatory cytokines [70].

Table 8.3 Cytokine milieu and effects in cancer cachexia

Cytokine	Effects
TNF-α	Lipolysis, muscle degradation, increased glucose turnover
Interferon-gamma	Potentiates lipolysis, decreases protein synthesis
Interleukin-1	Induces anorexia, early satiety, peripheral proteolysis, potentiates release of IL-6
Interleukin-6	Severe wasting
Proteolysis-inducing factor	Skeletal muscle degradation
Lipid-mobilizing factor	Lipolysis

In the presence of injury, infection, and inflammation, TNF is important to local host defenses. Unfortunately, its systemic effects may be deleterious. The administration of TNF leads to metabolic changes that are associated with cachexia, such as lipolysis, muscle catabolism, and increased glucose turnover and utilization [69]. Tumor necrosis factor-α enhances lipolysis through activation of HSL. It also decreases lipogenesis by inhibiting production of lipoprotein lipase [71]. With respect to proteolysis, TNF and other cytokines have been found to mediate the ubiquitin-proteasome pathway and nitric oxide synthase (NOS) expression [72]. High levels of nitric oxide inhibit key enzymes of oxidative phosphorylation and can impair contractile performance of skeletal muscle [70].

The evidence for a central role of TNF in induction of cachexia comes primarily from animal models. Tachyphylaxis to TNF develops rapidly in response to intermittent infusion and is most likely a result of saturation of TNF receptors [71]. Several investigators have proposed that constitutive TNF production by tumor cell lines can avoid tachyphylaxis in the majority of subjects [73, 74]. However, there is also evidence that repeat TNF administration over a long period of time can still result in tolerance [75]. The end organ effects of TNF are dependent upon the site of production/administration. When it is produced locally in the brain, anorexia ensues, while muscle inoculation causes chronic cachexia and muscle atrophy [76].

Another way to demonstrate TNF involvement in cancer cachexia is to measure its concentration in serum. Evidence from multiple studies concerning TNF serum concentrations in cancer cachexia is conflicted. Some authors report consistently elevated levels of TNF, while others do not [69]. These inconsistencies may relate to the variable nature of cancer cachexia and the inaccurate measurement of bound TNF (that may still be active). In some situations, antibodies used to neutralize TNF in-vivo can relieve the anorexia and cachexia observed in cancer patients [70]. It is important to note, however, that no single anti-cytokine agent has been shown to reverse all of the features of cancer-associated wasting; cancer cachexia is attributable to alterations in the overall host cytokine milieu involving many factors [70].

Interferon-γ possesses biological activities that overlap those of TNF. Its effects on fat and protein metabolism are similar in that it potentiates lipolysis, inhibits lipoprotein lipase, and decreases protein synthesis [71]. Additionally, animal models have demonstrated that implantation of tumors that produce IFN induces cancer cachexia syndrome, but passive immunization against it can eliminate this response [77]. As is the case with TNF, serum levels of IFN are not consistently elevated. Antibodies to IFN are able to suppress some of the metabolic changes that are found in cancer cachexia [71].

Interleukin-1 and IL-6 are the cytokines shown to play important roles in cancer cachexia. Interleukin-1 seems to act centrally to induce anorexia by causing early satiety and increases proteolysis peripherally [71, 75]. However, the major contribution of IL-1 to the development of cancer cachexia may reside in its ability to enhance the production and release of IL-6 [78]. Intereukin-6 can be detected in the serum of tumor-bearing animals, where it functions to increase hepatic gluconeogenesis and proteolysis [79, 80]. In animal models, IL-6 has been shown to induce a more severe wasting than TNF [71]. Similar to TNF and IFN, animal models have demonstrated that cachexia can be eliminated by administration of an antibody to IL-6. A major difference between IL-6 and TNF is that the former is readily detected in the serum of patients with cancer, and the extent of amplification correlates with tumor burden. It is suggested that IL-6 mediates cancer cachexia indirectly, through different mechanisms than TNF and IL-1 [71].

In addition to cytokines, several hormones and neuropeptides have recently been identified as having important functions relating to cancer cachexia. Leptin is an adipocyte-derived hormone that regulates adipose tissue mass. It reduces appetite, increases REE, and regulates insulin levels [68]. Leptin affects appetite and energy expenditure via hypothalamic neuropeptides. Specifically, a loss in body fat reduces leptin levels, and thereby decreases REE. Conversely, food intake resulting in a gain of body fat will prompt an increase in REE. This process is mediated by increased activity of ghrelin and neuropeptide Y (NPY) and decreased production of corticotropin-releasing factor (CRF) and melanocortin [70]. Persistently increased levels of leptin can lead to unfavorable metabolic alterations that contribute to cancer cachexia [81]. Neuropeptide Y (NPY) is an appetite stimulant and reduced levels lead to anorexia. In cancer cachexia, NPY receptors are resistant to it [48]. Conversely, CRF and melanocortin are appetite suppressants. The production of both of these is stimulated by TNF, IL-1, and IL-6.

Serotonin is another hormone that is emerging as a contributor to cancer cachexia due to its role in promoting anorexia [70]. Interestingly, cisplatin releases serotonin from enterochromaffin cells, which binds to serotonin receptors; this may underlie the anorexia often associated with cisplatin administration, as some serotonin receptors regulate appetite [82, 83]. Other types of serotonin receptors that are activated by cisplatin decrease hypothalamic ghrelin secretion, which may also cause anorexia [82].

As it has been mentioned before, lipolysis and proteolysis are at the heart of the weight-losing process in cancer patients. Proteolysis-inducing factor (PIF) and lipid-mobilizing factor are central to these pathways and are predominantly produced by tumor cells. Transcripts of PIF have been isolated in breast, prostate, and colon cancer cell lines, while it is absent in human tissue other than brain and skin [84]. Proteolysis-inducing

factor activates RNA-dependent protein kinase, which leads to the activation of NF-κB. In turn, NF-κB generates increased expression of the ubiquitin-proteasome proteolytic pathway. Additionally, PIF is partially responsible for a decrease in skeletal muscle protein synthesis [72]. Lipid-mobilizing factor is detectable in weight-losing cancer patients, but not weight-stable cancer patients [85]. Its role in lipolysis is to regulate hormone-sensitive lipase.

Immune Function–Nutrient Interactions in Cancer Patients

Certain nutrients can have profound cellular effects. Nutrients such as glutamine, arginine, nucleic acids, and fatty acids have the potential to modulate immune function. This may be especially important in patients with cancer, who are beset with metabolic disturbances and are immunosuppressed. At the same time, exaggerated inflammatory responses with elevated levels of IL-6 have been reported in patients who received supplemental nutrition [86]. It must be kept in mind that clinically there are no definitive markers of immune function and therefore it is challenging to measure the precise mechanism by which immune-enhancing interventions impact nutritional outcomes. Thus, a close look at the various nutrients that may impact immunity is warranted.

Glutamine is the most abundant amino acid in plasma. It constitutes more than half of the body's amino acid pool [87]. It is considered to be a nonessential amino acid, as it is synthesized in skeletal muscle by transamination of other amino acids. However, catabolism-inducing states like surgery, sepsis, and trauma can lead to a spike in glutamine consumption, outstripping the body's production. For this reason, glutamine should be viewed as a "conditionally essential" amino acid [88]. One of glutamine's major functions is to shuttle nitrogen between organs. Another is to serve as fuel for rapidly proliferating cells such as enterocytes, colonocytes, lymphocytes, and fibroblasts [89]. Glutamine is also central to multiple processes in intermediary metabolism. These include the synthesis of purines and pyrimidines, modification of proteins and lipids to allow for signal transduction and secretion, and neutralization of oxidative stress associated with rapid metabolism and other causes [90].

It was shown as early as 1955 that tumor cells metabolize glutamine at far higher rates than any other amino acid [91]. More recent research has determined that c-myc plays a key role in glutamine uptake and degradation, and that glutamine affects several signaling pathways that promote tumor growth [90]. The reason behind its importance in tumor cell metabolism is that glutamine, much like glucose, generates ATP and provides intermediates for macromolecular synthesis. Not surprisingly, the skeletal muscle of cancer patients has been shown to be depleted of glutamine [92]. For this reason, it has been hypothesized that glutamine supplementation for cancer patients may improve immune function by resupplying this fuel to the noncancer tissues that are starved of it. The hypothesized glutamine enhancement of tumor growth has not been observed [93].

There are several ways to administer glutamine. Enteral administration is usually in combination with other immunonutrients and has been demonstrated to ameliorate immunosuppressive and inflammatory responses in surgical cancer patients [94]. There are few data available regarding single agent enteral glutamine supplementation, and there is no evident beneficial effect on nutrition status or clinical outcomes [95]. Parenteral administration of glutamine is problematic because it is unstable in solution. Therefore, it is generally given as a dipeptide. Parenteral administration has been associated with improved nitrogen balance and a shorter postoperative hospital stay in surgical patients. When given parenterally to bone marrow transplant patients, glutamine may decrease the incidence of mucositis and potentiate lymphopenia after intensive chemotherapy or stem cell transplantation [96–98]. A recent meta-analysis of randomized-control trials in surgical patients revealed that parenteral glutamine administered alone reduced the rate of infectious complications and lowered hospital length of stay, without having any impact on mortality [87]. It appears that the benefits of this immunonutrient to cancer

patients are more clearly realized with parenteral administration, while combining it with other nutrients may offer advantages when given enterally. A randomized, double-blind study combined enteral and parenteral glutamine administration in bone marrow transplantation patients; the short-term effects were not significant, but there was a suggestion of improved long-term survival [99].

Arginine is another amino acid that has been studied for its role as an immune-enhancing nutrient during cancer treatment. Like glutamine, it is a nonessential amino acid that becomes conditionally essential during catabolic states [100]. It functions as a substrate for protein, creatinine, polyamine, and nitric oxide synthesis. In cancer patients, arginine improves nitrogen balance and boosts host immune function. This is accomplished by augmenting natural killer cell activity and macrophage cytotoxicity through stimulation of protein synthesis of the host, but not the cancer cells [100]. This amino acid is rarely added to parenteral nutrition. It has, however, been studied extensively as an enteral immunonutrient, both in combination and as a sole agent [94]. When given alone, arginine reduced the incidence of wound complications, hospital length of stay, and improved both disease-free and overall survival in head and neck cancer patients [101, 102].

Nucleic acids are another nutrient that has been studied in cancer patients. Synthetic polyribonucleotides stimulate immune function, possibly via modulation of intracellular regulatory enzymes [100]. Nucleic acids seem to modulate both the cell-mediated and humoral immune systems through an increased production of IFN. As sole agents, nucleotides have only been studied in parenteral form, and the results have been contradictory. In the setting of breast cancer, improved disease-free survival was demonstrated in patients who received nucleic acids [103]. However, the same authors found no benefit in patients with colorectal cancer [104]. The paucity of data on this nutrient as a solitary agent limits conclusions about its potential benefits.

Essential polyunsaturated fatty acids (PUFAs) are either of the omega-6 (n-6) series derived from linoleic acid or the omega-3 (n-3) series derived from linolenic acid. One of the main physiologic functions of essential fatty acids is to maintain the structure and function of cell membranes. By virtue of this involvement, PUFAs can alter the expression of membrane-bound receptors. They are also central to the synthesis of intermediate compounds, such as prostaglandins, leucotrienes, and hydroxyacids. These eicosanoids affect cellular metabolism through regulation of intracellular calcium and modulation of inflammation and host defenses [100]. Omega-3 PUFAs increase the production of eicosanoids that improve immune response, while attenuating inflammatory response. Single agent enteral supplementation with omega-3 PUFAs has been shown to increase total energy expenditure and physical activity in pancreatic cancer patients [105]. This nutrient has been studied more extensively in combination with arginine and nucleic acids (Table 8.4).

Table 8.4 Factors that may improve immunity

Nutrient	Effects
Glutamine	Synthesis of purines/pyrimidines Modification of proteins/lipids Neutralization of oxidative stress Assist in generating ATP
Arginine	Substrate for protein, creatinine, polyamine, nitric oxide synthesis Improves nitrogen balance
Nucleic acids	Modulation of intracellular regulatory enzymes
Omega 3 and 6 fatty acids	Production of eicosanoids that improve immune response while attenuating inflammatory response

Enteral formulations containing combinations of these immunonutrients (so-called immune-enhancing formulae) have been studied in preoperative, perioperative, and postoperative settings. A well-designed trial of early postoperative feeding after resection of upper gastrointestinal malignancy detected no benefits for an enteral formula containing immunosupplements [106]. However, this study did not exclude well-nourished patients, and it makes sense that nutrition-directed interventions are less likely to benefit patients who are not malnourished. Multiple other studies have demonstrated improvement of intermediate endpoint immune parameters with the use of immune-enhancing formulae [94, 107]. More clinically relevant benefits were also observed in trials

demonstrating a lower incidence of infections and a shorter length of stay when immune-enhancing formulae are used [108–110]. Several meta-analyses have since shown a decreased rate of infectious complications with immune-enhancing enteral formulae, with a greater impact in surgical as opposed to critically ill patients [111, 112]. From these data, it is clear that nutritional supplementation with immunonutrients holds benefit for cancer patients, with the most potent combination being that of arginine, nucleic acids, and omega-3 PUFAs.

Surgery in Cancer Patients

It is well established that poor nutrition status is associated with poor postoperative outcomes in cancer patients [4]. Although this observation rightfully focuses attention on the use of nutrition interventions to improve patient outcomes, it must be noted that many of the parameters used to define nutrition status (see below) are also acute phase reactants and/or markers of severity of disease. It is evident that severity of disease is also associated with poor outcomes. Therefore, although nutrition status is undoubtedly important, it is not surprising that nutrition-directed interventions are only modestly effective. The magnitude of the contribution of nutrition-based therapies to cancer outcomes is likely modest in comparison to disease-directed therapies.

Nutrition-directed therapies should not be expected to benefit well-nourished patients. In fact, there are clear data that some nutrition-directed therapies such as the routine use of parenteral nutrition in well-nourished patients are actually harmful [113]. A prerequisite for the use of nutritional therapy in surgery patients must therefore be the presence of malnutrition. Based on a validated assessment of preoperative nutrition status, a practical approach can be developed to optimize outcomes.

Traditional nutrition assessment parameters such as serum albumin, total lymphocyte count, skin test reactivity (as markers of immunocompetence), anthropometric changes (triceps skinfold test), and body composition may be confounded by the severity of the underlying cancer [114]. For example, hypoalbuminemia is associated with poor healing, sepsis, and increased surgical mortality and morbidity [113]. However, acute phase response proteins in the perioperative setting can confound the use of traditional nutrition indicators such as serum albumin and prealbumin. There is some evidence that neither serum albumin nor weight loss alone are specific predictors of perioperative complications; however, they may be useful in the context of multivariable models [115].

Several nutrition assessment formulas have been developed to predict morbidity and mortality in surgical patients [116]. However, cancer patients are unique in their physiology. In the past the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N) and the Academy of Nutrition and Dietetics have issued recommendations that all cancer patients undergo nutrition screening as critical component of their initial evaluation [117–119]. What is uniformly stated by experts in the field is that no single parameter is a definitive, encompassing factor that comprehensively captures the nutritional state of a cancer patient. That being said, the ideal screening tool for such a task needs to offer ease of use, reliability, validity, sensitivity, and cost-effectiveness [117].

There are screening tools that meet many of the above criteria. Some examples include: The Patient-Generated Subjective Global Assessment (PG-SGA, a modification of an earlier tool called the Subjective global Assessment), the Mini Nutritional Assessment (MNA), the Malnutrition Screening Tool (MST), the Malnutrition Universal Screening Tool (MUST), and the Nutritional Risk Screening (NRS) [120–127].

Of the choices listed above, the authors and many clinicians use the PG-SGA as a screening tool (Table 8.5). The PG-SGA has a patient-completed portion (documenting weight history, oral intake, activity) and a clinician portion (documenting the specific cancer type and its effects on nutrition requirements/metabolic demand, and a physical assessment). The patient and clinician sections are each scored on a scale of 4–8. A total score of nine or greater indicates that the patient is at nutrition risk which may be characterized as

Table 8.5 Patient-generated subjective global assessment (PG-SGA)

- Patient portion:
  - Weight loss in past month, past 6 months
  - Current oral intake compared to baseline
  - Current physical activity compared to baseline
- Clinician component:
  - Disease and related metabolic demands
    Cancer, wound, age > 65, AIDS, pulmonary/cardiac cachexia
  - Metabolic Demands
    Fevers, sepsis, steroids
  - Physical exam and assessment

mild, moderate, or severe. The result is an assessment of the presence and degree of malnutrition, which can then be used to guide the development of a nutrition care plan [128]. Longitudinal use of the PG-SGA can help determine the response to the nutrition care plan and guide modifications as appropriate [129].

Effect of Surgery on Nutrition in Cancer Patients

As discussed in detail above, the metabolic milieu is unique in cancer patients and can vary based on cancer type. Patients who need surgery as part of their treatment algorithm may be at increased risk of detrimental nutritional consequences. This is most relevant in gastrointestinal surgery whereby there may be a prolonged period of no oral intake. In the following section we will discuss indications for nutritional intervention in the context of surgery for the cancer patient.

Nutrition Support in Surgical Patients with Cancer

Evidence-based guidelines for the use of nutrition support (enteral and parenteral) have been developed by multiple organizations, including The American Society for Parenteral and Enteral Nutrition and the European Society for Parenteral and Enteral Nutrition (E.S.P.E.N) [130]. Table 8.6 summarizes the A.S.P.E.N. guidelines. The oral route for nutrition care is optimal because it is generally very safe and cost-effective. Preferably via education and supplementation in the form of protein powders and supplements, patients can optimize their caloric intake to be nutritionally robust. If there are anatomic or physiologic factors that prohibit oral intake, access to the GI tract may be obtained via a gastrostomy or a jejunostomy feeding tube. The enteral route for nutrition support is generally preferred over parenteral nutrition because it is more cost-effective and is associated with fewer infection-related complications [130]. If enteral nutrition support is not feasible (e.g., bowel obstruction, malabsorption secondary to short gut syndrome, enterocutaneous fistulae, etc.), then the parenteral route is an option.

Table 8.6 Nutrition support guideline recommendations during adult anticancer treatment (A.S.P.E.N. Clinical Guidelines) [130]

1.	Patients with cancer are nutritionally at-risk and should undergo nutrition screening to identify those who require formal nutrition assessment with development of a nutrition care plan.
2.	Nutrition support therapy should not be used routinely in patients undergoing major cancer operations.
3.	Perioperative nutrition support therapy may be beneficial in moderately or severely malnourished patients if administered for 7-14 days preoperatively, but the potential benefits of nutrition support must be weighed against the potential risks of the nutrition support therapy itself and of delaying the operation.
4.	Nutrition support therapy should not be used routinely as an adjunct to chemotherapy.
5.	Nutrition support therapy should not be used routinely in patients undergoing head and neck, abdominal, or pelvic irradiation.
6.	Nutrition support therapy is appropriate in patients receiving active anticancer treatment who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time (7–14 days).
7.	The palliative use of nutrition support therapy in terminally ill cancer patients is rarely indicated.
8.	ω-3 Fatty acid supplementation may help stabilize weight in cancer patients on oral diets experiencing progressive, unintentional weight loss.
9.	Patients should not use therapeutic diets to treat cancer.
10.	Immune-enhancing enteral formulas containing mixtures of arginine, nucleic acids, and essential fatty acids may be beneficial in malnourished patients undergoing major cancer operations.

Preoperative Nutrition Support

Preoperative nutrition support has been hypothesized to benefit patients undergoing cancer surgery by mitigating the consequences of suboptimal nutrition on postoperative morbidity and mortality. The routine (routine referring to administration regardless of the patient's nutrition status) use of preoperative parenteral nutrition is not appropriate. The most frequently cited relevant study evaluating the use of perioperative total parenteral nutrition in surgical patients is the Veterans Affairs Cooperative study published in 1991[113]. The investigators studied 395 patients (99 % male) who required a laparotomy or noncardiac thoracotomy, 66 % of whom had cancer (gastrointestinal cancer (51 %), lung cancer (11 %), or other cancer (4 %)). On entry to the study the subjects were stratified according to nutrition status (no or mild malnutrition, moderate malnutrition, or severe malnutrition). They were randomly assigned to receive either TPN for 7–15 days before surgery and 3 days afterward (the TPN group) or no perioperative TPN (the control group). The patients were subsequently monitored for complications for 90 days after surgery. At 30 days after surgery, there was a statistically significant improvement in nutrition status in the TPN group as determined by the subjective global assessment (SGA). Patients with mild malnutrition did not benefit from TPN and actually had more infectious complications. In contrast, in severely malnourished patients who received TPN, the rate of noninfectious complications and "healing" complications (e.g., wound dehiscence, anastomotic leak, fistula formation) was significantly lower. Their conclusion was that the use of preoperative TPN should be limited to patients who are severely malnourished unless there are other specific indications. These results were similar to findings by Muller et al. who demonstrated reduced morbidity and mortality when TPN was provided before gastrointestinal surgery in patients who were severely malnourished [129].

There have been additional studies comparing preoperative parenteral nutrition, enteral nutrition, and standard oral intake. Meijerink et al. studied malnourished patients with gastric or colorectal cancer and demonstrated no differences in mortality; however there were reduced intra-abdominal abscess with parenteral nutrition in those who were severely malnourished [131].

Forschi et al. compared preoperative enteral nutrition versus standard oral intake in patients with percutaneous biliary drains undergoing surgery and demonstrated that there was reduced morbidity and mortality in the enteral nutrition group [132].

Although the use of immune enhancing formulas remains controversial, Senkal et al. demonstrated decreased infectious complications and decreased cost of complications in patients who received both pre- and postoperative enteral nutrition with an immune-enhancing formula containing omega 3 fatty acids, arginine, and RNA [133]. Similar beneficial findings have been found by other groups [109, 134].

Perioperative Nutrition Support

As in most clinical settings, judgment for the use of perioperative nutrition is paramount. It is clear that the perioperative use of nutritional support may be useful in specific circumstances. Based in part on the data above, the 2009 A.S.P.E.N. clinical guidelines for nutritional support therapy during adult anticancer treatment state that perioperative nutrition support therapy may be beneficial in moderately or severely malnourished patients if administered for 7–14 days preoperatively. However, they state that the potential benefits of nutrition support must be weighed against the potential risks of the nutrition support therapy itself delaying the operation [21]. Their review of the data indicates that the majority of parenteral versus standard oral intake studies find no differences in morbidity or mortality with the use of parenteral nutrition versus standard oral diet [21, 113, 129–132, 135–138]. Additionally, little difference has been found in morbidity and mortality in studies comparing enteral to parenteral nutrition [131, 133, 139–146]. The caveat is that enteral nutrition is favored because it is thought to be more cost-effective and to facilitate glycemic management. Based on the review of

the available studies, it appears that most studies report no difference in morbidity or mortality in enteral nutrition versus standard oral intake in patients with malignancy. This has been studied both in the preoperative and postoperative setting [106, 132, 147, 148].

In 1997, Heslin et al. published a prospective randomized trial of early enteral feeding via an operatively placed jejunostomy tube after resection of upper gastrointestinal malignancy [106]. The purpose of this study was to determine whether early postoperative enteral feeding with an immune-enhancing formula (IEF) decreases morbidity, mortality, and length of hospital stay in these patients. The study was performed with the knowledge that feeding with an IEF improved outcomes in trauma and critical care patients. The study randomized 195 patients to IEF via jejunostomy or control. The tube feedings were supplemented with arginine, RNA and omega-3 fatty acids begun on postoperative day 1. Their results demonstrated no significant differences in the number of minor, major, or infectious complications between the groups. There was one patient with bowel necrosis associated with the IEF requiring operation. Hospital mortality was 2.5 % and the median length of hospital stay was 11 days, which was not different between groups. They concluded that early enteral feeding with an IEF was not beneficial and should not be used in a routine fashion after surgery for upper gastrointestinal malignancies. A subsequent study by a group in the United Kingdom reached similar conclusions [149].

Special Considerations

Esophageal Cancer

As many as 79–100 % of esophageal cancer patients present with dysphagia and weight loss [150, 151]. These symptoms may persist after esophagectomy. Loss of the lower esophageal sphincter, dysmotility of the remnant portion of the esophagus, gastric dysmotility following vagotomy, and bile reflux from disruption of the pylorus all contribute to a high incidence of postoperative foregut dysmotility [152]. Patients may also suffer from the dumping syndrome which is characterized by post-prandial hypotension, flushing, and diarrhea. With the loss of the stomach as a reservoir for early digestion, there is abnormal rapid movement of hyperosmotic, undigested food into the small bowel and subsequent hypersecretion of succus and extracellular fluid into the bowel lumen. Nutritional counseling focuses on the use of frequent, small, energy dense meals consumed without large volumes of liquid and that avoid concentrated carbohydrates and fats.

Postoperatively, patients may still have some complaints of dysphagia either secondary to the reflux noted above or from anastomotic strictures. Strictures can significantly prohibit oral intake and are most often managed by serial dilations. During the postoperative adjustment period, feeding jejunostomy tubes are frequently utilized as a bridge to bolster nutrition. Additionally, if there are postoperative complications such as anastomotic leak, the feeding jejunostomy allows for enteric access for enteral nutrition.

Gastric Cancer

Following gastric surgery, there may be problems with both malabsorption and absence of an adequate reservoir for oral intake [153]. Iron absorption may be compromised if the duodenum is bypassed. With major gastric resections, there may be insufficient intrinsic factor synthesis which can lead to vitamin B12 malabsorption and deficiency with resultant development of megaloblastic anemia and dementia. These patients will require 1,000 mcg of monthly intramuscular Vitamin B12 supplementation for the entirety of their lives. It is important to counsel patients preoperatively regarding this possibility. To address the lack of reservoir function, patients are counseled on a post-gastrectomy diet that may include six smaller meals daily and the avoidance of concentrated carbohydrates and fats to prevent dumping.

Small Bowel Resection

The small bowel is the site of both the digestion and the absorption of nutrients. If large segments of bowel are resected, both of these functions can be compromised. Additionally, there are specific consequences that are unique to the loss of segments of small bowel that have specialized absorptive function.

The duodenum functions to neutralize the acidic chyme that exits the stomach. It is also the site where food meets pancreatic enzymes and bile salts to continue the digestive process initiated in the stomach. The duodenum additionally is the major site for absorption of magnesium, calcium, and iron and is the site of release of hormones that regulate gallbladder and pancreatic function (cholecystokinin and secretin).

The jejunum is the absorptive powerhouse for carbohydrates, protein, and water-soluble vitamins. Larger segmental jejunum resections may lead to malabsorptive diarrhea and thus contribute to malnutrition. The ileum functions to absorb lipids, fat-soluble vitamins, cholesterol, bile salts, and vitamin B12. Patients who have diverting or end ileostomies are at significant risk for electrolyte abnormalities and are encouraged to ingest approximately one liter more electrolyte-containing liquids than their stoma output to avoid dehydration [154].

If there is extensive loss of jejunum and/or ileum, the malabsorption that ensues may become so severe that volume and caloric needs cannot be met enterally. The clinical severity of symptoms relates to multiple factors, including the length of bowel resected, the physiologic status of the remaining bowel, the presence or absence of colon, and the presence or absence of the gastrointestinal tract sphincters that slow transit time and prevent reflux (the gastroesophageal sphincter, the pylorus, and the ileocecal valve). These patients may require prolonged or even lifelong supplementation with parenteral nutrition if/until small bowel hypertrophy and adaptation occur [155]. Mainstays of the treatment of patients with small bowel malabsorption and short bowel syndrome include use of: (1) Easily absorbed oral electrolyte containing solutions to prevent electrolyte imbalances and dehydration; (2) Proton pump inhibitors to suppress the hyper-secretion of gastric acid and fluid that results from the hypergastrinema seen in patients with short bowel syndrome; (3) Cholestyramine to bind bile acids and prevent their entry into the colon where they cause an irritative diarrhea; (4) Antimotility agents to slow small bowel and colon transit time.

The small bowel is also a major contributor to bacterial homeostasis. Specifically, if transit time is decreased and acidic small bowel contents reach the colon, carbohydrates can be fermented by bacteria into D-lactic acid. Build up of D-lactic acid may result in lactic acidosis, yielding increased serum D-lactate, an increased anion gap, and decreased serum bicarbonate [117]. This can occur in short bowel syndrome or after jejuno-ileal bypass surgery and present as altered mental status, slurred speech, and ataxia most frequently after ingestion of a high carbohydrate meal [156]. Recommendations to avoid this are to restrict large carbohydrate meals, antibiotics, and probiotics.

Pancreatic Cancer

Pancreatic resection for pancreas cancer, whether proximal or distal, can result in diabetes and/or malabsorption [157]. The majority of the exocrine function of the pancreas resides in the uncinate and head, whereas much of the neuroendocrine function is found in the body and tail. Patients who have undergone a pancreaticoduodenectomy are also at risk of suffering from dumping syndrome. For malabsorption symptoms following pancreatic resection (weight loss, bloating, foul smelling diarrhea, post-prandial cramping), it is often more practical to proceed directly to oral pancreatic enzyme replacement than to undertake a complex and costly physiologic evaluation.

Liver and Gallbladder Cancer

Liver neoplasms are unique in that there are some specific electrolyte derangements in the immediate postoperative period. After major hepatectomy,

patients often present with profound hypophosphatemia that is hypothesized to be secondary to both liver regeneration and phosphorous wasting in the urine. The precise mechanism has not been fully elucidated but this is a consideration clinicians must keep in mind. Patients may also suffer from ascites in the perioperative period that may compromise their ability to eat and cause anorexia. Operative placement of feeding tubes in these patients should be discouraged because of the high rate of complications of these tubes in patients with ascites.

Colon Cancer

The function of the colon is primarily to absorb water and electrolytes. The right colon contributes most to this function; removal of the ascending colon with the ileocecal valve often leads to a period of more frequent and less formed bowel movements. During this period, patients should be counseled to avoid dehydration. This can be especially problematic in older patients. Additionally, if there is impaired intestinal peristalsis, bacterial overgrowth may ensue. It is thought that although clinically patients may have an improvement in as early as a few weeks, it can take over two years to undergo structural and functional adaptation to compensate nutritionally after colon resection [158].

Practical Notes to the Perioperative Nutritional Support of Cancer Patients

Based on the issues discussed in this chapter, a practical approach to nutrition care in cancer surgery patients can be stated.

All cancer patients in whom surgery is contemplated should undergo nutrition screening. If concerns are identified, a formal nutrition assessment should be performed. This assessment should include patient reported information, clinical assessment data, and objective laboratory tests. The PG-SGA combined with a complete history and physical examination and a comprehensive metabolic panel including a serum albumin level and a complete blood count suffice for most patients.

In those patients in whom significant malnutrition and/or nutrient deficiencies are identified that may compromise surgical outcomes, a detailed nutrition care plan should be created. This may involve dietary counseling, oral supplements, micronutrient and electrolyte repletion, and/or the use of enteral or parenteral nutrition. Pretreatment placement of a feeding tube may occasionally be beneficial. Careful, serial monitoring of the results of the nutrition care plan and for complications, often by a registered dietitian, is crucial.

At the time of operation, the likely perioperative needs of patients should be considered so that appropriate enteral and/or parenteral access may be established at the time of the cancer resection. These same considerations also apply postoperatively when they may be exacerbated by operative complications or changes in gastrointestinal physiology that may result from altered anatomy and function.

Lastly, as a general principle, the palliative use of nutrition support therapy in terminally ill cancer patients is rarely indicated [130]. If patients are to benefit from parenteral nutrition the general guidelines are that they: (1) must be physically and emotionally capable of participating in their own care; (2) should have an estimated life expectancy of >40–60 days; (3) have ample social and economic support at home with an in-home lay care taker; and (4) failed other less costly and invasive therapies.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30. PubMed PMID: 23335087.
2. Eaton L. World cancer rates set to double by 2020. BMJ. 2003;326(7392):728. PubMed PMID: 12676827; Pubmed Central PMCID: 1125643.
3. Meropol NJ, Schulman KA. Cost of cancer care: issues and implications. J Clin Oncol. 2007;25(2):180–6. PubMed PMID: 17210937.
4. August D, Huhmann M. Nutritional care of cancer patients. In: Norton J, Barie P, Bollinger R, Chang A, Lowry S, Mulvihill S, et al., editors. Surgery: basic

science and clinical evidence. 2nd ed. New York: Springer; 2008. p. 2123–49.
5. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):225–49. PubMed PMID: 19474385. Epub 2009/05/29. eng.
6. Warren S. The immediate cause of death in cancer. Am J Med Sci. 1932;185:610–5.
7. Inagaki J, Rodriguez V, Bodey GP. Proceedings: Causes of death in cancer patients. Cancer. 1974;33(2):568–73. PubMed PMID: 4591273.
8. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981;66(6):1191–308. PubMed PMID: 7017215.
9. Willett WC. Diet, nutrition, and avoidable cancer. Environ Health Perspect. 1995;103 Suppl 8:165–70. PubMed PMID: 8741778; Pubmed Central PMCID: 1518978.
10. Polednak AP. Estimating the number of U.S. incident cancers attributable to obesity and the impact on temporal trends in incidence rates for obesity-related cancers. Cancer Detect Prev. 2008;32(3):190–9. PubMed PMID: 18790577.
11. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220–41. PubMed PMID: 22700443.
12. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62(4):243–74. PubMed PMID: 22539238.
13. DeWys WD. Anorexia as a general effect of cancer. Cancer. 1979;43(5 Suppl):2013–9. PubMed PMID: 376105.
14. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491–7. PubMed PMID: 7424938.
15. Tan BH, Fearon KC. Cachexia: prevalence and impact in medicine. Curr Opin Clin Nutr Metab Care. 2008;11(4):400–7. PubMed PMID: 18541999.
16. McClement S. Cancer anorexia-cachexia syndrome: psychological effect on the patient and family. J Wound Ostomy Continence Nurs. 2005;32(4):264–8. PubMed PMID: 16030467.
17. Ottery FD. Supportive nutrition to prevent cachexia and improve quality of life. Semin Oncol. 1995;22(2 Suppl 3):98–111. PubMed PMID: 7740324.
18. Puccio M, Nathanson L. The cancer cachexia syndrome. Semin Oncol. 1997;24(3):277–87. PubMed PMID: 9208884. Epub 1997/06/01. eng.
19. Studley H. Percentage of weight loss. JAMA. 1936;106:458–60.
20. Mullen JT, Davenport DL, Hutter MM, Hosokawa PW, Henderson WG, Khuri SF, et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. Ann Surg Oncol. 2008;15(8):2164–72. PubMed PMID: 18548313.
21. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer–a systematic review of the epidemiological literature. Nutr J. 2012;11:27. PubMed PMID: 22531478; Pubmed Central PMCID: 3408376.
22. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.
23. August DA, Huhmann MB. Nutritional support of the cancer patient. In: Ross CA, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, editors. Modern nutrition in health and disease. Philadelphia, PA: Lippincott, Williams and Wilkins; 2013. p. 1194–213.
24. Kern KA, Norton JA. Cancer cachexia. JPEN J Parenter Enteral Nutr. 1988;12(3):286–98. PubMed PMID: 3292798.
25. Arbeit JM, Lees DE, Corsey R, Brennan MF. Resting energy expenditure in controls and cancer patients with localized and diffuse disease. Ann Surg. 1984;199(3):292–8. PubMed PMID: 6703790; Pubmed Central PMCID: 1353395.
26. Hyltander A, Drott C, Korner U, Sandstrom R, Lundholm K. Elevated energy expenditure in cancer patients with solid tumours. Eur J Cancer. 1991;27(1):9–15. PubMed PMID: 1826450.
27. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg. 1994;219(4):325–31. PubMed PMID: 7512810; Pubmed Central PMCID: 1243147.
28. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609–15. PubMed PMID: 16704954.
29. Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest. 2007;25(5):308–14. PubMed PMID: 17661205.
30. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72–7. PubMed PMID: 19647909.
31. Knox LS, Crosby LO, Feurer ID, Buzby GP, Miller CL, Mullen JL. Energy expenditure in malnourished cancer patients. Ann Surg. 1983;197(2):152–62. PubMed PMID: 6824369; Pubmed Central PMCID: 1353103.
32. Hansell DT, Davies JW, Burns HJ. The relationship between resting energy expenditure and weight loss in benign and malignant disease. Ann Surg. 1986;203(3):240–5. PubMed PMID: 3082302; Pubmed Central PMCID: 1251083.
33. Johnson G, Salle A, Lorimier G, Laccourreye L, Enon B, Blin V, et al. Cancer cachexia: measured and predicted resting energy expenditures for nutritional

needs evaluation. Nutrition. 2008;24(5):443–50. PubMed PMID: 18359195.
34. Vaisman N, Lusthaus M, Niv E, Santo E, Shacham-Shmueli E, Geva R, et al. Effect of tumor load on energy expenditure in patients with pancreatic cancer. Pancreas. 2012;41(2):230–2. PubMed PMID: 21926936.
35. Jebb SA, Osborne RJ, Dixon AK, Bleehen NM, Elia M. Measurements of resting energy expenditure and body composition before and after treatment of small cell lung cancer. Ann Oncol. 1994;5(10):915–9. PubMed PMID: 7696163.
36. Simons JP, Schols AM, Buurman WA, Wouters EF. Weight loss and low body cell mass in males with lung cancer: relationship with systemic inflammation, acute-phase response, resting energy expenditure, and catabolic and anabolic hormones. Clin Sci. 1999;97(2):215–23. PubMed PMID: 10409477.
37. Dempsey DT, Feurer ID, Knox LS, Crosby LO, Buzby GP, Mullen JL. Energy expenditure in malnourished gastrointestinal cancer patients. Cancer. 1984;53(6):1265–73. PubMed PMID: 6692317.
38. Fearon KC, Hansell DT, Preston T, Plumb JA, Davies J, Shapiro D, et al. Influence of whole body protein turnover rate on resting energy expenditure in patients with cancer. Cancer Res. 1988;48(9):2590–5. PubMed PMID: 3356019.
39. Fredrix EW, Wouters EF, Soeters PB, van der Aalst AC, Kester AD, von Meyenfeldt MF, et al. Resting energy expenditure in patients with non-small cell lung cancer. Cancer. 1991;68(7):1616–21. PubMed PMID: 1654199.
40. DuBois EF. Basal metabolism in health and disease. 3rd ed. Philadelphia: Lea and Febiger; 1936.
41. Kleiber M. The fire of life: an introduction to animal energetics. Malabar, FL: Krieger; 1961.
42. Harris JA. A biometric study of basal metabolism. Washington, DC: Carnegie Institute of Washington; 1919.
43. Barak N, Wall-Alonso E, Sitrin MD. Evaluation of stress factors and body weight adjustments currently used to estimate energy expenditure in hospitalized patients. JPEN J Parenter Enteral Nutr. 2002;26(4):231–8. PubMed PMID: 12090688.
44. MacDonald A, Hildebrandt L. Comparison of formulaic equations to determine energy expenditure in the critically ill patient. Nutrition. 2003;19(3):233–9. PubMed PMID: 12620525.
45. Bosy-Westphal A, Reinecke U, Schlorke T, Illner K, Kutzner D, Heller M, et al. Effect of organ and tissue masses on resting energy expenditure in underweight, normal weight and obese adults. Int J Obes Relat Metab Disord. 2004;28(1):72–9. PubMed PMID: 14647174.
46. Fearon KC. The Sir David Cuthbertson Medal Lecture 1991. The mechanisms and treatment of weight loss in cancer. Proc Nutr Soc. 1992;51(2):251–65. PubMed PMID: 1438334.
47. Agustsson T, Ryden M, Hoffstedt J, van Harmelen V, Dicker A, Laurencikiene J, et al. Mechanism of increased lipolysis in cancer cachexia. Cancer Res. 2007;67(11):5531–7. PubMed PMID: 17545636.
48. Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev. 2009;89(2):381–410. PubMed PMID: 19342610.
49. Tisdale MJ. Cancer cachexia. Curr Opin Gastroenterol. 2010;26(2):146–51.
50. Shaw JH, Wolfe RR. Fatty acid and glycerol kinetics in septic patients and in patients with gastrointestinal cancer. The response to glucose infusion and parenteral feeding. Ann Surg. 1987;205(4):368–76. PubMed PMID: 3105476.
51. Laurencikiene J, Stenson BM, Arvidsson Nordstrom E, Agustsson T, Langin D, Isaksson B, et al. Evidence for an important role of CIDEA in human cancer cachexia. Cancer Res. 2008;68(22):9247–54.
52. Dilman VM, Berstein LM, Ostroumova MN, Tsyrlina YV, Golubev AG. Peculiarities of hyperlipidaemia in tumour patients. Br J Cancer. 1981;43(5):637–43.
53. Hussey HJ, Tisdale MJ. Effect of polyunsaturated fatty acids on the growth of murine colon adenocarcinomas in vitro and in vivo. Br J Cancer. 1994;70(1):6–10. PubMed PMID: 8018542.
54. Tisdale MJ. Tumor-host interactions. J Cell Biochem. 2004;93(5):871–7.
55. Williams A, Sun X, Fischer JE, Hasselgren PO. The expression of genes in the ubiquitin-proteasome proteolytic pathway is increased in skeletal muscle from patients with cancer. Surgery. 1999;126(4):744–9. Discussion 9-50. PubMed PMID: 10520924.
56. Jeevanandam M, Legaspi A, Lowry SF, Horowitz GD, Brennan MF. Effect of total parenteral nutrition on whole body protein kinetics in cachectic patients with benign or malignant disease. JPEN J Parenter Enteral Nutr. 1988;12(3):229–36. PubMed PMID: 3134558.
57. Norton JA, Stein TP, Brennan MF. Whole body protein synthesis and turnover in normal man and malnourished patients with and without known cancer. Ann Surg. 1981;194(2):123–8. PubMed PMID: 6789786; Pubmed Central PMCID: 1345227.
58. Lundholm K, Bennegard K, Eden E, Svaninger G, Emery PW, Rennie MJ. Efflux of 3-methylhistidine from the leg in cancer patients who experience weight loss. Cancer Res. 1982;42(11):4807–11. PubMed PMID: 7127315.
59. Warren RS, Jeevanandam M, Brennan MF. Comparison of hepatic protein synthesis in vivo versus in vitro in the tumor-bearing rat. J Surg Res. 1987;42(1):43–50. PubMed PMID: 3543498.
60. Fearon KC, McMillan DC, Preston T, Winstanley FP, Cruickshank AM, Shenkin A. Elevated circulating interleukin-6 is associated with an acute-phase response but reduced fixed hepatic protein synthesis in patients with cancer. Ann Surg. 1991;213(1):26–31. PubMed PMID: 1898691; Pubmed Central PMCID: 1358306.
61. Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309–14.

62. Bongaerts GP, van Halteren HK, Verhagen CA, Wagener DJ. Cancer cachexia demonstrates the energetic impact of gluconeogenesis in human metabolism. Med Hypotheses. 2006;67(5):1213–22. PubMed PMID: 16797873.
63. Lelbach A, Muzes G, Feher J. Current perspectives of catabolic mediators of cancer cachexia. Med Sci Monit. 2007;13(9):RA168–73. PubMed PMID: 17767131.
64. Lundholm K, Edstrom S, Karlberg I, Ekman L, Schersten T. Glucose turnover, gluconeogenesis from glycerol, and estimation of net glucose cycling in cancer patients. Cancer. 1982;50(6):1142–50. PubMed PMID: 7104955.
65. Waterhouse C, Jeanpretre N, Keilson J. Gluconeogenesis from alanine in patients with progressive malignant disease. Cancer Res. 1979;39(6 Pt 1):1968–72. PubMed PMID: 445395.
66. Lundholm K, Holm G, Schersten T. Insulin resistance in patients with cancer. Cancer Res. 1978;38(12):4665–70. PubMed PMID: 719645.
67. Rofe AM, Bourgeois CS, Coyle P, Taylor A, Abdi EA. Altered insulin response to glucose in weight-losing cancer patients. Anticancer Res. 1994; 14(2B):647–50. PubMed PMID: 8010722.
68. Smiechowska J, Utech A, Taffet G, Hayes T, Marcelli M, Garcia JM. Adipokines in patients with cancer anorexia and cachexia. J Invest Med. 2010;58(3):554–9. PubMed PMID: 20215915.
69. Garcia-Martinez C, Costelli P, Lopez-Soriano FJ, Argiles JM. Is TNF really involved in cachexia? Cancer Invest. 1997;15(1):47–54. PubMed PMID: 9028389.
70. Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A. Cancer cachexia–pathophysiology and management. J Gastroenterol. 2013;48(5):574–94. PubMed PMID: 23512346; Pubmed Central PMCID: 3698426.
71. Toomey D, Redmond HP, Bouchier-Hayes D. Mechanisms mediating cancer cachexia. Cancer. 1995;76(12):2418–26. PubMed PMID: 8625066.
72. Lenk K, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. J Cachexia Sarcopenia Muscle. 2010;1(1):9–21. PubMed PMID: 21475693; Pubmed Central PMCID: 3060644.
73. Darling G, Fraker DL, Jensen JC, Gorschboth CM, Norton JA. Cachectic effects of recombinant human tumor necrosis factor in rats. Cancer Res. 1990;50(13):4008–13. PubMed PMID: 2354450.
74. Oliff A, Defeo-Jones D, Boyer M, Martinez D, Kiefer D, Vuocolo G, et al. Tumors secreting human TNF/cachectin induce cachexia in mice. Cell. 1987;50(4):555–63. PubMed PMID: 3607879.
75. Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptides. Curr Opin Clin Nutr Metab Care. 2004;7(4):427–34.
76. Tracey KJ, Morgello S, Koplin B, Fahey 3rd TJ, Fox J, Aledo A, et al. Metabolic effects of cachectin/tumor necrosis factor are modified by site of production. Cachectin/tumor necrosis factor-secreting tumor in skeletal muscle induces chronic cachexia, while implantation in brain induces predominantly acute anorexia. J Clin Invest. 1990;86(6):2014–24.
77. Matthys P, Dijkmans R, Proost P, Van Damme J, Heremans H, Sobis H, et al. Severe cachexia in mice inoculated with interferon-gamma-producing tumor cells. Int J Cancer. 1991;49(1):77–82.
78. Fischer E, Marano MA, Barber AE, Hudson A, Lee K, Rock CS, et al. Comparison between effects of interleukin-1 alpha administration and sublethal endotoxemia in primates. Am J Physiol. 1991;261(2 Pt 2):R442–52.
79. Gelin J, Moldawer LL, deMan P, Svanborg-Eden C, Lowry SF, et al. Appearance of hybridoma growth factor/interleukin-6 in the serum of mice bearing a methylcholanthrene-induced sarcoma. Biochem Biophys Res Commun. 1988;157(2):575–9.
80. Argiles JM, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Med Res Rev. 1999;19(3): 223–48.
81. Diakowska D, Krzystek-Korpacka M, Markocka-Maczka K, Diakowski W, Matusiewicz M, Grabowski K. Circulating leptin and inflammatory response in esophageal cancer, esophageal cancer-related cachexia-anorexia syndrome (CAS) and non-malignant CAS of the alimentary tract. Cytokine. 2010;51(2):132–7.
82. Yakabi K, Sadakane C, Noguchi M, Ohno S, Ro S, Chinen K, et al. Reduced ghrelin secretion in the hypothalamus of rats due to cisplatin-induced anorexia. Endocrinology. 2010;151(8):3773–82.
83. Schreiber R, Selbach K, Asmussen M, Hesse D, de Vry J. Effects of serotonin(1/2) receptor agonists on dark-phase food and water intake in rats. Pharmacol Biochem Behav. 2000;67(2):291–305.
84. Monitto CL, Dong SM, Jen J, Sidransky D. Characterization of a human homologue of proteolysis-inducing factor and its role in cancer cachexia. Clin Cancer Res. 2004;10(17):5862–9.
85. Todorov PT, McDevitt TM, Meyer DJ, Ueyama H, Ohkubo I, Tisdale MJ. Purification and characterization of a tumor lipid-mobilizing factor. Cancer Res. 1998;58(11):2353–8.
86. Bozzetti F. Effects of artificial nutrition on the nutritional status of cancer patients. JPEN J Parenter Enteral Nutr. 1989;13(4):406–20.
87. Wang Y, Jiang ZM, Nolan MT, Jiang H, Han HR, Yu K, et al. The impact of glutamine dipeptide-supplemented parenteral nutrition on outcomes of surgical patients: a meta-analysis of randomized clinical trials. JPEN J Parenter Enteral Nutr. 2010;34(5):521–9.
88. Coster J, McCauley R, Hall J. Glutamine: metabolism and application in nutrition support. Asia Pac J Clin Nutr. 2004;13(1):25–31.

89. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev. 2003; 29(6):501–13.
90. DeBerardinis RJ, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene. 2010;29(3):313–24.
91. Eagle H. Nutrition needs of mammalian cells in tissue culture. Science. 1955;122(3168):501–14.
92. O'Riordain MG, Fearon KC, Ross JA, Rogers P, Falconer JS, Bartolo DC, et al. Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. Ann Surg. 1994;220(2):212–21.
93. Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. Eur J Nutr. 2010;49(4):197–210.
94. Wu GH, Zhang YW, Wu ZH. Modulation of postoperative immune and inflammatory response by immune-enhancing enteral diet in gastrointestinal cancer patients. World J Gastroenterol. 2001;7(3): 357–62.
95. Coghlin Dickson TM, Wong RM, Offrin RS, Shizuru JA, Johnston LJ, Hu WW, et al. Effect of oral glutamine supplementation during bone marrow transplantation. JPEN J Parenter Enteral Nutr. 2000;24(2): 61–6.
96. Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Koller M, Konig W, et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg. 1998;227(2):302–8.
97. Piccirillo N, De Matteis S, Laurenti L, Chiusolo P, Sora F, Pittiruti M, et al. Glutamine-enriched parenteral nutrition after autologous peripheral blood stem cell transplantation: effects on immune reconstitution and mucositis. Haematologica. 2003;88(2):192–200.
98. Scheid C, Hermann K, Kremer G, Holsing A, Heck G, Fuchs M, et al. Randomized, double-blind, controlled study of glycyl-glutamine-dipeptide in the parenteral nutrition of patients with acute leukemia undergoing intensive chemotherapy. Nutrition. 2004;20(3):249–54.
99. Schloerb PR, Skikne BS. Oral and parenteral glutamine in bone marrow transplantation: a randomized, double-blind study. JPEN J Parenter Enteral Nutr. 1999;23(3):117–22.
100. Heys SD, Gough DB, Khan L, Eremin O. Nutritional pharmacology and malignant disease: a therapeutic modality in patients with cancer. Br J Surg. 1996; 83(5):608–19.
101. De Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, Aller R. High dose of arginine enhanced enteral nutrition in postsurgical head and neck cancer patients. A randomized clinical trial. Eur Rev Med Pharmacol Sci. 2009;13(4):279–83.
102. Buijs N, van Bokhorst-de van der Schueren MA, Langius JA, Leemans CR, Kuik DJ, Vermeulen MA, et al. Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. Am J Clin Nutr. 2010;92(5):1151–6.
103. Lacour J, Laplanche A, Delozier T, Berlie J, Mourali N, Julien JP, et al. Polyadenylic-polyuridylic acid plus locoregional and pelvic radiotherapy versus chemotherapy with CMF as adjuvants in operable breast cancer. A 6 1/2 year follow-up analysis of a randomized trial of the French Federation of Cancer Centers (F.F.C.C.). Breast Cancer Res Treat. 1991;19(1):15–21.
104. Lacour J, Laplanche A, Malafosse M, Gallot D, Julien M, Rotman N, et al. Polyadenylic-polyuridylic acid as an adjuvant in resectable colorectal carcinoma: a 6 1/2 year follow-up analysis of a multicentric double blind randomized trial. Eur J Surg Oncol. 1992;18(6):599–604.
105. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996–1002.
106. Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg. 1997;226(4):567–77. Discussion 77-80.
107. Braga M, Gianotti L, Cestari A, Vignali A, Pellegatta F, Dolci A, et al. Gut function and immune and inflammatory responses in patients perioperatively fed with supplemented enteral formulas. Arch Surg. 1996;131(12):1257–64. Discussion 64-5.
108. Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. Crit Care Med. 1998;26(1): 24–30.
109. Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology. 2002;122(7):1763–70.
110. Braga M, Vignali A, Zuliani W, Radaelli G, Gianotti L, Martani C, et al. Metabolic and functional results after laparoscopic colorectal surgery: a randomized, controlled trial. Dis Colon Rectum. 2002;45(8): 1070–7.
111. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA. 2001;286(8):944–53.
112. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. JPEN J Parenter Enteral Nutr. 2010; 34(4):378–86.
113. Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med. 1991;325(8):525–32.

114. Huhmann MB, August DA. Perioperative nutrition support in cancer patients. Nutr Clin Pract. 2012;27(5):586–92.
115. Jensen GL. Inflammation as the key interface of the medical and nutrition universes: a provocative examination of the future of clinical nutrition and medicine. JPEN J Parenter Enteral Nutr. 2006;30(5):453–63.
116. Hirsch S, de Obaldia N, Petermann M, Covacevic S, Burmeister R, Llorens P, et al. Nutritional status of surgical patients and the relationship of nutrition to postoperative outcome. J Am Coll Nutr. 1992; 11(1):21–4.
117. Directors ABo, the Clinical Guidelines Task F. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26(1 Suppl):1SA–138SA.
118. Identifying patients at risk: ADA's definitions for nutrition screening and nutrition assessment. Council on Practice (COP) Quality Management Committee. J Am Diet Assoc. 1994;94(8):838–9.
119. Mueller C, Compher C, Ellen DM, American Society for Parenteral and Enteral Nutrition Board of Directors. A.S.P.E.N. Clinical Guidelines: Nutrition screening, assessment, and intervention in adults. JPEN J Parenter Enteral Nutr. 2011;35(1):16–24.
120. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15–9.
121. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8–13. PubMed PMID: 3820522.
122. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: the mini nutritional assessment as part of the geriatric evaluation. Nutr Rev. 1996;54(1 Pt 2):S59–65. PubMed PMID: 8919685.
123. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. Nutrition. 1999;15(6):458–64. PubMed PMID: 10378201.
124. Ferguson ML, Bauer J, Gallagher B, Capra S, Christie DR, Mason BR. Validation of a malnutrition screening tool for patients receiving radiotherapy. Australas Radiol. 1999;43(3):325–7. PubMed PMID: 10901927.
125. Malnutrition Advisory Group. A consistent and reliable tool for malnutrition screening. Nurs Times. 2003;99(46):26–7. PubMed PMID: 14666817.
126. Bauer J, Capra S. Comparison of a malnutrition screening tool with subjective global assessment in hospitalised patients with cancer–sensitivity and specificity. Asia Pac J Clin Nutr. 2003;12(3):257–60. PubMed PMID: 14505986.
127. Kondrup J, Johansen N, Plum LM, Bak L, Larsen IH, Martinsen A, et al. Incidence of nutritional risk and causes of inadequate nutritional care in hospitals. Clin Nutr. 2002;21(6):461–8. PubMed PMID: 12468365.
128. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr. 2002;56(8):779–85. PubMed PMID: 12122555.
129. Ferguson M. Patient-generated subjective global assessment. Oncology. 2003;17(2 Suppl 2):13–4. Discussion 14–6. PubMed PMID: 12632872.
130. August DA, Huhmann MB, American Society for Parenteral and Enteral Nutrition Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr. 2009;33(5):472–500.
131. Meijerink WJ, von Meyenfeldt MF, Rouflart MM, Soeters PB. Efficacy of perioperative nutritional support. Lancet. 1992;340(8812):187–8. PubMed PMID: 1352609.
132. Foschi D, Cavagna G, Callioni F, Morandi E, Rovati V. Hyperalimentation of jaundiced patients on percutaneous transhepatic biliary drainage. Br J Surg. 1986;73(9):716–9. PubMed PMID: 3092894.
133. Senkal M, Zumtobel V, Bauer KH, Marpe B, Wolfram G, Frei A, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. Arch Surg. 1999;134(12):1309–16. PubMed PMID: 10593328.
134. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg. 2002;137(2):174–80. PubMed PMID: 11822956.
135. August DA, Kushner RF. The 1995 A.S.P.E.N. standards for nutrition support: hospitalized patients. Nutr Clin Pract. 1995;10(6):206–7.
136. Foschi D, Toti GL, Del Soldato P, Ferrante F, Galeone M, Rovati V. Adaptive cytoprotection: an endoscopic study in man. Am J Gastroenterol. 1986;81(11):1035–7. PubMed PMID: 3776949.
137. Borea G, Ceccarelli C, Rinaldi-Ceroni A, Galie M, Stancari V, Rivano MT, et al. Adenolymphomas of the parotid gland. Immunocytochemical study. Pathologica. 1986;78(1057):545–53.
138. Turi A, Di Prospero F, Foschi F, Campanari G, Romanini C. [Changes in the circulation pattern of serum melatonin in women with ovarian neoplasms]. Annali di ostetricia, ginecologia, medicina perinatale. 1986;107(4):207–9.
139. Trabucchi E, Foschi D, Colombo R, Baratti C, Del Soldato P, Centemero A, et al. Cytoprotection by PGE2, pirenzepine or vagotomy: a transmission and scanning electron microscopic study in rats. Pharmacol Res Commun. 1986;18(4):357–69.
140. Del Soldato P, Foschi D, Benoni G, Scarpignato C. Oxygen free radicals interact with indomethacin to cause gastrointestinal injury. Agents Actions. 1986;17(5–6):484–8.
141. Foschi D, Ferrante F, Varin L, Del Soldato P, Rovati V. Protection of gastric mucosa in rats. Differences

between vagotomy, atropine, and PGE2. Dig Dis Sci. 1986;31(3):289–96.
142. Morrison MH, Barber HE, Foschi PG, Hawksworth GM. The kinetics of 4-nitrophenol conjugation by perfused livers and hepatic microsomes from streptozocin-induced diabetic rats. J Pharm Pharmacol. 1986;38(3):188–94.
143. Carli P, De Giorgi V, Chiarugi A, Stante M, Giannotti B. Multiple synchronous cutaneous melanomas: implications for prevention. Int J Dermatol. 2002;41(9):583–5.
144. Patrono C, Dionisi-Vici C, Giannotti A, Bembi B, Digilio MC, Rizzo C, et al. Two novel mutations of the human delta7-sterol reductase (DHCR7) gene in children with Smith-Lemli-Opitz syndrome. Mol Cell Probes. 2002;16(4):315–8.
145. Carli P, De Giorgi V, Argenziano G, Palli D, Giannotti B. Pre-operative diagnosis of pigmented skin lesions: in vivo dermoscopy performs better than dermoscopy on photographic images. J Eur Acad Dermatol Venereol. 2002;16(4):339–46.
146. Prignano F, Coronnello M, Pimpinelli N, Cappugi P, Mini E, Giannotti B. Immunophenotypical markers, ultrastructure and chemosensitivity profile of metastatic melanoma cells. Cancer Lett. 2002;186(2): 183–92.
147. Giolitti A, Altamura M, Bellucci F, Giannotti D, Meini S, Patacchini R, et al. Monocyclic human tachykinin NK-2 receptor antagonists as evolution of a potent bicyclic antagonist: QSAR and site-directed mutagenesis studies. J Med Chem. 2002;45(16): 3418–29.
148. Giannotti B, Pimpinelli N. Modern diagnosis of cutaneous lymphoma. Recent Results Cancer Res. 2002;160:303–6.
149. Toscano A, Anaclerio S, Digilio MC, Giannotti A, Fariello G, Dallapiccola B, et al. Ventricular septal defect and deletion of chromosome 22q11: anatomical types and aortic arch anomalies. Eur J Pediatr. 2002;161(2):116–7. PubMed PMID: 11954747.
150. de Camargo OP, dos Santos Machado TM, Croci AT, de Oliveira CR, Giannotti MA, Baptista AM, et al. Primary bone lymphoma in 24 patients treated between 1955 and 1999. Clin Orthop Relat Res. 2002;397:271–80. PubMed PMID: 11953618.
151. Carli P, De Giorgi V, Nardini P, Mannone F, Palli D, Giannotti B. Melanoma detection rate and concordance between self-skin examination and clinical evaluation in patients attending a pigmented lesion clinic in Italy. Br J Dermatol. 2002;146(2):261–6.
152. Mangino M, Flex E, Digilio MC, Giannotti A, Dallapiccola B. Identification of a novel NOG gene mutation (P35S) in an Italian family with symphalangism. Hum Mutat. 2002;19(3):308.
153. Harmat NJ, Giannotti D, Nannicini R, Perrotta E, Criscuoli M, Patacchini R, et al. Insertion of 2-carboxysuccinate and tricarballylic acid fragments into cyclic-pseudopeptides: new antagonists for the human tachykinin NK-2 receptor. Bioorg Med Chem Lett. 2002;12(4):693–6.
154. Giannotti E, Vandin L, Repeto P, Comelli R. A comparison of the in vitro Comet assay with the in vitro chromosome aberration assay using whole human blood or Chinese hamster lung cells: validation study using a range of novel pharmaceuticals. Mutagenesis. 2002;17(2):163–70.
155. Gemma M, Tommasino C, Cerri M, Giannotti A, Piazzi B, Borghi T. Intracranial effects of endotracheal suctioning in the acute phase of head injury. J Neurosurg Anesthesiol. 2002;14(1):50–4.
156. Gianotti N, Setti M, Manconi PE, Leoncini F, Chiodo F, Minoli L, et al. Reverse transcriptase mutations in HIV-1 infected patients treated with two nucleoside analogues: the SMART study. Int J Immunopathol Pharmacol. 2002;15(2):129–39.
157. Gianotti L, Lanfranco F, Ramunni J, Destefanis S, Ghigo E, Arvat E. GH/IGF-I axis in anorexia nervosa. Eat Weight Disord. 2002;7(2):94–105.
158. Veraldi S, Rigoni C, Gianotti R. Leishmaniasis of the lip. Acta dermato-venereologica. 2002;82(6):469–70.

Sepsis and Nutrition

9

Laura J. Moore and Frederick A. Moore

Introduction

Sepsis continues to be a common and serious problem. As the population ages, the incidence of sepsis in the United States continues to climb. It is estimated that in the United States, there are greater than 1.1 million cases of sepsis per year [1] at an annual cost of $24.3 billion [2]. Sepsis remains the leading cause of death in non-cardiac intensive care units (ICUs) [2]. In spite of extensive research, sepsis related mortality remains prohibitively high [3–5]. In recent years, multiple professional organizations have developed evidence-based guidelines for the management of sepsis. The intent of such guidelines is to improve patient outcomes by aiding clinicians in the delivery of evidence-based care. Providing adequate nutritional support of critically ill patients, including those with sepsis, is a key factor in improving patient outcomes. The provision of early nutritional support via the enteral route can attenuate the metabolic response to stress, favorably modulate the host's immune response, reduce the risk nosocomial infections, and reduce the risk organ dysfunctions associated with critical illness [3]. In this chapter, we will review the current literature as it relates to the nutritional support of critically ill patients with sepsis.

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The Pathophysiology of Sepsis

In order to understand the potential impact of nutritional intervention in the septic patient, an understanding of the physiologic changes that occur in sepsis is required. The initial clinical manifestations of sepsis are the result of a complex series of interactions between the inciting organism and the host's innate immune response. This intricate cellular interaction involves numerous signaling pathways as well as the production of cytokines and chemokines. A detailed discussion of each of these pathways is beyond the scope of this text. However, a few key elements will be discussed.

Definition of Systemic Inflammatory Response Syndrome and Sepsis

In the early descriptions of multiple organ failure (MOF) in the late 1970s by Eiseman, Polk, and Fry, it was concluded that MOF occurred as a result of uncontrolled infection [4–6]. However, in the early 1980s, reports out of Europe by Faist and Goris showed that MOF could occur after

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severe blunt trauma without identifiable source of infection [7, 8]. Sepsis syndrome became a "junk" term to describe this type of patient. The key question became if it is not infection, what is the driving force behind the over exuberant inflammatory response that is causing organ injury. Popular theories in the mid-1980s included bacterial translocation, shock-induced whole body ischemia/reperfusion (I/R), and unrecognized impaired flow dependent oxygen consumption [9]. However, in 1989, Roger Bone defined this term "sepsis syndrome" to be an infection plus the presence of systemic illness [10]. This description was followed by the American College of Chest Physicians and the Society of Critical Care Medicines Consensus Conference in 1991 that defined the Systemic Inflammatory Response Syndrome (SIRS) as having two or more of the following criteria: (1) a temperature < 96 °F or >100.4 °F, (2) a heart rate of >90 beats/min, (3) a respiratory rate of >20 breaths/min or a $paCO_2$ of <32 mmHg, (4) a white blood cell count of >12,000 or <4,000 cells/mm^3 or >10 % bands. Sepsis was then defined as an infection plus SIRS [11].

In response to ongoing criticism from experts in the field, a second consensus conference was convened in 2001 to revise the original definitions. The updated consensus conference definitions included an expanded list of the signs and symptoms of sepsis [12]. The definitions of sepsis are listed in Table 9.1.

Table 9.1 SIRS and sepsis definitions

Systemic inflammatory response syndrome (SIRS) must have two or more:	1. Temperature >38 or <36 °C 2. Heart rate >90 beats/min 3. Respiratory rate >20 breaths/min or $paCO_2 < 24$ 4. White blood cell count >12,000 or <4,000 cells/mm^3 or >10 % bands
Sepsis	SIRS due to infection
Severe sepsis	Sepsis with evidence of organ dysfunction or hypoperfusion. Hypoperfusion abnormalities may include lactic acidosis, oliguria, or an acute alteration in mental status
Septic shock	Severe sepsis with hypotension (systolic blood pressure <90 mmHg) despite adequate fluid resuscitation or the requirement for vasopressors/inotropes to maintain blood pressure

Response to Infection: Characteristics of the Pathogen

The host response to infection can be triggered by bacterial, viral, and/or fungal infection. The specific characteristics of the inciting organism play a role in the body's response to the infectious stimuli. Each organism has specific virulence factors that enable the organism to evade the host's defenses. These virulence factors include antigenic variation of surface molecules, inhibition of complement activation, resistance to phagocytosis, production of exotoxins, and scavenging of reactive oxygen intermediates [13]. Cell-to-cell communication between organisms allows for signaling and up regulation of virulence factors. Perhaps one of the best described virulence factors is lipopolysaccharide (LPS), also known as endotoxin, which is a component of the outer cell wall of all gram negative bacteria. The presence of LPS provokes local and systemic inflammation, including proliferation of cytokines and activation of macrophages. The presence of LPS is essential to maintaining the integrity of the outer membrane of gram negative bacteria, acting as a protective barrier against lysozymes, antimicrobial agents, and host phagocytic cells.

Response to Infection: Characteristics of the Host

The human body is equipped with a variety of defense mechanisms against microorganisms. These include physical barriers such as the skin and mucosal surfaces, the innate immune response, and the adaptive immune response. Dysfunction of any of these components can lead to the development of sepsis. The recognition of pathogens by the innate immune response initiates a complex cascade of events that are intended to remove the pathogen from the host. This includes the release of reactive oxygen metabolites to destroy the pathogen, release of chemokines to

recruit additional neutrophils and lymphocytes, and the generation of a variety of systemic cytokines to further activate the host immune response. We are just beginning to understand the potential impact of genetic polymorphisms and the impact these may have on patient survival.

The immune response to sepsis represents a complex series of interactions characterized by the proliferation of both pro and anti-inflammatory mediators. A complete description of this process is beyond the scope of this manuscript but a brief explanation of the process is helpful to understanding the clinical manifestations of sepsis. The early phase of sepsis is generally considered to be a pro-inflammatory state. In response to infection, activated macrophages and CD4+ T cells systemically release tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and gamma interferon (IFN-γ). This inflammatory response is necessary for the host to overcome the infectious organism. Unfortunately, in a subset of sepsis patients this inflammatory response is not well balanced and can lead to an overwhelming SIRS response with resultant early MOF and a fulminant death.

Recognition of the Compensatory Anti-inflammatory Response Syndrome

Throughout the 1980s and into the 1990s, prominent investigators identified multiple defects in adaptive immunity that occurred as patients progressed through their critical illnesses that were associated with poor outcomes. In the mid-1990s, Roger Bone coined the term "compensatory anti-inflammatory response syndrome" (CARS) to describe the post-SIRS anti-inflammatory response and subsequent immunosuppression [14–16]. CARS was associated with late infections, which, in turn, were assumed to precipitate a second peak in late MOF [17]. In the late 1990s, the SIRS/CARS paradigm of early and late MOF had become the conceptual framework to explain the immunological trajectory of a complicated ICU course. Research focused on treating SIRS and better characterizing CARS. Multiple contributing mechanisms that characterized CARS were described including increased number of regulatory T cells [18], macrophage paralysis with resultant decreases in cytokine production [19], lymphocyte apoptosis [20], T cell anergy [14], suppressed T cell proliferation [21], and shifting from the Th1 to Th2 phenotype [22]. It is important to note that CARS is not merely the cessation of SIRS. In fact, CARS can exist days to weeks after the resolution of SIRS when pro-inflammatory cytokines are no longer present [23]. Some of the anti-inflammatory effects of CARS occur through enhanced apoptosis with resultant loss of CD4 and CD8 T cells, B cells, and lymphocytes that are responsible for the proliferation of pro-inflammatory mediators [24]. Loss of these immune effector cells leads to sepsis-induced immunosuppression which is responsible for the development of delayed secondary infections.

With improvements in SIRS management in the ICU, the number of patients that survive this initial SIRS-CARS phase of sepsis has dramatically increased. The result is that we are seeing increasing numbers of patients that stay in the ICU for weeks with a syndrome of moderate organ dysfunction, secondary infections, respiratory failure, and progressive protein catabolism with resultant loss of lean body mass and strength. This has led to the recognition of new clinical phenomenon named persistent inflammation, immunosuppression, and catabolism syndrome (PICS). First described by Moore and colleagues in 2012, PICS is characterized by simultaneous chronic low level inflammation and adaptive immunosuppression [25]. The clinical criteria for diagnosing PICS are presented in Table 9.2. The management of patients with PICS is challenging and requires a multidisciplinary approach includes developing anabolic nutritional interventions to modulate the patient's nutritional status, enhance immune responses and to push physical therapy with active strength training exercising.

Table 9.2 Persistent inflammation, immunosuppression, and catabolism syndrome (PICS)

Clinical determinants of PICS	Measurements
Persistent	Prolonged ICU stay > 14 days
Inflammation	C-reactive protein > 100 kg/dL
Immunosuppression	Total lymphocyte count $< 0.80 \times 10^9$ L^{-1}
Catabolism	Weight loss > 10 % during hospitalization of body mass index < 18
	Creatinine height index < 80 %
	Albumin level < 3.0 g/dL
	Pre-albumin level < 10 mg/dL
	Retinol binding protein level < 10 μg/dL

The Role of the Gastrointestinal Tract in the SIRS/CARS Paradigm

Septic shock is a prime inciting event for MOF. The lack of perfusion that defines shock states, directly injures the gut and with resuscitation causes a reperfusion injury that releases pro-inflammatory mediators that can amplify SIRS. This also initiates a local inflammatory response that results in a variety of gut dysfunctions (e.g., gastroparesis, gastric alkalization, ileus, duodenogastric reflux, impaired mucosal blood flow, epithelial apoptosis, increased permeability, impaired local gut immunity). Early isotonic crystalloid resuscitation can amplify inflammation, cause problematic edema, and promote ileus. Early laparotomy with bowel manipulation promotes gut inflammation, mucosal injury, and ileus. Standard ICU interventions worsen these gut dysfunctions, including vasopressor agents (decrease mucosal perfusion), stress gastritis prophylaxis (worsens gastric alkalization), narcotics (worsen ileus), antibiotics (promote bacterial overgrowth), and parenteral nutrition (gut disuse decreases local gut immunity that contributes to worsening Cars). Over a short period of time, the normally sterile upper GI tract becomes heavily colonized with potential pathogens, and the gut becomes the reservoir for bacteria and toxins that escape the gut via pulmonary aspiration of gastric contents or bacterial translocation that contribute to late nosocomial infections and late MOF [26].

How Early Enteral Nutrition Interrupts This Sequence of Events

The gastrointestinal tract is the largest immune organ in the body. As a result, it plays a significant role in the immune response to infection and sepsis. The provision of enteral nutrition (EN) stimulates splanchnic perfusion thereby support gut-associated lymphoid tissue (GALT) [27]. The delivery of EN helps maintain the functional and structural integrity of the intestinal epithelium, stimulates intestinal contractility thus preventing bacterial overgrowth, and aids the processing of naive CD4 lymphocytes with a resultant release of anti-inflammatory mediators into the systemic circulation [28].

In a variety of models (i.e., sepsis, hemorrhagic shock, and gut ischemia and reperfusion) intraluminal nutrients have been shown to reverse shock-induced mucosal hypoperfusion [29, 30]. In the lab, we showed that early EN also reverses impaired intestinal transit when given after a gut I/R insult [31]. Improved transit should decrease ileus-induced bacterial colonization [32]. Moreover, EN (specifically glutamine) improves the gut permeability defect that is induced by critical illness [33]. Finally, the gut is a very important immunologic organ and the severity of CARS can be lessened by feeding the gut [34]. A recent series of innovative lab studies has nicely documented that EN supports the function of the mucosal associated lymphoid tissue (MALT) that produces 70 % of the body's secretory IgA [35]. Naive T and B cells target and enter the GALT where they are sensitized and stimulated by antigens sampled from the gut lumen and thereby become more responsive to potential pathogens in the external environment. These stimulated T and B cells then migrate via mesenteric lymph nodes, the thoracic duct, and into the vascular tree for distribution to GALT and extra intestinal sites of MALT. Lack of enteral stimulation (i.e., use of TPN) causes a rapid and progressive decrease in T and B cells within GALT and simultaneous decreases in intestinal and respiratory IgA levels. Previously resistant lab animals, then challenged with pathogens via respiratory tree inoculation, succumb to overwhelming infections. These immunologic defects and susceptibility to infection are reversed within 3–5 days after restarting EN.

Perhaps more important than the benefits of provision of EN in critical illness are the negative physiologic consequences of withholding EN. Failure to provide luminal nutrients to the intestinal epithelium results in loss of both structural and functional integrity of these cells. This results in loss of the normal barrier function of the gut. Lack of EN results in decreased gut contractility with resultant bacterial overgrowth and the potential emergence of pathogenic organisms in the lumen. Proliferation of the pathogenic organisms within the gut can lead to attachment to the intestinal epithelium with resultant release of cytokines and programmed cell death [36]. Death of the intestinal epithelial cells leads to further defects in the gut barrier and increases permeability. This increase in permeability permits luminal bacteria to interface the gut's immune system resulting in diffuse activation of macrophages. The end result of these changes is the generation of a systemic pro-inflammatory state, thereby worsening the SIRS response already initiated by the inciting infection.

Development of Chronic Critical Illness

In the early 2000s, mortality from trauma-induced MOF decreased substantially, and the second peak of late MOF deaths disappeared [37, 38]. This was a result of fundamental changes in the initial care of trauma patients arriving with severe bleeding and consistent delivery of evidence-based-guideline (EBG)-driven standard operating procedures (SOPs) in the ICU [39, 40]. The same decrease in mortality and MOF was not observed with sepsis, however, for two reasons. First, early diagnosis of sepsis is difficult, allowing many patients to progress into septic shock, which has a prohibitively high mortality, despite aggressive interventions. This provided the rationale for routine sepsis screening [41]. Second, many interventions that are known to have an impact on outcome in sepsis were haphazardly administered. One approach to consistently implement EBG-driven SOPs is computerized clinical decision support (CCDS) [42]. Using the combination of sepsis screening and CCDS for sepsis management in our surgical ICU, we documented a surprising decrease in inhospital mortality for severe sepsis/septic shock from 34 % in 2006 to 14 % in 2009 [43]. However, when we studied the epidemiology of these patients, we recognized that many of the survivors lingered in the ICU with manageable organ dysfunctions [44]. Their clinical course was characterized by recurrent inflammatory insults (e.g., repeat operations and nosocomial infections), a persistent acute-phase response with ongoing loss of lean body mass despite optimal nutritional support, poor wound healing, and decubitus ulcers [25]. These patients (especially the elderly) are commonly discharged to long-term acute care facilities (LTACs) and skilled nursing facilities (SNFs) with significant cognitive and functional impairments from which they rarely fully rehabilitate.

Advances in critical care medicine have significantly improved patient survival during the acute phase of sepsis. This improvement in patient survival is due to ongoing performance improvement efforts that ensure the timely delivery of evidence-based guidelines for the management of sepsis [43, 45, 46]. An unexpected result of this improved survival is a growing population of patients that develop a condition referred to as chronic critical illness (CCI). CCI is defined by a prolonged dependence upon life support. This has classically been defined as a prolonged need for mechanical ventilation (>2 weeks) but additional features have also been described. These include profound weakness secondary to myopathy and neuropathy, increased vulnerability to infection, brain dysfunction manifesting as coma or delirium, and changes in body composition including loss of lean body mass, anasarca, and increased adiposity [47, 48]. Several risk factors have been identified for the development of CCI. These include Glasgow Coma Score < 15, the presence of sepsis, inadequate caloric intake, and elevated body mass index (BMI) [49]. It is estimated that 5–10 % of critically ill patients will develop CCI [50]. The long-term outcomes for patients that develop CCI are poor. One year mortality rates for CCI patients are estimated at 40–50 % [51]. Those patients that do survive beyond the 1 year mark are reported to have poor functional status and require substantial caregiver support and ongoing care in SNFs [52].

A key component in the prevention and management of patients with CCI is the delivery of adequate nutritional support. As mentioned above, failure to deliver adequate nutritional support at the onset of critical illness is an independent risk factor for the development of CCI. Patients that develop CCI are often malnourished and in a persistent catabolic state. The malnutrition that accompanies CCI is mediated by the inflammatory response to critical illness and is characterized by tissue proteolysis and reduction of free amino acids and glutamine in skeletal muscle [50]. The provision of nutritional support in CCI reverses the catabolic state and is essential to restoring muscle function. The primary goal of nutritional support in CCI is to provide adequate nitrogen to compensate for the significant nitrogen losses that have occurred during the acute phase of critical illness. Patients also commonly have neuroendocrine imbalances, with hyperglycemia, bone resorption, and vitamin D deficiency. This constellation of problems requires clinicians to carefully manage the nutritional support to avoid over and underfeeding as well as refeeding syndrome. The enteral route is recommended as first line therapy and should be utilized in all patients with a functional gastrointestinal tract. Patients with CCI that will require enteral nutritional support for >30 days benefit from the placement of a percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ) tube for long-term nutritional support.

Guidelines for Provision of Nutritional Support in the ICU

In 2009, The American Society for Parenteral and Enteral Nutrition (ASPEN) in cooperation with the Society of Critical Care Medicine (SCCM) published guidelines for the provision and assessment of nutritional support in the critically ill patient. These practice guidelines were developed through a systematic review of all available literature, primarily utilizing prospective randomized controlled trials to support the recommendations. The guidelines are designed to provide clinicians with a comprehensive summary of the best available evidence for the provision of nutritional support in the critically ill adult patient.

Initial Assessment of Nutritional Status

The traditional assessment of nutritional status involves a combination of anthropometric and biochemical variables. Due to extreme derivations in patient physiology due to the inflammatory response to critical illness, many of these traditional methods of nutritional assessment are not as useful. As a result, nutritional assessment in the ICU population presents a unique set of challenges to the clinician. In the setting of acute critical illness, hepatic protein synthesis shifts toward the production of acute-phase proteins. This shift in protein synthesis limits the value of utilizing the traditional constitutive protein markers (albumin, pre-albumin, retinol binding protein, and transferrin) utilized for nutritional assessment. Nutritional assessment in the ICU population should begin with a thorough history and physical exam focused on identifying clinical signs of malnutrition. A recent history of weight loss or poor oral intake signals the need for aggressive nutritional support.

Another key component in the nutritional assessment of the critically ill patient is an evaluation of the status of the gastrointestinal tract. While provision of enteral nutrition is the preferred method of delivery, the overall hemodynamic status of the patient must be taken into consideration. The development of ischemic bowel is a rare but potentially fatal complication of enteral nutrition, occurring in <1 % of all patients [53, 54]. Intravascular volume status must be assessed and hypotension must be reversed prior to the initiation of enteral nutrition. Infusion of nutrients into the gut in the setting of visceral hypoperfusion poses a significant risk of non-occlusive mesenteric ischemia. The absorption of intraluminal nutrients increases the metabolic demands of the enterocytes with a resultant risk of mesenteric ischemia in patients suffering from systemic hypoperfusion. It is not safe to

initiate enteral nutrition in patients with ongoing evidence of hypoperfusion. This is especially true in patients that are receiving high doses of vasopressors to support blood pressure, as this may precipitate bowel ischemia. The delivery of EN should be avoided in patients who are hypotensive [mean arterial pressure (MAP) of <60 mmHg] and in patients that are receiving catecholamines (norepinephrine, phenylephrine, epinephrine, dopamine) particularly if the dose of catecholamines is escalating to MAP [55].

Delivery of Early Enteral Nutrition

The initiation of early enteral nutrition (EN) should begin as soon as fluid resuscitation is complete and hemodynamic stability has been restored. Initiation of EN within the first 24–48 h is optimal. The provision of early EN results in a multitude of benefits for the critically ill patient. When feeds are initiated within 48 h of the onset of critical illness, there is attenuation of the inflammatory response, decreased gut permeability, and diminished levels of TNF-α [56]. As mentioned previously, the GI tract plays a significant role in the immune response to sepsis via the GALTs. The GALT contains 70–80 % of all immunoglobulin-secreting cells [57]. The functional and structural integrity of the gut epithelium is affected presence or absence of luminal nutrients. When nutrients are not provided to the gut, there is shortening of microvilli of the intestinal wall with resultant impairment of nutrient absorption. There is also impairment of the functional and structural integrity of intestinal epithelium which results in increased risk for systemic infection and greater likelihood for the development of MOF [27]. These deleterious effects are amplified as disease severity worsens. The delivery of early EN is beneficial because it helps to maintain gut epithelial integrity, modulates the systemic immune response, decreases the risk of developing secondary infection, and decreases mortality [58, 59].

The initiation of early EN in the ICU population is not dependent upon clinical evidence of bowel function (i.e., flatus, passage of stool). The presence of GI dysfunction in the critically ill population ranges from 30 to 70 % and is dependent upon multiple factors including premorbid conditions, mechanical ventilation, and medications. GI dysfunction may also be due to mucosal barrier disruption, altered motility, or mucosal atrophy. The presence of bowel sounds, often used to assess for clinical evidence of bowel function, is only indicative of GI contractility. The presence or absence of bowel sounds does not tell the clinician anything about mucosal integrity, gut epithelial barrier function, or absorptive capacity. Therefore, in the hemodynamically stable patient, EN should be initiated and advanced using standard EN protocols. The target goal rate of EN should be determined at the time of initiation of nutritional support. Energy requirements should be calculated through the use of predictive formulas or through the use of indirect calorimetry. The delivery of small volume trophic feeds may not be sufficient to maintain gut mucosal integrity. In order to achieve maximal benefit of EN, 50–65 % of the caloric goal should be achieved within the first 7 days of hospitalization.

The choice of gastric vs. small bowel feeding is dependent upon patient-specific factors. There is some evidence to suggest that small bowel feedings are associated with less gastroesophageal reflux [60]. There is also some evidence that small bowel feedings as compared to gastric feedings are associated with a decreased incidence of ventilator-associated pneumonia [61]. In those patients deemed to be at high risk for aspiration or those patients that have demonstrated intolerance to gastric feeding, small bowel feeding is preferred.

Enteral Nutrition vs. Parenteral Nutrition

The administration of early EN vs. parenteral nutrition (PN) has been debated in the medical literature for over 30 years. There is now a substantial body of clinical evidence that clearly demonstrates the benefits of EN over PN [3, 62, 63]. Most studies comparing EN to PN have not

demonstrated significant differences in patient mortality. However, the use of early EN has been shown to reduce infection complications, including the development of secondary infections. In a prospective, randomized controlled trial comparing early EN to early PN, Moore and colleagues showed that early EN was associated with reduced infections, specifically a reduction in pneumonia [64]. Similar decreases in infectious complications have been reported by others [65]. Additional benefits seen in patients receiving early EN include reduced hospital length of stay [56], decreased cost of nutritional therapy [56], and improved return of cognitive function [66].

Significant controversy still exists about the timing of initiation of PN in critically ill patients that cannot reach their caloric needs with EN alone. In a recent randomized, multicenter trial, Van den Berghe et al. compared early PN (within 48 h of ICU admission) to late PN (after day 8). This study showed that late initiation of PN was associated with a faster recovery and fewer complications as compared to the early initiation group [67]. The current ASPEN/SCCM guidelines recommend that the use of PN should be reserved for those patients in whom EN is not feasible after the first 7 days of ICU admission [55]. In the event that a patient that is unable to tolerate EN presents to the ICU with evidence of protein-calorie malnutrition (defined as recent weight loss of >15 % of actual body weight OR actual body weight <90 % of ideal body weight) then it is appropriate to initial PN as soon as SIRS has resolved. In this subset of patients, a meta-analysis by Heyland reported that the use of PN was associated with significantly fewer overall complications when compared to delivering no nutritional support [68]. Therefore, in severely malnourished patients with a contraindication to EN, early PN should be initiated.

Monitoring for Nutritional Adequacy

After the initial nutritional assessment, clinicians should determine each individual patient's nutritional goals to include caloric requirements. This is often expressed as a goal rate or goal volume of enteral nutrition to be delivered. Once nutritional support has been initiated, it is important to perform routine monitoring to assess the adequacy of the nutritional support that is being delivered and make modifications when necessary.

There are multiple diagnostic tests that can be utilized to assess nutritional adequacy. These include body measurement testing (weight change, anthropometric measures), body composition testing (determination of percent body fat, lean body mass, etc.), and laboratory testing (urine analysis, pre-albumin, etc.). In the setting of critical illness there can be short-term alterations in patient's fluid status, rendering the body composition modalities and monitoring based off of changes in patient weight useless in this population. The biochemical indices that are used are also affected by critical illness.

Serum proteins are often measured to help assess for nutritional adequacy. Pre-albumin is commonly used due to its short half-life of 2.5 days. Due to this relatively short half-life, one would expect to see a more rapid change in pre-albumin levels in response to nutritional intervention. However, in the critically ill patient, it is important to note that the serum pre-albumin level may be increased in patients with renal failure, in patients receiving corticosteroids, and those who have a persistent acute response. With ongoing stress the body reprioritizes hepatic protein synthesis after stressful insults away from reverse-phase reactants (e.g., pre-albumin) to acute-phase reactants (e.g., CRP). Additionally, serum pre-albumin levels may be decreased in patients with liver disease, those patients receiving hemodialysis, and patients with severe hyperglycemia. Given all of the alterations to serum protein markers in the setting of critical illness, the use of serum pre-albumin to assess nutritional adequacy is of limited use until there is resolution of the acute-phase response which can be monitored by weekly CRP determinations.

Immunonutrition

Optimal function of the immune system is dependent upon the presence of adequate nutrition. In the presence of malnutrition, the host's immune response to infection is impaired. Recent

advances in our understanding of the role of the gut in the host's immune response have led to increased interest in the concept of immunonutrition. The term immunonutrition refers to the delivery of a particular nutrient in order to induce a specific metabolic or immunologic function. The addition of specific substances to enteral nutrition formulas could potentially modulate the immune response, improve wound healing, and reduce the oxidative stress associated with sepsis. As a result, specific immune enhancing formulas have been developed by adding compounds such as L-glutamine, L-arginine, omega-3 fatty acids, and supraphysiologic doses of selenium, vitamins A, C, and E. In this section, we will review the potential benefits of immunonutrition in sepsis.

Arginine

Under normal conditions, arginine is considered to be a nonessential amino acid that is derived from oral protein intake or synthesized endogenously in the proximal renal tubule by the conversion of citrulline to arginine. Citrulline is primarily derived from the intestinal conversion of arterial and luminal glutamine via the glutamate-to-ornithine pathway. Under stressed conditions, arginine becomes an essential amino acid because the normal quantities produced to maintain muscle mass are insufficient due to increased turnover. Arginine is an essential component for the stimulation and release of growth hormone, prolactin, insulin, and glucagon. It is also a critical substrate for the synthesis of nitric oxide (NO) by the enzyme nitric oxide synthase (NOS). NO is an important mediator of vascular dilation, protein synthesis in the liver, and mitochondrial electron transport. L-Arginine is also an essential compound for T-lymphocyte proliferation and some cytokines.

In patients with sepsis, both plasma and muscle arginine levels are markedly decreased as compared to health individuals [69–71]. This state of arginine deficiency in sepsis is due to inadequate nutritional intake of protein as well as increased utilization by the liver and immune cells. In addition, the de novo production of arginine from citrulline in the proximal renal tubule is decreased to one third of the normal level during sepsis [72]. Low levels of plasma arginine have been correlated with worse prognosis in patients with sepsis [73], suggesting there may be a role for arginine supplementation in sepsis.

In studies of arginine supplementation in animal models and healthy volunteers, nutritional supplementation with arginine can enhance immune parameters following stress and elective surgery. However, the use of arginine supplementation in patients with sepsis has been associated with negative outcomes. In the setting of severe sepsis/septic shock, the delivery of immunonutrition containing arginine has been implicated in an intensification of the systemic inflammatory response with a resultant increase in patient morbidity [74]. A potential explanation for the adverse effects seen with high dose arginine supplementation in sepsis is an increase in NO production with resultant tissue injury and cardiovascular collapse [75]. In patients who are in septic shock requiring vasopressor, arginine administration could result in excessive NO production which could be deleterious. However, there is also evidence to suggest that arginine supplementation in patients with sepsis has a positive impact on patient outcomes [46, 47]. Recently Dr. Ochoa's and Dr. Moldawer's laboratories have recognized that surgical trauma and sepsis results in a persistent "emergency myeloipoesis" response with persistent expansion of myeloid derived suppressor cells (MDSCs) [76–79]. These immature innate immune cells are being released from the bone marrow and are honing to other hemopoeitic organs (e.g., lymph nodes and spleen). These cells express arginase-1 which diverts arginine away from nitric oxide metabolism. As a result arginase-1 activation depletes arginine in the local environment and without arginine lymphocytes become dysfunctional. This provides the rationale for administering supraphysiologic amounts of arginine after septic shock has resolved. Ongoing investigation into the role and mechanism of arginine supplementation in sepsis is needed. The lack of clarity regarding the metabolism of L-arginine in sepsis and the conflicting evidence with the current medical literature has led to a great degree of controversy

over the use of arginine supplementation in sepsis. In light of this, the current ASPEN/SCCM guidelines recommend that L-arginine supplementation be used with extreme caution in patients with severe sepsis/septic shock.

Glutamine

Under normal physiologic conditions, glutamine is the most abundant nonessential, free amino acid in the body. Glutamine is primarily stored in skeletal muscle and plays a role in protein synthesis and acid-base homeostasis in the kidney. In addition, glutamine is a critical nitrogen donor for rapidly dividing cells, such as those found in the gut and immune system. Other beneficial effects of glutamine include antioxidant effects (glutamine is a substrate for glutathione production), maintaining the gut barrier function by fueling enterocytes, and serving as an energy substrate for lymphocytes and neutrophils. In states of catabolic stress, such as sepsis, the bodies' stores of glutamine become rapidly depleted, rendering glutamine a "conditionally essential" amino acid during catabolic stress. This depletion of glutamine impairs the immune response thereby contributing to infections. Patients also experience weight loss and significant loss of muscle mass. Low circulating levels of glutamine during critical illness have been associated with increased mortality [80, 81].

Over the past decade, there has been substantial evidence that glutamine supplementation may improve outcomes in critically ill patients. Debate has continued to exist over the preferred route of glutamine administration (parenteral vs. enteral). The administration of enteral glutamine is well tolerated in critically ill patients with no known side effects [82]. The gut and liver metabolize the majority of enterally administered glutamine which may limit the systemic benefits of enteral glutamine administration in critically ill patients. Enteral administration of glutamine does have beneficial effects in the gut by repairing damaged intestinal epithelial cell layers and maintaining the gut barrier function of the GI tract. The addition of enteral glutamine to an enteral nutrition regimen has been shown to reduce hospital and ICU length of stay [83–85]. Given these potential benefits, it is recommended that enteral glutamine supplementation be administered to critically ill patients with sepsis. The recommended dose of enteral glutamine is 0.3–0.5 g/kg/day administered in two or three divided doses.

There have been several recent studies evaluating the potential use of parenteral glutamine supplementation. In 2008, Ziegler et al. conducted a double-blind, randomized, controlled study of alanyl-glutamine dipeptide supplemented parenteral nutrition in surgical ICU patients requiring parenteral nutrition. The primary outcome in this study was the development of nosocomial infections. While the administration of parental glutamine was shown to increase serum glutamine levels, there was no difference in infection rates between those patients that received supplemental parenteral glutamine and those that did not [86]. This study was followed by a large, multicenter, blinded 2-by-2 factorial study funded by the National Institutes of Health (NIH) evaluating glutamine and antioxidant supplementation in critically ill patients. This study assigned 1,223 critically ill adults to receive supplements of glutamine, antioxidants, both, or placebo. In this trial, there was a trend toward increased mortality among patients that received glutamine as compared to those that did not [87]. It is important to note, that in a subgroup analysis of 66 patients that had serum glutamine levels drawn, only 31 % of patients had low serum glutamine levels prior to supplementation. As a result of this trial, the authors concluded that any patient in MOF in the ICU should not receive glutamine [88]. However, in those critically ill patients without MOF, there may still be a role for glutamine supplementation. A meta-analysis by Novak et al. demonstrated the greatest beneficial effects to glutamine supplementation were seen in those patients that received high dose (>0.20 g/kg/day) of parenteral glutamine [89]. Unfortunately, at the time of preparing this manuscript, a parenteral formulation of glutamine is not currently available in the United States.

Omega-3 Fatty Acids

The term omega-3 fatty acids refers to three fatty acids: (1) alpha-linoleic acid (ALA), (2) eicosapentanoic acid (EPA), and (3) docosahexanoic acid (DHA). Both EPA and DHA are metabolites of ALA. These omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) which are a major component of cellular membranes. Dietary supplementation with PUFAs has been shown to reduce platelet aggregation, slow blood clotting, and limit the production of pro-inflammatory cytokines [90]. Ingestion of plant oils serves as our primary source of ALA, while EPA and DHA are derived from cold water fish such as sardines, mackerel, and tuna. Humans possess limited capacity to metabolize ALA to EPA and DHA, therefore dietary intake is the main source of these fatty acids.

During critical illness, there is significant downregulation in the enzymatic pathway that converts ALA to EPA and DHA and results in negligible production of EPA and DHA during critical illness. Both EPA and DHA produce anti-inflammatory effects that could be beneficial in patients with sepsis. These include inhibition of inflammatory gene expression, reduction of oxidative injury by stimulating glutathione production, and reducing leukocyte and platelet adhesion to the endothelium [91]. Omega-3 PUFAs inhibit the production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 [92].

In patients with sepsis, the administration of fish oil supplementation has yielded conflicting results. A recent systematic review by Marik showed an overall decrease in the number of infections, particularly secondary infections, in patients that received supplemental fish oil [93]. However, the administration of supplemental fish oil did not have any impact on length of stay or mortality. Another recent study by Pontes-Arruda et al. demonstrated that early administration of EN supplemented with EPA and antioxidant vitamins in patients with early sepsis resulted in a decreased incidence of progression to severe sepsis or septic shock [94]. However, once again there was no difference in mortality seen among patients that received supplemental omega-3 PUFAs. In contradiction to the above studies, Grau-Carmona compared septic patients that received standard enteral nutrition to those that received enteral nutrition plus omega-3 PUFA supplementation and did not find any difference in the development of secondary infections.

In spite of the lack of mortality benefit seen with omega-3 supplementation it is important to note that were no adverse effects associated with the administration of omega-3 PUFAs. While additional studies are needed, there does appear to be some benefit to the administration of supplemental omega-3 PUFAs with no known risk to the patient.

Antioxidant Vitamins and Trace Elements

During sepsis, free radical production is amplified and increased levels of reactive oxygen species are present. These reactive oxygen species can cause cellular injury through a variety of mechanisms. The host's endogenous antioxidant defense system includes the enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. These enzymes all contain heavy metals including manganese, selenium, and zinc. During times of metabolic stress, these enzymatic defenses can become overwhelmed and cells must resort to alternate antioxidants to prevent further cellular damage. These nonenzymatic antioxidants include selenium, zinc, vitamin C, vitamin E, and beta carotene.

A recent meta-analysis evaluating the role of antioxidant supplementation during critical illness showed a significant reduction in mortality with administration of supplemental antioxidants [95]. Of particular benefit was the administration of parenteral selenium which has shown a trend toward reducing mortality in patients with severe sepsis and septic shock. Additional studies are needed to further identify the optimum dose and ratio of administration of these substances during critical illness.

References

1. Hall MJ, Williams SN, Defrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. NCHS Data Brief. 2011;62: 1–8.
2. Lagu T, Rothberg MB, Shieh M-S, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012;40(3):754–61. doi:10.1097/CCM.0b013e318232db65.
3. Moore FA, Moore EE. The evolving rationale for early enteral nutrition based on paradigms of multiple organ failure: a personal journey. Nutr Clin Pract. 2009;24(3):297–304.doi:10.1177/0884533609336604.
4. Fry DE, Pearlstein L, Fulton RL, Polk Jr HC. Multiple system organ failure. The role of uncontrolled infection. Arch Surg. 1980;115(2):136–40.
5. Eiseman B, Sloan R, Hansbrough J, McIntosh R. Multiple organ failure: clinical and experimental. Am Surg. 1980;46(1):14–9.
6. Polk Jr HC, Shields CL. Remote organ failure: a valid sign of occult intra-abdominal infection. Surgery. 1977;81(3):310–3.
7. Faist E, Baue AE, Dittmer H, Heberer G. Multiple organ failure in polytrauma patients. J Trauma. 1983;23(9):775–87.
8. Goris RJ, te Boekhorst TP, Nuytinck JK, Gimbrère JS. Multiple-organ failure. Generalized autodestructive inflammation? Arch Surg. 1985;120(10):1109–15.
9. Moore FA, Moore EE. Evolving concepts in the pathogenesis of postinjury multiple organ failure. Surg Clin North Am. 1995;75(2):257–77.
10. Balk RA, Bone RC. The septic syndrome. Definition and clinical implications. Crit Care Clin. 1989;5(1): 1–8.
11. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–55.
12. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530–8.
13. Abbas AK, Lichtman AH. Cellular and molecular immunology. 5th ed. Amsterdam: Elsevier; 2005.
14. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med. 1996;24(7):1125–8.
15. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann Intern Med. 1996;125(8):680–7.
16. Bone RC. Toward an epidemiology and natural history of SIRS (systemic inflammatory response syndrome). JAMA. 1992;268(24):3452–5.
17. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40(4):501–10; discussion 510–2.
18. Monneret G, Debard A-L, Venet F, Bohe J, Hequet O, Bienvenu J, Lepape A. Marked elevation of human circulating CD4+ CD25+ regulatory T cells in sepsis-induced immunoparalysis. Crit Care Med. 2003;31(7): 2068–71.doi:10.1097/01.CCM.0000069345.78884.0F.
19. Munoz C, Carlet J, Fitting C, Misset B, Blériot JP, Cavaillon JM. Dysregulation of in vitro cytokine production by monocytes during sepsis. J Clin Invest. 1991;88(5):1747–54. doi:10.1172/JCI115493.
20. Hotchkiss RS, Swanson PE, Cobb JP, Jacobson A, Buchman TG, Karl IE. Apoptosis in lymphoid and parenchymal cells during sepsis: findings in normal and T- and B-cell-deficient mice. Crit Care Med. 1997;25(8):1298–307.
21. De Waal MR, Haanen J, Spits H, Roncarolo MG, te Velde A, Figdor C, et al. Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class II major histocompatibility complex expression. J Exp Med. 1991;174(4):915–24.
22. Delano MJ, Scumpia PO, Weinstein JS, Coco D, Nagaraj S, Kelly-Scumpia KM, et al. MyD88-dependent expansion of an immature GR-1(+) CD11b(+) population induces T cell suppression and Th2 polarization in sepsis. J Exp Med. 2007;204(6):1463–74. doi:10.1084/jem.20062602.
23. Moldawer LL. Interleukin-1, TNF alpha and their naturally occurring antagonists in sepsis. Blood Purif. 1993;11(2):128–33.
24. Muenzer JT, Davis CG, Chang K, Schmidt RE, Dunne WM, Coopersmith CM, Hotchkiss RS. Characterization and modulation of the immunosuppressive phase of sepsis. Infect Immun. 2010;78(4): 1582–92. doi:10.1128/IAI.01213-09.
25. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501. doi:10.1097/TA.0b013e318256e000.
26. Hassoun HT, Kone BC, Mercer DW, Moody FG, Weisbrodt NW, Moore FA. Post-injury multiple organ failure: the role of the gut. Shock. 2001;15(1):1–10.
27. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. Am J Surg. 2002; 183(4):390–8.
28. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. Nutr Clin Pract. 2009;24(3): 305–15. doi:10.1177/0884533609335176.
29. Kazamias P, Kotzampassi K, Koufogiannis D, Eleftheriadis E. Influence of enteral nutrition-induced splanchnic hyperemia on the septic origin of splanchnic ischemia. World J Surg. 1998;22(1): 6–11.

30. Flynn Jr WJ, Gosche JR, Garrison RN. Intestinal blood flow is restored with glutamine or glucose suffusion after hemorrhage. J Surg Res. 1992;52(5):499–504.
31. Grossie Jr VB, Weisbrodt NW, Moore FA, Moody F. Ischemia/reperfusion-induced disruption of rat small intestine transit is reversed by total enteral nutrition. Nutrition. 2001;17(11–12):939–43.
32. Nieuwenhuijs VB, Verheem A, van Duijvenbode-Beumer H, Visser MR, Verhoef J, Gooszen HG, Akkermans LM. The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. Ann Surg. 1998;228(2):188–93.
33. De-Souza DA, Greene LJ. Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. Crit Care Med. 2005;33(5):1125–35.
34. Kang W, Kudsk KA. Is there evidence that the gut contributes to mucosal immunity in humans? JPEN J Parenter Enteral Nutr. 2007;31(3):246–58.
35. Kang W, Gomez FE, Lan J, Sano Y, Ueno C, Kudsk KA. Parenteral nutrition impairs gut-associated lymphoid tissue and mucosal immunity by reducing lymphotoxin Beta receptor expression. Ann Surg. 2006;244(3):392–9. doi:10.1097/01.sla.0000234797.42935.46.
36. Alverdy J, Zaborina O, Wu L. The impact of stress and nutrition on bacterial-host interactions at the intestinal epithelial surface. Curr Opin Clin Nutr Metab Care. 2005;8(2):205–9.
37. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Arch Surg. 2005;140(5):432–8. doi:10.1001/archsurg.140.5.432; discussion 438–40.
38. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med. 2012;40(4):1129–35. doi:10.1097/CCM.0b013e3182376e9f.
39. Cuschieri J, Johnson JL, Sperry J, West MA, Moore EE, Minei JP, et al. Benchmarking outcomes in the critically injured trauma patient and the effect of implementing standard operating procedures. Ann Surg. 2012;255(5):993–9. doi:10.1097/SLA.0b013e31824f1ebc.
40. Gonzalez EA, Moore FA. Resuscitation beyond the abdominal compartment syndrome. Curr Opin Crit Care. 2010;16(6):570–4. doi:10.1097/MCC.0b013e3283409d16.
41. Moore LJ, Jones SL, Kreiner LA, McKinley B, Sucher JF, Todd SR, et al. Validation of a screening tool for the early identification of sepsis. J Trauma. 2009;66(6):1539–46. doi:10.1097/TA.0b013e3181a3ac4b; discussion 1546–7.
42. Sucher JF, Moore FA, Todd SR, Sailors RM, McKinley BA. Computerized clinical decision support: a technology to implement and validate evidence based guidelines. J Trauma. 2008;64(2):520–37.
43. McKinley BA, Moore LJ, Sucher JF, et al. Computer protocol facilitates evidence-based care of sepsis in the surgical intensive care unit. J Trauma. 2011;70(5):1153–66. doi:10.1097/TA.0b013e31821598e9; discussion 1166–7.
44. Moore LJ, McKinley BA, Turner KL, Todd SR, Sucher JF, Valdivia A, et al. The epidemiology of sepsis in general surgery patients. J Trauma. 2011;70(3):672–80. doi:10.1097/TA.0b013e31820e7803.
45. Moore LJ, Turner KL, Todd SR, McKinley B, Moore FA. Computerized clinical decision support improves survival in intra abdominal surgical sepsis. Am J Surg. 2010;200:839–43.
46. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, et al. The surviving sepsis campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med. 2010;38(2):367–74.
47. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med. 2010;182(4):446–54. doi:10.1164/rccm.201002-0210CI.
48. Nelson JE, Meier DE, Litke A, Natale DA, Siegel RE, Morrison RS. The symptom burden of chronic critical illness. Crit Care Med. 2004;32(7):1527–34.
49. Loss SH, Marchese CB, Boniatti MM, Wawrzeniak IC, Oliveira RP, Nunes LN, Victorino JA. Prediction of chronic critical illness in a general intensive care unit. Rev Assoc Med Bras. 2013;59(3):241–7. doi:10.1016/j.ramb.2012.12.002.
50. Hollander JM, Mechanick JI. Nutrition support and the chronic critical illness syndrome. Nutr Clin Pract. 2006;21(6):587–604.
51. Macintyre NR. Chronic critical illness: the growing challenge to health care. Respir Care. 2012;57(6):1021–7.
52. Carson SS. Outcomes of prolonged mechanical ventilation. Curr Opin Crit Care. 2006;12(5):405–11.
53. McClave SA, Chang W-K. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? Nutr Clin Pract. 2003;18(4):279–84.
54. Melis M, Fichera A, Ferguson MK. Bowel necrosis associated with early jejunal tube feeding: a complication of postoperative enteral nutrition. Arch Surg. 2006;141(7):701–4. doi:10.1001/archsurg.141.7.701.
55. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316.
56. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27(5):355–73.

57. Langkamp-Henken B, Glezer JA, Kudsk KA. Immunologic structure and function of the gastrointestinal tract. Nutr Clin Pract. 1992;7(3):100–8.
58. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ. 2001;323(7316):773–6.
59. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut. 1996;39(6):833–5.
60. Lien HC, Chang CS, Chen GH. Can percutaneous endoscopic jejunostomy prevent gastroesophageal reflux in patients with preexisting esophagitis? Am J Gastroenterol. 2000;95(12):3439–43. doi:10.1111/j.1572-0241.2000.03281.x.
61. Heyland DK, Drover JW, Dhaliwal R, Greenwood J. Optimizing the benefits and minimizing the risks of enteral nutrition in the critically ill: role of small bowel feeding. JPEN J Parenter Enteral Nutr. 2002;26(6 Suppl):S51–5; discussion S56–7.
62. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma—a prospective, randomized study. J Trauma. 1986;26(10):874–81.
63. Moore FA, Moore EE, Kudsk KA, Brown RO, Bower RH, Koruda MJ, et al. Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. J Trauma. 1994;37(4):607–15.
64. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma—reduced septic morbidity. J Trauma. 1989;29(7):916–22; discussion 922–3.
65. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, et al. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg. 1992;215(5):503–11. discussion 511–3.
66. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med. 1999;27(11):2525–31.
67. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17. doi:10.1056/NEJMoa1102662.
68. Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW. Total parenteral nutrition in the surgical patient: a meta-analysis. Can J Surg. 2001;44(2):102–11.
69. Luiking YC, Poeze M, Ramsay G, Deutz NEP. Reduced citrulline production in sepsis is related to diminished de novo arginine and nitric oxide production. Am J Clin Nutr. 2009;89(1):142–52. doi:10.3945/ajcn.2007.25765.
70. Luiking YC, Poeze M, Ramsay G, Deutz NEP. The role of arginine in infection and sepsis. JPEN J Parenter Enteral Nutr. 2005;29(1 Suppl):S70–4.
71. Luiking YC, Poeze M, Dejong CH, Ramsay G, Deutz NE. Sepsis: an arginine deficiency state? Crit Care Med. 2004;32(10):2135–45.
72. Luiking YC, Deutz NEP. Exogenous arginine in sepsis. Crit Care Med. 2007;35(9 Suppl):S557–63.
73. Freund H, Atamian S, Holroyde J, Fischer JE. Plasma amino acids as predictors of the severity and outcome of sepsis. Ann Surg. 1979;190(5):571–6.
74. Stechmiller JK, Childress B, Porter T. Arginine immunonutrition in critically ill patients: a clinical dilemma. Am J Crit Care. 2004;13(1):17–23.
75. Suchner U, Heyland DK, Peter K. Immune-modulatory actions of arginine in the critically ill. Br J Nutr. 2002;87 Suppl 1:S121–32.
76. Galbán C, Montejo JC, Mesejo A, Marco P, Celaya S, Sánchez-Segura JM, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med. 2000;28(3):643–8.
77. Popovic PJ, Zeh 3rd HJ, Ochoa JB. Arginine and immunity. J Nutr. 2007;137(6 Suppl 2):1681S–6S.
78. Zhu X, Herrera G, Ochoa JB. Immunosuppression and infection after major surgery: a nutritional deficiency. Crit Care Clin. 2010;26(3):491–500. doi:10.1016/j.ccc.2010.04.004, ix.
79. Cuenca AG, Delano MJ, Kelly-Scumpia KM, Moreno C, Scumpia PO, Laface DM, et al. A paradoxical role for myeloid-derived suppressor cells in sepsis and trauma. Mol Med. 2011;17(3–4):281–92. doi:10.2119/molmed.2010.00178.
80. Oehler R, Pusch E, Dungel P, Zellner M, Eliasen MM, Brabec M, Roth E. Glutamine depletion impairs cellular stress response in human leucocytes. Br J Nutr. 2002;87 Suppl 1:S17–21.
81. Roth E, Oehler R. Hypothesis: muscular glutamine deficiency in sepsis—a necessary step for a hibernation-like state? Nutrition. 2010;26(5):571–4. doi:10.1016/j.nut.2009.08.007.
82. Cavalcante AAM, Campelo MWS, de Vasconcelos MPP, Ferreira CM, Guimarães SB, Garcia JH, de Vasconcelos PR. Enteral nutrition supplemented with L-glutamine in patients with systemic inflammatory response syndrome due to pulmonary infection. Nutrition. 2012;28(4):397–402. doi:10.1016/j.nut.2011.07.011.
83. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, et al. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit Care Med. 2003;31(10):2444–9. doi:10.1097/01.CCM.0000084848.63691.1E.
84. Garrel D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns. JPEN J Parenter Enteral Nutr. 2004;28(2):123; author reply 123.
85. Jones C, Palmer TE, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. Nutrition. 1999;15(2):108–15.

86. Estívariz CF, Griffith DP, Luo M, Szeszycki EE, Bazargan N, Dave N, et al. Efficacy of parenteral nutrition supplemented with glutamine dipeptide to decrease hospital infections in critically ill surgical patients. JPEN J Parenter Enteral Nutr. 2008; 32(4):389–402. doi:10.1177/0148607108317880.
87. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1489–97. doi:10.1056/NEJMoa1212722.
88. Heyland DK, Dhaliwal R. Role of glutamine supplementation in critical illness given the results of the REDOXS study. JPEN J Parenter Enteral Nutr. 2013;37(4):442–3. doi:10.1177/0148607113488421.
89. Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med. 2002;30(9):2022–9. doi:10.1097/01.CCM.0000026106.58241.95.
90. Alexander JW. Immunonutrition: the role of omega-3 fatty acids. Nutrition. 1998;14(7–8):627–33.
91. Mizock BA. Immunonutrition and critical illness: an update. Nutrition. 2010;26(7–8):701–7. doi:10.1016/j.nut.2009.11.010.
92. Cohen J, Chin wD. Nutrition and sepsis. World Rev Nutr Diet. 2013;105:116–25. doi:10.1159/000341280.
93. Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008;34(11):1980–90. doi:10.1007/s00134-008-1213-6.
94. Pontes-Arruda A, Martins LF, de Lima SM, Isola AM, Toledo D, Rezende E, et al. Enteral nutrition with eicosapentaenoic acid, γ-linolenic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT study. Crit Care. 2011;15(3):R144. doi:10.1186/cc10267.
95. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med. 2005;31(3):327–37. doi:10.1007/s00134-004-2522-z.

Intestinal Failure

10

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Introduction

Intestinal failure can be generically defined as "symptoms and pathophysiologic state associated with inadequate nutrient assimilation of surgical or medical etiology." Intestinal failure is a complex disease entity with myriad etiologies, which include not only surgical resection resulting in Short Bowel Syndrome (SBS), but etiology such as enterocutaneous fistulae, loss of mucosal absorptive surface from inflammatory of infectious etiology, significant alterations in GI motility, or high grade obstructive lesions (Table 10.1). In most cases, gut failure is associated with the inability to maintain energy, protein, fluid, electrolytes, or micronutrient balances with volitional intake [1]. Gut autonomy is the goal in management and treatment of gut failure. Autonomy is defined as the ability to absorb adequate nutrient to sustain life without the supplementation of PN.

This chapter will address gut failure in the adult population. Although many of the principles are similar in pediatric gut failure, addressing pediatric gut failure is beyond the scope and objective of this chapter.

Epidemiology of Intestinal Failure

The lack of precise definitions of intestinal failure makes the actual prevalence almost impossible to accurately estimate. The symptoms of intestinal failure can include some or all of the following: diarrhea, dehydration, weight loss, macro and micronutrient deficiency, and/or obstructive symptoms. According to the Oley Foundation, approximately 40,000 patients with intestinal failure were receiving home parenteral nutrition (HPN) support in 1992, and 35 % of the cases were secondary to SBS [2]. In a European survey, it was indicated that the incidence of intestinal failure requiring home PN was four cases per one million [3]. Other estimates in the United States suggest that 41 % of SBS patients will require full PN support, and 12 % will require intravenous fluids and electrolytes alone [1]. In a study of 124 consecutive patients with SBS on PN from two centers in France, survival at 2 years was 86 and 75 % at 5 years [4]. At 2 years, 49 % continued to require PN, and 45 % at

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Table 10.1 Etiology of short bowel syndrome

Adults	Children
Vascular	Prenatal
• Thrombosis or embolus to SMA	• Intestinal atresia
• Thrombosis SMV	• Volvulus
• Volvulus	• Abdominal wall defects
	• Embolic
Postoperative	Postnatal
• Trauma	• Thrombosis or emboli
• Bariatric complications	• Necrotizing enterocolitis
• Closed loop bowel obstruction	• Crohn's
	• Volvulus
	• Trauma
	• Hirschsprung's
Miscellaneous	
• Crohn's	
• Radiation	
• Neoplasms	

5 years. In a separate study, the Mayo Clinic experience showed similar survival statistics [5].

Etiologies of Intestinal Failure

Etiologies that contribute to intestinal failure are either structural or functional. Intestinal failure related to SBS results from repeated surgical resections of small bowel, such as with Crohn's disease, massive enterectomy from vascular catastrophe (mesenteric arterial embolism, volvulus, trauma, tumor, and venous thrombosis), necrotizing enterocolitis, intestinal atresias, and extensive agangliosis. Functional SBS includes conditions such as chronic intestinal pseudo-obstruction syndrome, severe chronic segmental dysmotility, refractory sprue, radiation enteritis, and congenital villus atrophy (Table 10.1).

Normal Digestion and Absorption of Nutrients

The normal human small intestine reaches full length by the age of 9, and is estimated to be between 4 and 8 m, depending on the method of measuring and the techniques used to evaluate length, including radiologic, or measurements taken at autopsy or the time of surgery [6–8]. SBS is loosely defined when there is <200 cm of bowel remaining. A subset of patients with SBS will experience intestinal failure, which is defined as an inability to increase oral intake sufficiently, or an inability to absorb sufficient energy, despite significant increased intake, therefore requiring PN support [9].

The majority of the digestive and absorptive processes take place in the duodenum and proximal jejunum (usually within the first 100 cm of small bowel). The protein digestion process begins in the stomach, when gastric pepsinogen is converted to pepsin by gastric acid. Pepsin then starts the protein digestion process primarily by unraveling the tertiary structure of proteins, so that completion of digestion and absorption can take place in the duodenum. The rate and volume of delivery of chyme from the stomach is closely controlled by a variety of hormonal and neural controls, allowing for efficient mixing with pancreatobiliary secretions. The gallbladder and pancreas are stimulated by the acidification and presence of nutrients in the duodenal lumen. The mucosal endocrine cells release cholecystokinin (CCK) and secretin into the portal circulation, which feeds back to secondarily stimulate more biliary and pancreatic secretion.

The jejunum has long villi, sizeable absorptive surfaces, highly concentrated digestive enzymes, and carrier proteins. As previously mentioned, this is the primary digestive and absorptive site for most nutrients. Over 90 % of macronutrients (carbohydrates, lipids, and amino acids) are absorbed in the proximal 100–150 cm of the intestines. The villi are longer, and the crypts are deeper in the proximal jejunum than in the ileum; therefore, the loss of part of the jejunum initially compromises nutrient absorption more than the loss of an ileal segment of the same length, because of the morphologic and functional differences in the segment of small bowel. The ileum, however, is eventually able to compensate for the jejunal loss, but the jejunum is unable to fully compensate for ileal absorption. The ileum has specialized receptors for the absorption of bile

salts and vitamin B12, which are not present or inducible in the jejunum.

Normal digestion and absorption are also highly dependent on gradual gastric emptying of partially digestive nutrients and the mixing of these nutrients with bile and pancreatic enzymes in the duodenum, allowing for efficient nutrient absorption in the jejunum. Patients with proximal jejunostomy lose the inhibitory mechanisms that delay gastric emptying, which then results in rapid gastric emptying and rapid intestinal transit. This results in inadequate mixing of pancreaticobiliary and food, yielding poor enzymatic digestion and micelle formation, which in turn results in inadequate absorption. The ileocecal valve, along with normal neuronal mechanisms, acts as a brake to slow intestinal transit and increase nutrient-enterocyte contact time, facilitating enhanced absorption.

If carbohydrates are malabsorbed in the proximal gut and reach the colon, these carbohydrates can be fermented by bacterial enzymes in the colon, resulting in the production of short-chain fatty acids, which are absorbed by specific receptors on the colonocytes. It is estimated that the intracolonic digestive process can generate in the range of 300–1,000 kcal/day [10]. The loss of the ileocecal valve can also result in reflux of colonic bacteria into the small bowel, resulting in small bowel overgrowth. This can worsen nutrient and vitamin B12 malabsorption, and deconjugate bile salts, worsening diarrhea. The bacteria in the distal small bowel will compete with enterocytes for nutrient assimilation (Table 10.2).

In addition to nutrient malabsorption, the loss of intestinal absorptive surface area often results in significant losses of electrolytes, water, minerals, and trace elements through fecal losses. The proximal small bowel receives approximately 7–9 L of fluid and electrolytes from endogenous secretions and oral intake per day, with 6–8 L being reabsorbed. In a normal human, only 100–150 mL of water is lost in the stool each day. The colon has a large reserve absorptive capacity, where 3–4 L of solution can be absorbed. The presence or absence of the colon, along with multiple other factors, plays a key role in a patient's ability to attain gut autonomy (Fig. 10.1).

Table 10.2 Effect of small bowel bacteria overgrowth on nutrients

Macronutrient/ mechanism	Effect
Fat	Malabsorption • Bacterial deconjugation of bile acids • Production of lithocholic acids (toxic)
Carbohydrate	Metabolism • Bacterial fermentation of carbohydrate • Production of hydrogen, CO_2 • Maldigestion, osmotic load, diarrhea, pain
Protein	Metabolism • Degradation of proteins, reduced AA absorption • Lower enterokinase, less pancreatic proteases
Vitamins	Alterations in metabolism • Bacterial utilization of B12 • Malabsorption of fat-soluble A, D, K, E • Bacteria produce folate, vitamin K

Clinical Presentation of Intestinal Failure

Factors Influencing Intestinal Failure

The type and severity of clinical manifestations of intestinal failure are highly variable, and numerous factors will affect the clinical presentation. In some patients, caloric needs are adequately met with volitional intake, or enterally with formulae, but vitamin and mineral deficiencies may occur. Meanwhile, in other patients, fluid and electrolyte losses are the predominant clinical problems, while nutrient absorption is sufficient.

Small intestinal length is an important determinant of intestinal function. In adults, the average length of the small intestine is approximately 480 cm. Adults with residual small intestines (with less than 180 cm of absorptive surface either by resection, mucosal abnormality, or fistula) are at risk for developing gut failure. In particular, those patients with less than 60 cm of functional small intestine are unlikely to ever be independent of PN or reach gut autonomy [11, 12].

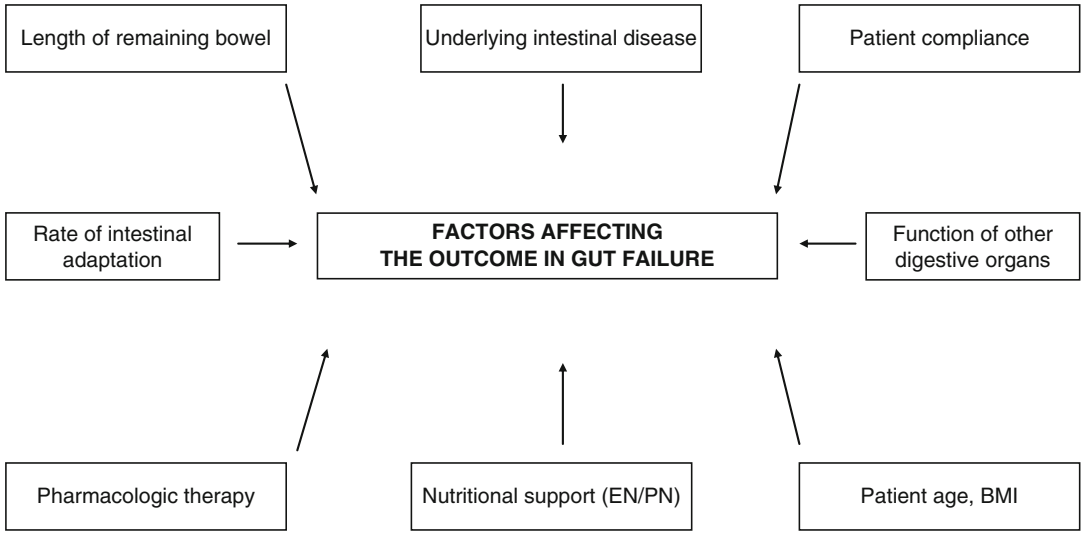

Fig. 10.1 Factors affecting the outcome of gut failure

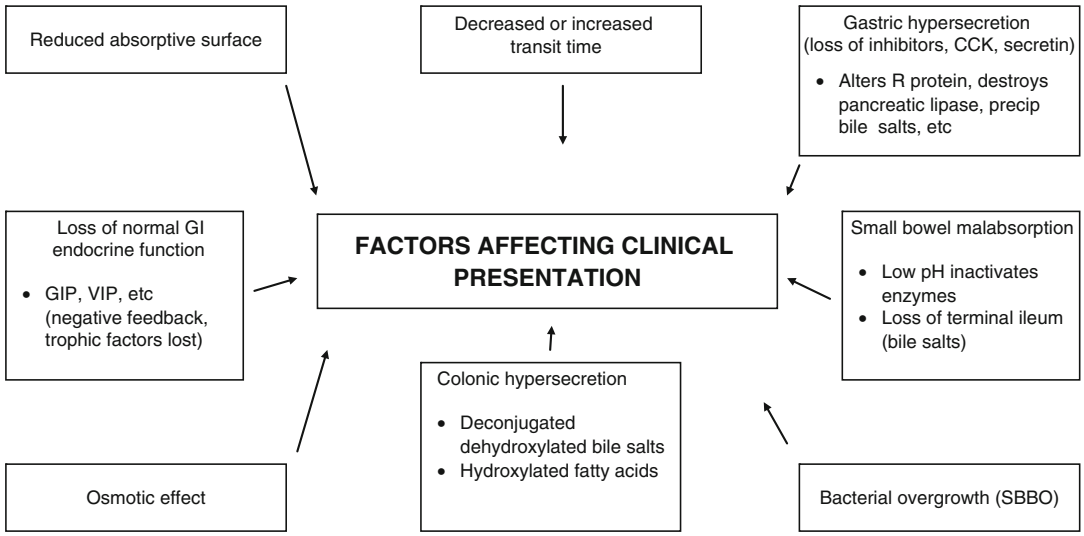

Fig. 10.2 Factors affecting clinical presentation of gut failure

In addition to small intestinal length, several other factors contribute to intestinal function, including the removal of a segment of small bowel, the presence or absence of an ileocecal valve, presence of a colon, intestinal motility, function and health of the remaining small bowel, and the gradual process of intestinal adaptation after surgical resection (Fig. 10.2).

Site of Intestinal Resection

The symptoms associated with gut failure, or SBS, are dependent on the physiology of the remaining small intestines, because each segment of the small bowel has unique functional capacities and differing abilities to adapt [9, 13, 14]. The jejunum has long villi, large absorptive

surfaces, highly concentrated digestive enzymes, and carrier proteins. This is the primary digestive and absorptive site for most nutrients. After large segments of jejunum are resected, or the mucosal absorptive surface is injured, there is a temporary reduction in absorption of most nutrients. The jejunum, however, exhibits modest adaptive changes by increasing functional capacity, including increasing mucosal weight, DNA, and protein [15, 16].

Specialized Functions of the Ileum

The ileum has specialized functions not available in the rest of the small bowel, including specific receptors for vitamin B12 and bile acids absorption, which are present only in the distal ileum. In adults, if more than 60 cm of ileum is resected, vitamin B12 malabsorption will occur. If greater than 100 cm of ileum was resected, it can lead to disruption of the enterohepatic circulation, resulting in bile salt deficiency and fat malabsorption. In addition to the specialized absorptive surface, the ileal mucosa serves as the source of peptide YY, which is secreted when unabsorbed lipids are present in the ileum. Peptide YY, through this feedback, delays gastric emptying and facilitates absorption of nutrients in the small intestine. This essentially allows for longer proximal gut luminal exposure and better absorption. The loss of this "ileal brake" may contribute to worsening diarrhea, commonly observed in SBS, or high out proximal fistula.

Presence of the Ileocecal Valve

The importance of the ileocecal valve in short bowel and gut failure cannot be overstated. It serves as an important barrier to reflux of colonic material into the small intestine and is responsible for the regulation of the passage of fluid and nutrients from the ileum into the colon. The loss of the ileocecal valve reduces small intestine transit time, which in cases of loss of mucosal absorptive surface impairs nutrient absorption. In particular, the loss of the ileocecal valve is associated with a longer duration of the requirement for PN [17]. Infants with less than 30 cm of small bowel and lacking the ileocecal valve were less likely to be liberated from PN [18]. Furthermore, the absence of the ileocecal valve commonly promotes small bowel bacterial overgrowth; if the overgrowth is significant, it can alter vitamin B12 absorption and bile salt metabolism [19, 20].

The colon has a role in the absorption of water, electrolytes, and short chain fatty acids (SCFAs). The colon may also slow intestinal transit, via feedback loops. In addition to its role in sodium and water absorption, the colon plays a small, but significant role in energy absorption via absorption of SCFAs. An estimated 10–20 % of the total daily energy requirement can be absorbed from the colonic mucosa, via specific receptors for SCFAs [21]. The undigested carbohydrates in the proximal gut are fermented by colonic bacteria-yielding SCFAs. In patients with SBS with a remaining colon, it has been shown that the colon can absorb as much as 20 % of the energy requirements for patients on a soluble fiber diet, yielding fermentable substrates for the colonic bacteria [10, 22].

Phases of Intestinal Adaptation Following Resection

After a massive enterectomy, or loss of mucosal absorptive surface, the intestine begins to adapt within days of the loss. This adaptation can continue for over 2 years before it reaches maximal maturity. Intestinal adaptation can be categorized into three different phases—Phase 1 is the acute phase, which can last for 1–2 weeks. Phase 2 is the primary period of intestinal adaption, which can take up to 2 years. Phase 3 is the late period after full intestinal adaptation has occurred. Each presentation will be dependent upon the specific etiology, preexisting conditions, and extent of bowel, either lost or nonfunctional.

Phase 1 can be characterized as the acute phase, which may last for 1–2 weeks. This phase is characterized by considerable fluid and electrolyte losses, often resulting in voluminous diarrhea [23].

During this early phase, the highest priority goals are the administration of PN to make up for the malabsorptive component and prevention of fluid and electrolyte abnormalities. An H2-receptor antagonist (H2RA), or proton pump inhibitor (PPI), should be considered, at least initially intravenously, to suppress gastric hypersecretion. By minimizing gastric hypersecretion, a decrease in pancreatic and biliary secretion is noted, secondary to removing the stimulus for excessive pancreatic exocrine secretion stimulated by acidification of the duodenum. In patients with jejunal resection, gastric emptying of liquids is more rapid, although the total intestinal transit time may remain normal. The "ileal brake" can compensate for this ileal resection-induced increased transit time [23]. Additionally, in intestinal patients and patients without a residual colon, there is a loss of inhibition on gastric emptying, because there is significant decrease in peptide YY, glucagon-like peptide 1, and neurotensin [24]. Once the patient's volume status and electrolytes are stabilized, slow introduction of enteral feeding is indicated. This can be administered either by volitional intake or by feeding tube. A percutaneous gastrostomy tube can be considered, if long-term need is expected (>30 to 60 days). Continuous tube feedings in the postoperative period have been shown to increase net absorption of lipids, proteins, and energy, compared to intermittent oral feeding [25]. Furthermore, enteral feedings, either via volitional intake or tube feeding, have been shown to stimulate long-term intestinal adaptation [26].

Phase 2 can take up to 2 years for maturation to fully complete. During this phase, the intestine adapts to ensure maximal efficiency of the absorption per unit length. Muscular hypertrophy is noted along with mucosa and villous hyperplasia. The result is an increase in cell number, as well as cell size [27]. The intestine hypertrophies, and the villus height increases, effectively increasing the surface area for more efficient absorption [8, 28]. Several factors contribute to the intestinal adaptation process including: presence of colon, presence of ileocecal valve, length and segment of remaining bowel, health and function of the remaining bowel, patient's age, and patient's comorbid conditions [29]. Several factors will contribute to the patient's ability to adapt, including active mucosal inflammatory disease, such as Crohn's disease, radiation enteritis, carcinoma, or pseudo-obstruction involving the remaining bowel, all of which will have a diminished adaptation response. In patients with large segments of resected or nonfunctional bowel, PN is initially the mainstay of nutrition support. As the patient tolerates, and as nutrition parameters allow, PN should be transitioned to enteral nutrition (EN). Oral intake should also be initiated, as tolerated. The ultimate goal is to achieve gut autonomy.

Phase 3 is the late period after full adaptation has taken place. Generally, the length of remaining bowel necessary to prevent long-term dependence of PN is approximately 100 cm, in the absence of a functional colon, or 60 cm of small intestine in the presence of a normally functioning colon [8, 28]. In animal models for SBS and now in some human trials, enteroglucagon, glucagon-like peptide II (GLP-2), epidermal growth factor, growth hormone, CCK, gastrin, insulin, and neurotensin appear to contribute to the intestinal adaptation response [30]. Patients should resume normal oral intake, if possible, with variable supplementary support from either PN or EN, as necessary to maintain nutritional requirements.

Diagnostic Method and Clinical Assessment

Clinical laboratory assessment of nutritional status in gut failure is similar to the clinical assessment for any acute or chronic disease. No specific lab testing, other than that for serum citrulline levels has shown benefit over routine nutrition parameters. Citrulline is a nonprotein amino acid produced by the enterocyte, which has been proposed as a biomarker for short bowel. Several clinicians routinely dealing with gut failure have suggested that measuring serum citrulline may constitute an objective, quantitative, relatively simple, and reproducible parameter to give an estimate of the quantity of functional enterocyte mass. Serum citrulline appears to be relatively

independent of current nutritional status, the presence of gut local inflammation, and the exact etiology of the loss of mucosa mass. Serum citrulline is also independent of age and the various etiologies of SBS, such as villous atrophy, radiation enteritis, chemotherapy-induced enteropathy, and acute rejection of small bowel transplant [31–34].

Radiologic Evaluation of Gut Failure

The radiologic evaluation of gut failure should be tailored to the etiology of the failure and considerations of the plan for future potential interventions. An attempt should be made to evaluate viable length of bowel. The UGI, with small bowel follow-through, is the mainstay to evaluate length, gross structure of the small bowel mucosa, and presence of entero-enterofistulae. Fistulagrams should be part of any evaluation of enterocutaneous fistula. Fistulagrams can be extremely helpful in determining whether or not surgery, if any, will be of value in correcting some of the metabolic complications of gut failure. Whenever possible, these diagnostic radiologic studies should be done with a member of the primary team taking care of the patient to insure adequate communication of findings.

Many of the anatomical relationships noted earlier can also be seen on CT or CT enterography. It can be critical prior to any consideration for surgical exploration that all possible anatomic information be obtained. The team may include the need to obtain both UGI with SBFT and CT enterography [35, 36].

Medical and Surgical Management—Acute Phase

Fluid and Electrolytes

After a massive enterectomy, or loss of large segments of mucosal absorptive surface, the initial management of patients with gut failure primarily involves supportive care, including management of sepsis and postoperative complications. This initial step needs to ensure hemodynamic stability and aggressive fluid and electrolyte replacements. Volume status and weight should be closely monitored (e.g., stomal, fecal, and urinary losses) to ensure optimal hydration and electrolyte balance status. Histamine H2RA, or PPIs, should be given intravenously to suppress hypergastrinemia-induced gastric acid hypersecretion and limit volume loss [7, 22, 37]. PPIs have been shown to be more effective than H2RA in decreasing gastric volume secretion. These are usually given at a dose higher than the routine acid reducing level (e.g., Omperazole 40 mg BID or TID).

Although most patients with intestinal failure require PN in the early phases of management in patients with a residual jejunum, glucose-polymer-based oral rehydration solutions should be used to decrease dehydration and parenteral fluid requirements. Glucose promotes salt and water absorption by solvent drag [38]. The optimal sodium concentration should be at least 90 mmol/L, which is the concentration of the small bowel effluent [39]. Oral solutions with lower sodium concentration may result in increased sodium losses. For patients with a residual colon in continuity, oral rehydration solution may still be of value, but the amount of sodium in the solution may be not extremely critical, because the colon can absorb sodium and water against a steep electrochemical gradient [38].

In addition to sodium losses, large quantities of magnesium can be lost in the jejunal and ileal effluent [40]. Magnesium deficiency may result in secondary calcium deficiency, because hypomagnesemia impairs the release of parathyroid hormone [41]. These electrolytes, therefore, should be monitored and replaced as appropriate (Table 10.3).

Nutrition in Acute Management

Generally, most patients with massive enterectomy will need to be supported, at least initially, with PN. For normally nourished patients, PN should be given at roughly 25–30 kcal/kg/day,

Table 10.3 Methods to control high ostomy or stool output (goal < 2.0 L/day)

Treatment	Result	Recommendations/guidelines
Opiates	Slows small bowel motility and decreases secretion, increases absorption, increases anal sphincter tone	• Over the counter – Immodium (Loperimide) – Does not cross blood–brain barrier – Tolerance can be pushed to 10–20 mg/dose – Metabolism via first pass – Hepatic – Increases sphincter tone • Lomotil (diphenoxylate) – Max 12 tabs/day – Drowsiness (crosses blood–brain barrier) – Anticholinergic side effect of dry mouth – Decrease gastric emptying – Commercial elixir problematic (contains sorbitol) • Paregoric liquid – Good for feeding tubes • Tincture of opium – (10 cm^3 TID) – Start 0.15 mg. 75 TID to QID, caution CNS side effects – Regular dosing is key
Other		• Clonidine – (0.05 mg BID to 0.15 mg BID) – Use with other antisecretory agents – Alpha 2—adrenergic agonist
Histamine 2-receptor antagonists (H2RAs)	Reduces gastric secretions	
Proton pump inhibitors (PPIs)	Decreases gastric and indirectly biliopancreatic secretions	Doses up to 20–40 mg BID to TID
Fiber supplements	Soluble: ferments to SCFA to increase energy Insoluble: serves as colloid and helps solidify stool	
Octreotide	Reduces GI secretions and motility	• 100–300 mg TID SQ – Side effects rise with dose

based on ideal body weight [29]. Initially, serum glucose should be monitored at least four times daily, and should have a goal between 120 and 180 mg/dL, with insulin added at an initial dose 0.1 U/g of dextrose as needed. Intravenous lipids are generally used to supply 20–30 % of infused calories. Protein should be delivered in the range of 1.5–2.0 g/kg/day, based on ideal body weight.

Micronutrients should also be supplemented. Water-soluble vitamins are absorbed in the proximal jejunum, so it is unusual to have deficiencies, except in patients with relatively high jejunostomies. Thiamine deficiency has been reported in gut failure patients on PN and should be replaced to prevent Wernicke's encephalopathy and Beriberi [42, 43]. Erythrocyte transketolase appears to be the most accurate biomarker for thiamine deficiency, and activity should be determined. Empiric therapy should be started with 100 mg of thiamine daily [29]. In patients with >60 cm terminal ileum resection, vitamin B12 should be replaced at 300 μg/month either

subcutaneously [44, 45] or intranasally. This option has been approved, but remains relatively expensive. Fat soluble vitamin (A, D, E, and K) deficiencies are common in patients with gut failure, or for those having undergone surgically related bowel malabsorptive procedures. This includes bariatric procedures, like duodenal switch or roux-en-y gastric bypass, where fat-soluble vitamin deficiency has been reported in up to 60 % of patients. Beside the malabsorptive effect of resection or bypass, the short bowel patient may develop steatorrhea, which subsequently results in decreased micelle formation and fat digestion [46]. Trace metals, such as zinc and selenium are lost in the feces and will generally need replacement.

Pharmacology—Acute Phase

Pharmacologic management during the acute phase generally involves decreasing gastric secretions and intestinal losses. H2RAs should be given intravenously to suppress hypergastrinemia-induced gastric acid hypersecretion and limit volume loss (as noted earlier). Octreotide, a long-acting analog of native somatostatin, is occasionally used in the acute setting for its antisecretory function. Octreotide inhibits the secretory stimulants of serotonin, gastrin, secretin, CCK, vasoactive intestinal polypeptide (VIP), and motilin [47].

Clonidine, which acts via an alpha-adrenergic agonist's mechanism, commonly for blood pressure control, has also been shown to have antidiarrheal properties. It has limited benefit and must be used with caution in the intestinal failure population, as these patients commonly have hypovolemia, and the use could cause hypotension. Agents to slow transit and minimize diarrhea include antidiarrheals, such as Loperamide, or diphenoxylate-atropine, which exert their effects on intestinal opioid receptors, slowing bowel transit through reduction of circular and longitudinal muscle activity. Diphenoxylate crosses the blood–brain barrier, and can cause central nervous system side effects such as confusion, euphoria, lethargy, and dizziness [48]. In patients with less than 100 cm of ileum resected, unabsorbed bile acids pass on to the colonic lumen and are metabolized by bacteria to lithocholic acid, resulting in secretory diarrhea. In the patient with colon present and limited distal ileum population, cholestyramine can be given at maximum doses of 24 g/day, which will bind unabsorbed bile acids and prevent bile acid induced (choleretic) diarrhea. If cholestyramine is used, it is important to monitor for fat soluble vitamin deficiency.

Narcotics are occasionally used in refractory diarrhea, as they can dramatically decrease transit time. Narcotic agents such as codeine, morphine, paregoric, and tincture of opium have been used with success and should be individualized as needed. No randomized controlled trials have been done for these agents in intestinal failure; consequently, these should be used with caution, secondary to the significant side effects these narcotic agents have. Pancreatic enzymes have limited to no benefit in intestinal failure, although they are occasionally tried.

Intestinal Failure Management in the Chronic Phase

Enteral Nutrition

EN, either taken as volitional intake or via feeding tube, should be started gradually, as noted in the earlier sections. Several publications have suggested partially hydrolyzed proteins or peptides and simple carbohydrates may be of benefit when making a formula selection, although no randomized clinical trials have proven benefit over a more complex diet. The exact makeup of the diet seems less important than just the presence of nutrients in the lumen of the bowel.

Specific amino acids and fats have some theoretical benefit in gut failure. These specific nutrients include short and medium chain fatty acids (SCFA, MCT) and glutamine. MCTs have the advantage of dual absorptive mechanisms, via the lymphatic system, and directly into the portal vein by enterocyte mechanisms. Although beneficial in many malabsorptive etiologies, no significant study has shown dramatic benefit of specific nutrients in SBS or other etiologies of gut failure.

Glutamine, considered a conditionally essential amino, has been shown to be the primary fuel for the small bowel enterocyte. As such, it has been subject to numerous clinical trials in various animal and human models of bowel compromise. It appears to be most beneficial when combined with human recombinant growth hormone and high-soluble fiber diets. The results of these studies suggest a positive influence of glutamine and human recombinant growth hormone on weight gain and energy absorption. This effect appears to be self-limited to short-term benefit while receiving this combination and rapidly returns to pretreatment status upon stopping the glutamine and growth hormone [49, 50].

Dietary Restriction

In normal absorptive physiology, oxalate in the diet binds tightly to dietary calcium in the proximal small bowel and is excreted in the stool as calcium oxalate. With fat malabsorption, however, dietary calcium preferentially binds to free fatty acids, allowing oxalate to pass into the colon, where it is taken up the colonic mucosa, especially in the inflamed colon. Once absorbed and circulating, oxalate is filtered by the kidney, is concentrated, and results in nephrocalcinosis and nephrolithiasis [28]. Patients with SBS with colon continuity, therefore, should be on a low-oxalate containing diet (Table 10.4).

Table 10.4 Management principles in chronic gut failure

Management principle	Suggested action
Avoid restrictive diets	• Attempt to attain maximum contact of absorptive surface to luminal nutrients • Small frequent meals, relatively isotonic liquid formula, vitamin, and mineral supplements as needed
High carbohydrate and high fat	• High complex CHO (soluble fibers) for patients with colons to allow production of short chain fatty acids to increase energy supply
Avoid large volume of free water intake	• Encourage isotonic nutritional electrolyte fluids or oral rehydration drinks
Ok to suppress biliopancreatic secretions in short term	• H2RAs, PPI, or octreotide
Increase rates of absorptive surface adaptation	• Hormones – Growth hormone/ glutamine – GLP-2 derivatives

Home Parenteral Nutrition

Initially PN is infused continuously. PN should be considered a temporary fix, while all attempts to utilize the remaining viable intestine are made. The need for PN may be life long, if adaptation has not compensated for the loss of mucosal mass within 1–2 years. Once a patient is stable, PN should be infused intermittently over 10–16 h, with a 30–60 min taper, as tolerated by cardiac, renal, and volume status [51, 52].

The transition from hospital to home total PN should involve extensive education of the patients and their families, prior to hospital discharge [52]. Instructions should be given not only for catheter care, but working knowledge of intravenous pump and sterile principles for dressing changes should be provided. In addition, the issues of maintaining hydration, glycemic control, and consequences of not maintaining electrolyte and volume appropriately should be addressed.

Pharmacology in the Chronic Management of Intestinal Failure

In addition to motility agents previously discussed (e.g., Loperamide, diphenoxylate-atropine), somatostatin analogs, such as Octreotide, can be considered. Octreotide analogs exert their antidiarrheal effect by inhibiting most of pro-secretory substances, such as serotonin, gastrin, vasoactive-inhibitory polypeptide, secretin, motilin, and pancreatic polypeptide. Use of Octreotide results in the reduction of fluid and electrolyte output [53], but Octreotide and other somatostatin analogs also have several metabolic drawbacks. Octreotide has been known to increase gallbladder stasis,

resulting in cholelithasis [54]. Doses of Octreotide (usually over 250 μg three times per day) cause alterations in blood glucose levels, due to inhibitory effects on insulin secretion.

Glucagon-like Peptide 2 analogs have recently been approved by the Food and Drug Administration for use in humans. They are marketed under the name Teduglutide for patients with gut failure resulting from short bowel. GLP-2, which is secreted from the distal small bowel colon mucosa, has been shown to be the key agent in stimulating intestinal adaptation [55, 56]. In 2005, Jeppesen examined the use of Teduglutide for 21 days in SBS patients and reported a significant decrease in fecal wet weight and loss of nutrients in the stool, while increasing villus height and crypt depth [56]. Several other studies have supported these claims, which resulted in fewer days of PN needed. Several potential side effects must be considered to include mucosal overgrowth at the ostomy site, potentially leading to bowl obstruction (reported from 4 to 9 %). The potential promotion of other GI intestinal epithelial tumors must be considered.

Microbiome in Intestinal Failure

It has now been well validated that intestinal microbiota influences the physiology, nutritional status, immune function, and overall health status of the host [57, 58]. Patients with intestinal failure have an extremely "artificial" microbiologic environment. Invasive techniques (which eliminate or dramatically alter natural barriers) and the use of multiple medications (which affect GI motility, luminal pH, blood flow, and mucosal oxygenation) radically influence gut microbiota. These changes in the gut microbiota accompany the often major changes in intravascular volume and blood flow to the GI tract, which commonly occurs in the gut failure population. Therapeutic measures commonly involved and used in hospitalized and ICU patients can cause dramatic changes in the mucosal redox potential and pH within the epithelial cell.

In addition to the iatrogenic issues causing changes in the microbiome, the physiologic stress response of the host induced by illness, surgery, or trauma has been shown to cause significant changes on the mucosal microenvironment, through alterations in pH, redox potential, and mucosal energy supply [59]. Several investigators have reported in a variety of stress models, including gastrointestinal failure, where a rapid depletion in intestinal luminal phosphate is noted. This luminal phosphate depletion induces normally nonpathogenic bacteria, viable in the intestinal lumen, to undergo a phenotypic change and become extremely pathogenic in some species. These stress-induced mucosal changes result in upregulation of virulence factors in the endogenous bacteria, which facilitate attachment and invasion of the host epithelial barrier [60, 61].

Microbiota presiding in the host GI tract is felt to interact not only between species, but also with the intestinal mucosa of the host. Many of these effects yield benefits. The ability to manipulate and potentially exploit these microbial changes noted in intestinal failure has become the focus of research only in recent years [62, 63].

In intestinal failure, the potential to capitalize on the beneficial effects of the bacterial symbiotic relationships has significant possibilities to alleviate many of abnormalities seen in failure. These mechanisms of benefit include enhancement of the physical epithelial barrier, by increasing production of mucins (which adhere to intestinal mucosa), production of bacterial antimicrobial peptides inhibiting overgrowth of pathogens, concomitant inhibition of pathogen adhesion, and competitive exclusion of the pathogenic microorganisms [64]. Certain microbiota has been shown to aid specifically in maintaining integrity of gap junctions [65], while others enhance host-cell antimicrobial peptide production, which reduces epithelial adherence of pathogens [66]. Manipulation of the host microbiota in the ICU setting has been shown to modulate metabolic and immune responses [62]. Novel investigative approaches of the microbiome in intestinal failure may help shift the paradigm for the future. The best clinical outcomes may include manipulations of gut bacteria in intestinal failure, not from attempting to kill gut bacteria, as is commonly done today. The concept of

bioecological control in intestinal failure is currently in its infancy and will rapidly develop.

Surgery in Intestinal Failure

Surgery is rarely indicated in management of intestinal failure. Once sepsis is controlled and abscesses are drained, the need for surgery is for occasional access for EN support. Percutaneous endoscopic gastrostomy (PEG) is occasionally helpful for both feeding and in serving as a venting gastrosomy for chronic obstruction or pseudo-obstruction. If remaining colon or distal small bowel is present and not in continuity, one should consider restoring bowel continuity. Even placing short segments of colon back into continuity can aid tremendously with fluid and electrolyte balance. Bowel lengthening procedures, commonly used in short bowel patients in pediatrics, such as Serial Transverse Enteroplasty and the Bianchi procedure have limited, if any, use in adults [67]. Small bowel transplant is obviously the ultimate surgical option for intestinal failure, and is reported with variable success, depending on populations involved [68, 69].

Complications of Management in Intestinal Failure

Complications of Long-Term Parenteral Nutrition

Hepatic Complications

Long-term PN use can result in a broad spectrum of liver conditions, including steatosis, steatohepatitis, fibrosis, cholestasis, and cirrhosis [70–72]. A report from France suggests that <50 % of adult patients on PN for >5 years will develop complications [73]. In a report from the United States, as many as 15 % of patients on PN >1 year will develop end-stage liver disease [74]. Recent studies suggested that liver disease associated with long-term PN is not likely caused by insufficient production of nutrients required for normal hepatic function, but rather direct toxic effects of PN [75–78]. The incidence of parenteral nutrition-induced liver disease (PNLD) has been significantly decreased with the use of fish oil-containing lipid emulsions [79].

Catheter-Related Complications

Safe and accurate delivery of HPN relies upon PN administered via meticulously maintained central venous catheters by motivated patients and/or well-trained care givers. To limit complications, patients and caregivers should have ready access to a multidisciplinary team of professionals to troubleshoot any problems before life-threatening situations occur. Early diagnosis and treatment of complications, including catheter-associated blood stream infection (reported incidence 0.14–0.83 episodes/patient-year on HPN), and central venous thrombosis (reported incidence 0.03 episodes/patient-year) is important to minimize morbidity and mortality. There is a significant variation in the reported incidence of both hepatobiliary complications (19–75 %) and advanced liver disease (0–50 %). Long-term survival remains higher on home PN than that with intestinal transplantation. The role of intestinal lengthening procedures has yet to be validated in adults. In a 1994 report, the Oley Foundation registry indicated that PN patients were hospitalized approximately once per year for catheter-related complications [2]. Messing et al. found that among patients with intestinal failure requiring chronic PN, mortality was over 50 % during a 64-month median follow-up, with more than 30 % of those deaths related to sepsis [8]. This is very similar to what is reported today with 5-year survival rates in large HPN programs; results are reported as being between 60 and 78 %, with survival primarily related to underlying diagnosis and sepsis [51].

Moukarzel et al. found that in long-term pediatric PN patients, the mean life span of a central catheter was 22.4 months, with 25 % of catheters being removed, secondary to thrombus [80]. In 1,154 years of patient follow-up, the estimated incidence of catheter thrombosis is approximately 0.2 episodes per 1,000 catheter days [81]. When all usual central veins have been used, alternatives include translumbar or transhepatic access to the inferior vena cava.

Other Long-Term Parenteral Nutrition Complications

Renal dysfunction [82], metabolic bone disease [83], memory deficits [84], and biliary complications [8] have been reported among patients who require long-term PN.

Conclusions

1. Patient therapy and goals should be individualized to meet postsurgical intestinal anatomy or the extent of viable functional bowel following an insult and mucosal loss.
2. The introduction of oral nutrition or tube feeding into the lumen of the bowel is essential to maximize adaptation of remaining functional bowel.
3. The importance of patient and family education working closely with a multidisciplinary team cannot be overemphasized. This education needs to include the management of fluid and electrolyte imbalance, oral rehydration principles, the use of antimotility agents, the medications to optimize outcome and minimize readmissions, and the consequences for failing to comply with instruction.
4. Parenteral nutrition is a key element for almost all patients with gut failure, especially in the early phases. The majority of patients will attain gut autonomy and be able to liberate themselves from the need of PN within 1–2 years.
5. It is common for patients with gut failure to need occasional supplemental intravenous fluid and electrolyte supplementation, even when they are able to maintain body weight and nutrition status with EN or volitional oral intake. The appropriate and timely use of pharmacologic agents such as antimotility, antisecretory, mucosal growth stimulants, and less commonly surgery must be highly individualized due to the variety of etiologies and variable presentation of intestinal failure.

References

1. O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol. 2006;4:6–10.
2. North American Home Parenteral and Enteral Nutrition Patient Registry. Annual Report with Outcome Profiles 1985-1992. Albany, NY: The Oley Foundation; 1994 [cited 2013 Dec 6]. Available from: http://oley.org/documents/Patient_Registry_AnnualReportFinal.pdf
3. Van Gossum A, Neve J. Trace element deficiency and toxicity. Curr Opin Clin Nutr Metab Care. 1998;1:499–507.
4. Carbonnel F, Cosnes J, Chevret S, Beaugerie L, Ngo Y, Malafosse M, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. JPEN J Parenter Enteral Nutr. 1996;20:275–80.
5. Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition-treated patients: 20 years of experience at the Mayo Clinic. Mayo Clin Proc. 1999;74:217–22.
6. Fanucci A, Cerro P, Fraracci L, Ietto F. Small bowel length measured by radiography. Gastrointest Radiol. 1984;9:349–51.
7. Nightingale JM, Bartram CI, Lennard-Jones JE. Length of residual small bowel after partial resection: correlation between radiographic and surgical measurements. Gastrointest Radiol. 1991;16:305–6.
8. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117:1043–50.
9. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124:1111–34.
10. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343:373–6.
11. Thompson JS, Rochling FA, Weseman RA, Mercer DF. Current management of short bowel syndrome. Curr Probl Surg. 2012;49:52–115.
12. Efsen E, Jeppesen PB. Modern treatment of adult short bowel syndrome patients. Minerva Gastroenterol Dietol. 2011;57:405–17.
13. Jeong SH, Lee HJ, Bae HJ, Kim Y, Yoo MW, Yoon YK, et al. Factors affecting postoperative dietary adaptation in short bowel syndrome. Hepatogastroenterology. 2009;56:1049–52. 14.
14. Longshore SW, Wakeman D, McMellen M, Warner BW. Bowel resection induced intestinal adaptation: progress from bench to bedside. Minerva Pediatr. 2009;61:239–51.

15. De Francesco A, Malfi G, Delsedime L, David E, Pera A, Serra R, et al. Histological findings regarding jejunal mucosa in short bowel syndrome. Transplant Proc. 1994;26:1455–6.
16. Vanderhoof JA, Kollman KA, Griffin S, Adrian TE. Growth hormone and glutamine do not stimulate intestinal adaptation following massive small bowel resection in the rat. J Pediatr Gastroenterol Nutr. 1997;25:327–31.
17. Goulet O, Baglin-Gobet S, Talbotec C, Fourcade L, Colomb V, Sauvat F, et al. Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. Euro J Pediatr Surg. 2005;15:95–101.
18. Goulet OJ, Revillon Y, Jan D, De Potter S, Maurage C, Lortat-Jacob S, et al. Neonatal short bowel syndrome. J Pediatr. 1991;119:18–23.
19. Dibaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. Clin Gastroenterol Hepatol. 2006;4:11–20.
20. Kaufman SS, Loseke CA, Lupo JV, Young RJ, Murray ND, Pinch LW, et al. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. J Pediatr. 1997;131:356–61.
21. Tappenden KA. Emerging therapies for intestinal failure. Arch Surg. 2010;145:528–32.
22. Jeppesen PB, Mortensen PB. Significance of a preserved colon for parenteral energy requirements in patients receiving home parenteral nutrition. Scand J Gastroenterol. 1998;33:1175–9.
23. Nightingale JM, Kamm MA, van der Sijp JR, Morris GP, Walker ER, Mather SJ, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a 'colonic brake'. Gut. 1993;34:1171–6.
24. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. Gut. 1996; 39:267–72.
25. Joly F, Dray X, Corcos O, Barbot L, Kapel N, Messing B. Tube feeding improves intestinal absorption in short bowel syndrome patients. Gastroenterology. 2009;136:824–31.
26. Gong JF, Zhu WM, Yu WK, Li N, Li JS. Role of enteral nutrition in adult short bowel syndrome undergoing intestinal rehabilitation: the long-term outcome. Asia Pac J Clin Nutr. 2009;18:155–63.
27. Kelly DG, Tappenden KA, Winkler MF. Short bowel syndrome: highlights of patient management, quality of life, and survival. JPEN J Parenter Enteral Nutr. 2014;38(4):427–37.
28. Nightingale JM, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. Gut. 1992;33: 1493–7.
29. American Gastroenterological Association. American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124:1105–10.
30. Sham J, Martin G, Meddings JB, Sigalet DL. Epidermal growth factor improves nutritional outcome in a rat model of short bowel syndrome. J Pediatr Surg. 2002;37:765–9.
31. Stultz JS, Tillman EM, Helms RA. Plasma citrulline concentration as a biomarker for bowel loss and adaptation in hospitalized pediatric patients requiring parenteral nutrition. Nutr Clin Pract. 2011;26(6):681–7.
32. Cynober L, Moinard C, De Bandt JP. The 2009 ESPEN Sir David Cuthbertson. Citrulline: a new major signaling molecule or just another player in the pharmaconutrition game? Clin Nutr. 2010;29:545–51.
33. Kaore SN, Amane HS, Kaore NM. Citrulline: pharmacological perspectives and its role as an emerging biomarker in future. Fundam Clin Pharmacol. 2013;27:35–50.
34. Piton G, Manzon C, Cypriani B, Carbonnel F, Capellier G. Acute intestinal failure in critically ill patients: is plasma citrulline the right marker? Intensive Care Med. 2011;37:911–7.
35. Oliveira C, de Silva N, Wales PW. Five-year outcomes after serial transverse enteroplasty in children with short bowel syndrome. J Pediatr Surg. 2012;47:931–7.
36. Vantini I, Benini L, Bonfante F, Talamini G, Sembenini C, Chiarioni G, et al. Survival rate and prognostic factors in patients with intestinal failure. Dig Liver Dis. 2004;36:46–55.
37. Jacobsen O, Ladefoged K, Stage JG, Jarnum S. Effects of cimetidine on jejunostomy effluents in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1986;21:824–8.
38. Fordtran JS, Rector Jr FC, Carter NW. The mechanisms of sodium absorption in the human small intestine. J Clin Invest. 1968;47:884–900.
39. Ladefoged K, Olgaard K. Fluid and electrolyte absorption and renin-angiotensin-aldosterone axis in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1979;14:729–35.
40. Selby PL, Peacock M, Bambach CP. Hypomagnesaemia after small bowel resection: treatment with 1 alpha-hydroxylated vitamin D metabolites. Br J Surg. 1984;71:334–7.
41. Anast CS, Winnacker JL, Forte LR, Burns TW. Impaired release of parathyroid hormone in magnesium deficiency. J Clin Endocrinol Metab. 1976;4:707–17.
42. Alloju M, Ehrinpreis MN. Shortage of intravenous multivitamin solution in the United States. N Engl J Med. 1997;337:54; author reply-5.
43. Schiano TD, Klang MG, Quesada E, Scott F, Tao Y, Shike M. Thiamine status in patients receiving long-term home parenteral nutrition. Am J Gastroenterol. 1996;91:2555–9.
44. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized,

open-label, parallel-group study. Clin Ther. 2011;33:358–71.
45. Lin J, Kelsberg G, Safranek S. Clinical inquiry: Is high-dose oral B12 a safe and effective alternative to a B12 injection? J Fam Pract. 2012;61:162–3.
46. Edes TE, Walk BE, Thornton Jr WH, Fritsche KL. Essential fatty acid sufficiency does not preclude fat-soluble-vitamin deficiency in short-bowel syndrome. Am J Clin Nutr. 1991;53:499–502.
47. O'Keefe SJ, Peterson ME, Fleming CR. Octreotide as an adjunct to home parenteral nutrition in the management of permanent end-jejunostomy syndrome. JPEN J Parenter Enteral Nutr. 1994;18:26–34.
48. Karim A, Ranney RE, Evensen KL, Clark ML. Pharmacokinetics and metabolism of diphenoxylate in man. Clin Pharmacol Ther. 1972;13(3):407–19.
49. Wales PW, Nasr A, de Silva N, Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. Cochrane Database Syst Rev. 2010 (6):CD006321.
50. Guo M, Li Y, Wang Z, Wu B, Wang J, Li J. Morphological adaptation in adult short bowel syndrome undergoing intestinal rehabilitation. J Invest Surg. 2013;26:1–5.
51. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther. 2013;37:587–603.
52. Kumpf VJ, Tillman EM. Home parenteral nutrition: safe transition from hospital to home. Nutr Clin Pract. 2012;27:749–57.
53. Nightingale JM, Walker ER, Burnham WR, Farthing MJ, Lennard-Jones JE. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. Aliment Pharmacol Ther. 1989;3:367–73.
54. Pazzi P, Gamberini S, Buldrini P, Gullini S. Biliary sludge: the sluggish gallbladder. Dig Liver Dis. 2003;35 Suppl 3:S39–45.
55. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. Gastroenterology. 2001;120:806–15.
56. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut. 2005;54:1224–31.
57. Morowitz MJ, Babrowski T, Carlisle EM, Olivas A, Romanowski KS, Seal JB, et al. The human microbiome and surgical disease. Ann Surg. 2011;253:1094–101.
58. Bengmark S. Nutrition of the critically ill; a 21st-century perspective. Nutrients. 2013;5:162–207.
59. Alverdy JC. During critical illness the gut does not pass the acid test. Crit Care. 2012;16:150.
60. Zaborina O, Zaborin A, Romanowski K, Babrowski T, Alverdy J. Host stress and virulence expression in intestinal pathogens: development of therapeutic strategies using mice and C elegans. Curr Pharm Des. 2011;17:1254–60.
61. Long J, Zaborina O, Holbrook C, Zaborin A, Alverdy J. Depletion of intestinal phosphate after operative injury activates the virulence of P aeruginosa causing lethal gut-derived sepsis. Surgery. 2008;144:189–97.
62. Morrow LE, Gogineni V, Malesker MA. Probiotics in the intensive care unit. Nutr Clin Pract. 2012;27:235–41.
63. Katayama M, Xu D, Specian RD, Deitch EA. Role of bacterial adherence and the mucus barrier on bacterial translocation: effects of protein malnutrition and endotoxin in rats. Ann Surg. 1997;225:317–26.
64. Turroni F, Ventura M, Butto LF, Duranti S, O'Toole PW, Motherway MO, et al. Molecular dialogue between the human gut microbiota and the host: a Lactobacillus and Bifidobacterium perspective. Cell Mol Life Sci. 2014;71(2):183–203.
65. Feng Y, Ralls MW, Xiao W, Miyasaka E, Herman RS, Teitelbaum DH. Loss of enteral nutrition in a mouse model results in intestinal epithelial barrier dysfunction. Ann N Y Acad Sci. 2012;1258:71–7.
66. Sherman PM, Johnson-Henry KC, Yeung HP, Ngo PS, Goulet J, Tompkins TA. Probiotics reduce enterohemorrhagic Escherichia coli O157:H7- and enteropathogenic E. coli O127:H6-induced changes in polarized T84 epithelial cell monolayers by reducing bacterial adhesion and cytoskeletal rearrangements. Infect Immun. 2005;73:5183–8.
67. Thompson J, Sudan D. Intestinal lengthening for short bowel syndrome. Adv Surg. 2008;42:49–61.
68. Lauro A, Zanfi C, Pellegrini S, Catena F, Cescon M, Cautero N, et al. Isolated intestinal transplant for chronic intestinal pseudo-obstruction in adults: long-term outcome. Transplant Proc. 2013;45:3351–5.
69. Yildiz BD. Where are we at with short bowel syndrome and small bowel transplant. World J Transplant. 2012;2:95–103.
70. Bowyer BA, Fleming CR, Ludwig J, Petz J, McGill DB. Does long-term home parenteral nutrition in adult patients cause chronic liver disease? JPEN J Parenter Enteral Nutr. 1985;9:11–7.
71. Briones ER, Iber FL. Liver and biliary tract changes and injury associated with total parenteral nutrition: pathogenesis and prevention. J Am Coll Nutr. 1995;14:219–28.
72. Stanko RT, Nathan G, Mendelow H, Adibi SA. Development of hepatic cholestasis and fibrosis in patients with massive loss of intestine supported by prolonged parenteral nutrition. Gastroenterology. 1987;92:197–202.
73. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132:525–32.
74. Chan S, McCowen KC, Bistrian BR, Thibault A, Keane-Ellison M, Forse RA, et al. Incidence, prognosis, and etiology of end-stage liver disease in patients receiving home total parenteral nutrition. Surgery. 1999;126:28–34.

75. Buchman AL, Ament ME, Sohel M, Dubin M, Jenden DJ, Roch M, et al. Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a placebo-controlled trial. JPEN J Parenter Enteral Nutr. 2001;25:260–8.
76. Buchman AL, Dubin M, Jenden D, Moukarzel A, Roch MH, Rice K, et al. Lecithin increases plasma free choline and decreases hepatic steatosis in long-term total parenteral nutrition patients. Gastroenterology. 1992;102:1363–70.
77. Buchman AL, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, et al. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. Hepatology. 1995;22:1399–403.
78. Xu ZW, Li YS. Pathogenesis and treatment of parenteral nutrition-associated liver disease. Hepatobiliary Pancreat Dis Int. 2012;11:586–93.
79. Cowan E, Nandivada P, Puder M. Fish oil-based lipid emulsion in the treatment of parenteral nutrition-associated liver disease. Curr Opin Pediatr. 2013;25: 193–200.
80. Moukarzel AA, Haddad I, Ament ME, Buchman AL, Reyen L, Maggioni A, et al. 230 patient years of experience with home long-term parenteral nutrition in childhood: natural history and life of central venous catheters. J Pediatr Surg. 1994;29: 1323–7.
81. Mailloux RJ, DeLegge MH, Kirby DF. Pulmonary embolism as a complication of long-term total parenteral nutrition. JPEN J Parenter Enteral Nutr. 1993;17: 578–82.
82. Buchman AL, Moukarzel A, Ament ME, Gornbein J, Goodson B, Carlson C, et al. Serious renal impairment is associated with long-term parenteral nutrition. JPEN J Parenter Enteral Nutr. 1993; 17:438–44.
83. Buchman AL, Moukarzel A. Metabolic bone disease associated with total parenteral nutrition. Clin Nutr. 2000;19:217–31.
84. Buchman AL, Sohel M, Brown M, Jenden DJ, Ahn C, Roch M, et al. Verbal and visual memory improve after choline supplementation in long-term total parenteral nutrition: a pilot study. JPEN J Parenter Enteral Nutr. 2001;25:30–5.

Enteral Nutrition

11

Eric H. Bradburn and Bryan Collier

While there is little argument in the literature of the benefits of early enteral feeding, this practice on the wards is surrounded by controversy as well as mythology. Despite recommendations by A.S.P.E.N. and other nutritional societies, patients remain trapped in battles between starvation and protecting surgical anastomoses, Nil Per Os (n.p.o.) orders and nasogastric (NG) tubes, and "trickle feeds" vs. nocturnal feeds with little data application other than surgeon preference [1, 2]. This chapter will attempt to outline the current concepts for optimizing enteral support and provide the reader with a template to apply current best evidence to his or her surgical practice.

Basic Science of Enteral Feeding

The renaissance for enteral feeding has come with a greater understanding of the innate and adaptive immune systems. The gastrointestinal (GI) tract is the largest immune body in the human system and one of the first lines of defenses we have against environmental pathogens. Gut mucosal defenses mechanisms include: luminal factors such as gastric acid and secretory IgA and IgM, antimicrobial factors which prevent colonization of pathogens, physical barriers such as mucous layers and tight junctions, and mechanical factors such as desquamation and peristalsis that are all vital for maintaining homeostasis [3]. In addition, the adaptive immunity component of the gut includes specialized lymphoid tissue referred to as gut-associated lymphoid tissue (GALT) and mucosal associated lymphoid tissue (MALT). The GALT produces the majority of the immunoglobulins in the human body. Normal stimulation by luminal nutrients is critical for the maintenance of all these physiologic functions [3, 4]. Current evidence demonstrates that lack of nutrient stimulation for as little as 5 days results in decreases in secretory IgA, reduction in GALT tissues, alterations in gut mucosal barriers, and increases in activation of inflammatory cytokines [3]. Furthermore, starvation results in the loss of enteric hepatic circulation and hormonal stimulation that can lead to bacterial overgrowth, cholestasis, and potential for bacteria or endotoxin translocation. The overall impact of not feeding is a profound impact on the patient's immune system.

Nutritional Assessment and Practice Guidelines

The first process in any nutritional support algorithm should begin with a nutritional assessment. History and physical exam are paramount and an

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Table 11.1 Mnemonic "CAN WE FEED?" to facilitate safe initiation of enteral nutrition [5]

*C*ritical Illness Severity
*A*ge
*N*utrition Risk Screening
*W*ait for Resuscitation
*E*nergy Requirements
*F*ormula
*E*nteral Access
*E*fficacy
*D*etermine Tolerance

understanding of the patient's comorbid conditions is valuable when beginning nutrition. This process will allow you to risk stratify patients to determine whether they would benefit from early enteral feeding. Simply asking the question: "Can this patient eat?" is half the battle. Thus, in a patient with a functional GI tract that is continuous and can take nutrition per os, there are few if any contraindications to just beginning a diet. Keeping it simple is the key. We recommend the institution of a practical approach utilizing the CAN WE FEED? mnemonic published by Miller et al. [5]. This is illustrated in Table 11.1. While we understand the original intent of this mnemonic was for intensive care unit (ICU) patients, we think it is a simple straightforward quality process that can be applied to the surgical patient at any level of care. It covers the complete spectrum when addressing the nutritional needs of the patient.

Early Enteral Feeding a Priority

So feed early. The benefits to the surgical patient are numerous. Numerous studies in animals have showed a lack of nutrients to the gut disrupt the gut–blood barrier and intestinal mucosa atrophies leading to the potential for translocation of bacteria [6, 7]. Randomized trials have shown that patients receiving early enteral nutrition have fewer infectious complications and reductions in both ICU and hospital length of stay [8, 9]. Furthermore, a meta-analysis by Peter et al. concluded a clear advantage for early feeding [10]. Whether the patient is immediately postop from major GI surgery, traumatically injured, or has suffered thermal burns early nutrition will be key to a timely and complete recovery with fewer complications. Feeding the gut is the only way to maintain the normal homeostatic pathways throughout the human system. Maintaining a high priority for enteral nutrition maintains stimulation of the small bowel that allows for the release of hormones which maintain normal gallbladder and pancreatic functions. Parenteral nutrition lacks this advantage and can lead to cholestasis and increase risk of infections. Enteral feeds also maintain the normal acid–base balance within the intestinal lumen which is important for the maintenance of normal bacterial flora [4]. One can surely debate what does "early" truly mean in the case enteral feeding. Certainly the literature offers a wide range between 24 and 96 h as a definition for early [8, 11–13]. But the bottom line is—it just makes the most physiologic sense to begin as early as possible.

How Much to Feed: Full Versus Trophic

The goal of most nutritional plans is to achieve near target caloric goals. This remains a challenge with critically ill patients. Obstacles to achieving goals include issues related to feeding intolerance, ileus, serial surgical interventions, and access. Recent evidence suggests that hypocaloric or trophic feeds (60–70 % goal) may be associated with improved outcomes [14]. Rice et al. randomized over 200 patients with acute respiratory failure to receive either trophic (10 mL/h) or full enteral nutrition for 6 days [15]. This study found no differences in trophic feeds versus full energy nutrition with regards to mortality and ventilator free days. Interestingly, patients who received initial trophic enteral nutrition had fewer episodes of feeding intolerance. The EDEN trial, recently completed, addressed the same topic and found that trophic feeding did not have any impact on ventilator free days or mortality. Furthermore, this study demonstrated no additional benefits or reduction in infectious complications over full enteral nutrition. Moreover, the full nutrition group had more

episodes of emesis, higher gastric residual volumes, and increased rates of constipation [16]. It would appear from the current evidence that the recommendation in most population of surgical patients is in support of hypocaloric or trophic feeding that achieves 60–70 % of targets. In fact with trophic feeding there appears to be less enteral nutrition related complications. Caloric deficit has been associated with worse outcomes. Studies from the 1980s and in the twenty-first century seem to replicate that the critical care patient suffers these worse outcomes as the caloric deficit increases, ranging from as low as four to six thousand calories [17, 18]. This would essentially equate to 3 days without any nutrition provision, assuming a 2,000 calorie requirement. These results would support early feeds to be started immediately at goal, to avoid any calorie deficit that could accrue and subsequently place the patient at risk for worse outcomes. However, as reported by *prospective* studies, providing aggressive early goal enteral nutrition has not demonstrated improved outcomes [16]. Therefore, the authors return to the simple statement to start nutrition early, within the first 2 days of the patient's hospital stay. If the enteral route is chosen, start it early at approximately 50 % goal (make the math easy), so that those personnel who are not registered dieticians can provide an order to execute the early enteral nutrition provision.

Early Postoperative Feeding and the Surgical Anastomosis

There is little dispute over the beneficial effects of starting nutrition in the first 24–48 h for a patient admitted to the ICU. However, there are fewer consensuses over the surgical patient with fresh anastomosis or new ostomy. Braga et al. in their study of over 650 major GI procedures demonstrated that early feeding was safe [19]. There was a low complication rate at 1.7 % and early enteral nutrition related mortality was calculated at 0.1 %. Yet still the surgeon remains reluctant to feed the fresh anastomoses. In another study, 53 patients underwent small bowel resection and primary anastomosis, the majority these patients were fed within 48 h postoperatively only one patient required reoperation to treat an anastomotic disruption [20].

The colorectal data is even clearer on early feeding safety [21]. A study by the French Society of Gastrointestinal Surgery demonstrated that only 57 % of the surgeon surveyed abided by evidence-based standards, and when asked specifically about early enteral feeding only 30 % would feed within 48 h. However, the library of literature to come from the Enhance Recovery after Surgery (ERAS) guidelines clearly support nutrition intact *hours* in the colorectal patient. Minimal complications are noted and patients recovery sooner and are discharged earlier [22–25].

The most compelling data for early postoperative feeding in the setting of a surgical anastomosis comes from Han-Geurts and colleagues who compared two groups of postoperative patients. Group one was with the standard approach waiting for bowel function to return. Group two was offered food on postoperative day one. This study demonstrated no significant differences between the groups with regards to complication rates [26]. Another study performed by Zhou et al. addressed the incidence of anastomotic leak rate in early feeding protocols [27]. In this randomized prospective trial, patients were randomized to early feeding or standard NG tube decompression with delayed oral intake until return of bowel function. The compelling observation in this study was that anastomotic leaks occurred at a less frequent rate in the patients that were in the early enteral group. We recommend beginning PO or tube feeding within 24–48 h of anastomotic creation in the setting of restoration of continuity and hemodynamic stability.

Feeding Access

A.S.P.E.N. recommends a hospitalized patient be fed within 7–14 days of admission [11]. Therefore if the patient is unable to receive nutrition during that time frame or it is anticipated the time frame will be extended, some form of nutritional supplementation and access will be necessary.

We recommend a priority on the initiation of tube feeds as soon as reasonably possible. Many routine elective surgical cases can be fed PO within this time period. Therefore, access may not be relevant. However, in the critically ill surgical, trauma, and burn patient careful thought and priority should be given to these patients, even *prior* to emergent cases. A failure to consider the potential need for postoperative nutritional access can be highly detrimental to the patient and create a conundrum in postoperative care. For example, in the case of the poly trauma patient with severe traumatic brain injury requiring laparotomy or damage control, strong consideration for long-term GI should occur.

Nasogastric or nasojejunal tubes can be easily placed in the operative theater during exploratory laparotomy. These tubes are also placed at bedside with little difficulty but lower success rate for distal access. Our current protocol allows for the placement of these feeding tubes by our nursing staff. We require a kidneys, ureter, bladder (KUB) X-ray to confirm placement. We do not delay tube feeds if we do not achieve a postpyloric position. Several studies have borne out that aspiration risk is not affected by feeding tube position [28]. Mainly, the postpyloric position is desirable because of the small bowel's tolerance to tube feeds vs. the stomach. Only with persistent signs and symptoms of poor gastric emptying or intolerance would we pursue small bowel access.

Other methods of placement of small bowel feeding tubes have been implemented which do not require radiographic confirmation. Recently, the use of electromagnetically guided placement devices (EMPD) has been safely trialed. Powers et al. demonstrated a 97.2 % success rate using EMPD and a nurse driven protocol [29]. Only 8 % of the 904 feeding tubes placed in this study required X-ray confirmation. In another study by the same authors they verified the agreement between EMPD and radiographs achieving a 99.5 % agreement rate [30]. The clear advantages to a protocol using EMPD are patient safety related to misplacement of the feeding tube, reduction in radiation exposure, possible earlier initiation of tube feeds, and cost reduction related to multiple radiographs. Though blind, endoscopic, and fluoroscopic placements of small bore small bowel feeding access have been described, the least invasive and logistically easiest method appears to be using the EMPD. However, all techniques should be in the surgeon's armamentarium to facilitate efficient enteral access.

There is currently no standard recommendation for optimal timing for placement of surgical feeding access. Patient selection for placement of a surgical access should consider patient's prognosis, current critical issues, the complications involved and tube insertion and care, and the length of time feeding access will be required. As previously discussed, the nasoenteric tube is adequate for those patients requiring short-term feeding access. However, the complications of nasoenteric tube mandate a risk and benefit analysis for the consideration for enterostomy. The risks include sinusitis, septic necrosis, patient discomfort, epistaxis, and misplacement/migration of tube into the lung resulting in pneumothorax or pulmonary aspiration. While there is no consensus on the placement of surgical feeding tubes most will agree if access is needed for greater than 4 weeks enterostomy should be performed. These feeding tubes come with their own challenges. However, are necessary in many patients for optimal outcomes. The complications of enterostomy tubes include infection, pressure necrosis, skin breakdown, granulation tissue, tube occlusions, and tube displacement.

The basic types of surgical place feeding tubes are the gastrostomy and jejunostomy. There are several variations from these positions which can include extensions from the gastrostomy into the jejunum and options for endoscopic, open and laparoscopic placement of these tubes. When considering what type of feeding tube to place one must include factors such as anatomy, previous surgeries, and prognosis. Also environmental factors may impact placement such as patient location and availability of skilled practitioners with the ability to place feeding access with quality and efficiency. It is these authors preference when placing surgical feeding tubes to utilize the gastrojejunostomy, open or percutaneous

techniques. The gastrojejunostomy tube offers several unique advantages over gastrostomy and jejunostomy alone. The gastrojejunostomy allows for access to both the stomach and proximal small bowel via only one defect in the intestinal tract; more tolerant small bowel feeds while simultaneously decompressing the stomach. Given the high incidence of gastric dysmotility or gastroparesis in the critically ill patient this tube seems well adapted to use in these scenarios.

Gastric Dysmotility/Gastroparesis

Gastric dysmotility or gastroparesis as a common occurrence in the postsurgical patient. The main cause of gastric dysmotility is related to the disruption of hormonal balances and catecholamines that are present in this patient population [31]. This can be a vexing issue for any protocol with a priority for early enteral feeding. A tincture of time might be the best medicine in these cases to allow for catecholamine and inflammatory cytokines to dissipate. However, in our experience the best approach is a highly protocolized pathway to combat this entity. The small bowel is much more tolerant to early enteral feeding than the stomach. However, the majority of patients receives and tolerates gastric feeds, especially if started at less than goal as described earlier. Our protocol dictates that if the gastric residual volume exceeds 500 cc, tube feeds are stopped for 2 h and then restarted. If there are subsequent issues with high gastric residuals, we start the patient on intravenous metaclopramide and erythromycin. Over the next 24–72 h if this process is not successful we consider the use of small bowel access via the previously described techniques (Table 11.2). The evidence for the use of erythromycin as a promotility agent is based on the work by Boivin et al. [32, 33]. Erythromycin was given intravenously (IV) every 8 h and found to result in less interruption of tube feeds for high gastric residuals. Subsequently, more enteral formula was administered. This has been further substantiated in a randomized placebo controlled trial which again showed patients given erythromycin achieved a higher rate of goal tube feeds versus placebo. These authors state that there are potential side effects to erythromycin mainly the risk of torsades de pointes and the potential for multidrug-resistant organisms [32, 34, 35]. However, there is little evidence to suggest that erythromycin has a substantial impact on the gut flora. We recommend a trial of prokinetic agents for 72 h when intolerance to gastric feeds is encountered.

Table 11.2 Protocol for the initiation and access of enteral nutrition

Enteral Nutrition (EN)
• Initiation of EN – Start Formula at 50 % of goal (~25–30 mL/h) within 24–48 h of admission – Advance as tolerated to goal by day 5 with improvement of SIRS or critical illness – If not at 60 % of goal after 7 days, consider PN supplementation (refer to protocol)
• Withhold EN if hemodynamically unstable (rising lactate, pressors)
• EN Access – Placement ■ Begin with blind bedside nasogastric feeding tube ■ Consider bedside electromagnetic, endoscopic, fluoroscopic, or intraoperative placement ■ OGT and NGT placement confirmed by physical exam and X-ray ■ Small bore feeding tube placement confirmed by KUB or electromagnetic placement – Gastric access ■ Short-term: OGT, NGT, small bore feeding tube ■ Long-term (>30 days): PEG (initiate TF 6 h post PEG placement) – Postpyloric access ■ Short term: If placement unsuccessful after two attempts consider endoscopic placement of PEG/J (long term) ■ Indications Gastroparesis with persistent high (500 mL) Gastric Residual Volume (GRV) despite prokinetic agents or recurrent emesis Severe active pancreatitis (endoscopic placement for jejunal feeds) Open abdomen
Abdominal Trauma Index (ATI) > 15

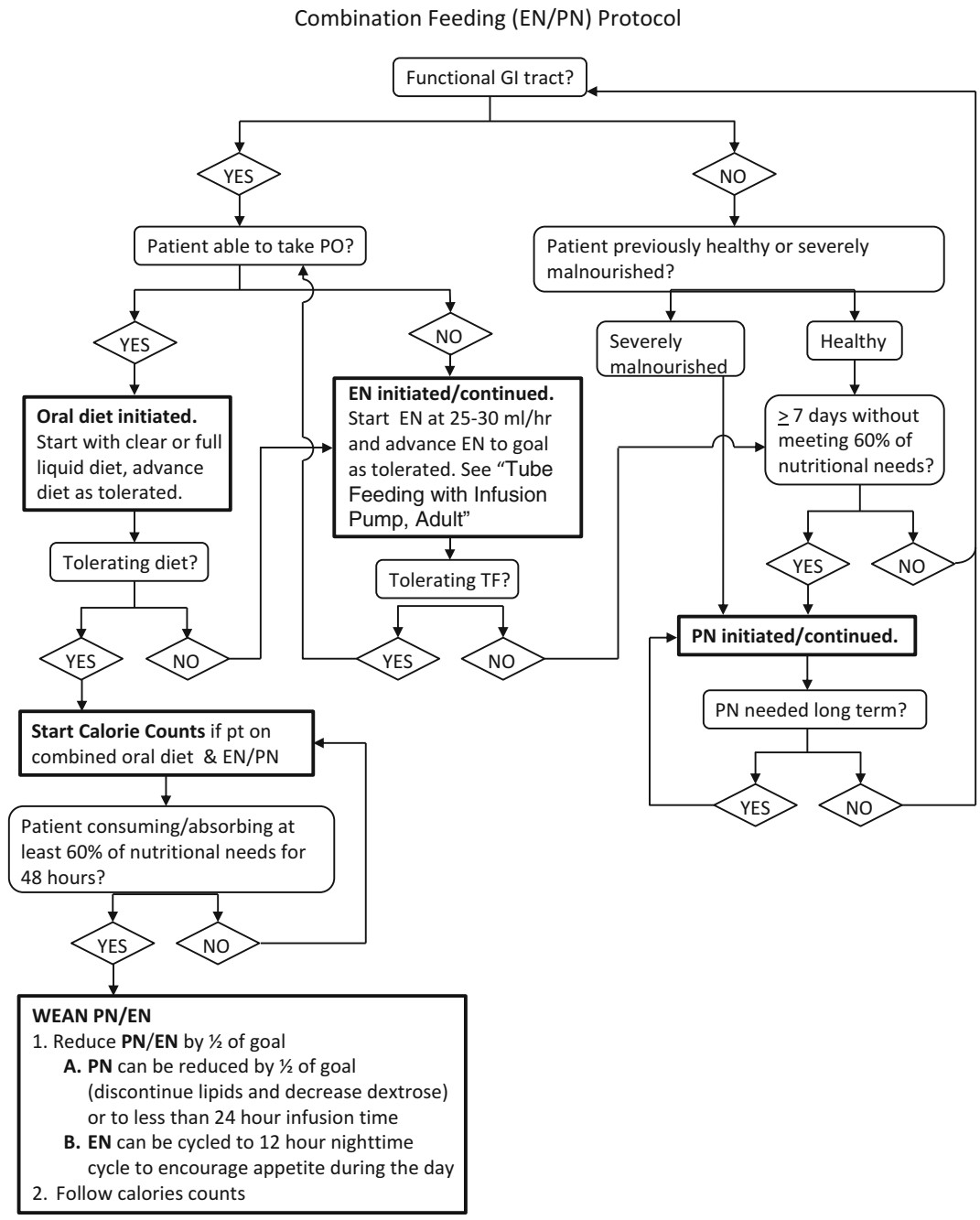

Fig. 11.1 Nutrition protocol for use of Enteral Nutrition (EN) and Parenteral Nutrition (PN) in critically ill patients

Regardless of the reasons for unsuccessful use of enteral nutrition, at some point, parenteral nutrition (PN) should be entertained. Though the battle to continue to the use of enteral nutrition should continue, PN can be started. The risks and benefits of PN are outside of the scope of this chapter. However, Fig. 11.1 shows how we incorporate both forms of nutritional support in the care of the critically ill and injured.

Enteral Nutrition and Disease States

Various disease states warrant special consideration when comes to the employment of enteral nutrition. This may be one of the most controversial and misunderstood areas as it applies to the actual application of evidence in the enteral nutrition paradigm. This is likely due to a lack of complete understanding of the innate and acquired immune systems and there interdependence on enteral nutrition. Moreover, the impact that catabolic stress plays in the mortality of a surgical patient. We will discuss pancreatitis, enteroatomospheric fistulas, and sepsis as they relate to enteral nutrition. Descriptions of enteral nutrition with trauma and burn pathology are described elsewhere.

Acute Pancreatitis

The cornerstone of nutritional support of acute pancreatitis for decades has been fluids and fasting. It was not till the recognition the extreme catabolic stress of fasting places on the human organism has led to a greater understanding and priority for the initiation of enteral feeding. The dated belief that parenteral nutrition is superior for the support of acute pancreatitis lacks evidence [36]. Though intuitively the concept of avoiding food may subsequently stimulate pancreatic secretion thus aggravating pancreatic inflammation seems physiologically sound. However, the evidence is that enteral nutrition is associated with fewer complications, reduction and length of hospital stay, as well as better outcomes [37]. In a systematic review of the literature, Gramlich and others demonstrated significant decreases in infectious complications when enteral nutrition was employed over parenteral nutrition. While there was no difference in mortality in this review there were significant cost benefit associated with enteral nutrition [38]. In the recent work, Yi performed a meta-analysis of eight randomized control trials demonstrated a clear superiority of total enteral nutrition versus TPN. This meta-analysis showed that enteral nutritional support leads to decreases in mortality, fewer complications, reduction in organ failure, and additional surgical intervention [37]. This and other studies have lead major societies such as American College of Gastroenterology and A.S.P.E.N. to recommend that oral feedings be initiated immediately if there are no contraindications [36]. A patient with severe pancreatitis, the standard of care remains enteral nutrition. With regards to TPN, it is important to note that there was a study of TPN versus no nutritional therapy in the management of acute pancreatitis. Noteworthy in this study was the fact that early TPN patients did worse than those who received only IV fluids and no nutritional support. Patients receiving TPN in this study had longer hospitalizations and a greater incidence of catheter-related sepsis. It is our practice to begin oral intake as soon as nausea and emesis are no longer present. In more severe cases, we place nasojejunal feed tubes and initiate enteral feeds when resuscitation is completed and hemodynamics are no longer labile.

Any discussion of the nutritional support of acute pancreatitis should include the concept of pharmaconutrition. Glutamine by far is one of the most interesting and most studied pharmaconutrients in the arena of surgical metabolism. Glutamine provides energy for enterocytes, lymphocytes, macrophages, and neutrophils, and may be an important component of the mucosal physiology. Numerous randomized control trials have demonstrated benefit for glutamine supplementation in the surgically critical patient and trauma victim. A meta-analysis published in 2013 favored glutamine supplementation in acute pancreatitis, but in the eight randomized control trials reviewed, only intravenous glutamine showed benefit. However, a recent large prospective study with septic shock patients did not show benefit [39]. Therefore, the enthusiasm with glutamine has waned.

Enterocutaneous Fistula

One of the most challenging problems in surgery remains the enterocutaneous fistula (ECF).

Despite the many advances and techniques available, ECF are challenging even to the seasoned surgeon. The vexing issue is the complex interplay of multiple parallel and sometimes competing processes involved in the care of these patients. A balanced approach is essential to control sepsis, minimizing fistula output, keeping electrolytes and fluid balance, and all the while striving to provide nutrition so that the fistula can heal. Traditionally, a fasting state is employed and pharmacotherapies targeted to reduce GI secretions have been the standard. The impact on mortality with these approaches has been variable. In the early 1960s, with the advent of TPN, mortality improved for the patient with ECF. Yet still it was recognized that without the pleothropic effects of enteral feeding further efforts to reduce mortality would be inhibited.

Recently, the Penn Trauma Group outlined in a review a clear systematic approach to the metabolic and nutritional treatment of ECF. Clinically, we employ a similar approach in our treatment of ECF. Schwab and coauthors recommend a three staged approach. This process is outlined in Fig. 11.2.

Phase I entails the diagnosis, resuscitation, and institution of TPN. The goal of this phase is to reduce the inflammatory and catabolic state that will create road blocks to the healing process. Phase II defines anatomy, provides adequate drainage, and involves a complete nutritional assessment, as well as consideration of appropriate feeding access. This is critical. It determines how much bowel is present that will allow for adequate absorption of nutrients. An assessment for feeding access is performed during this phase. If necessary, balloon catheters are placed within distal areas of the fistula so that proximal fistula effluent can be for refed. Nutritional assessment and active monitoring to achieve a positive nitrogen balance is key. A standard recommendation of achieving 20–30 kcal/kilo/day of nonprotein calories and 1.5–2.5 g/kg/day of protein are reasonable initial goals. A high degree of priority should be placed on nutritional monitoring which should include weight, prealbumin, albumin, and C-reactive protein. If your patient is on TPN during the initial phases—an emphasis on discontinuation of TPN should be placed to favor the early enteral process. Various groups have demonstrated that many ECF patients are able to transition to full enteral nutrition [40].

There should be a strong consideration for immunomodulating adjuncts in the treatment plan for ECF. Though studies remain controversial, many of these studies are under powered for mortality and therefore the benefits of formulas which contained elements such as glutamine, arginine, omega-3 fatty acids, and vitamin C have shown minimal impact. However, there is minimal risk to these adjuncts therefore we recommend the employment of immuno nutrition when feasible.

In addition, agents which potentially impact fistula output may benefit and impact early closure. Antimotility agents such as loperamide and opium compounds can be employed safely. Proton pump inhibitors, octreotide, and somatostatin have shown variable results but reduce secretions which can be advantageous if fistula outputs are liters per day. Bulking agents can be considered such as dietary fiber. We have employed a myriad of these modalities in combination and recommend a very in the individualized approach when dealing with ECF.

Sepsis

With regards to enteral feeding in the setting of the septic patient, we recommend strict adherence to the Surviving Sepsis Campaign National Guidelines [41, 42]. These guidelines clearly favor enteral feeding over the use of TPN. The institution of enteral feeding should begin within 48 h and one should avoid long-term fasting due to the high catabolic state in sepsis. The data regarding timing of enteral feeding in the setting of pressors is largely inferred. However, the risk for intestinal ischemia is real for a very small group of patients, less than 1 % [43]. Therefore, hypocaloric tube feeds with the goal of achieving 50 % of daily goals in the initial phases are warranted. Enteral feeding should not begin until fluid resuscitation is completed and pressor requirements are stable or decreasing. We do not advise

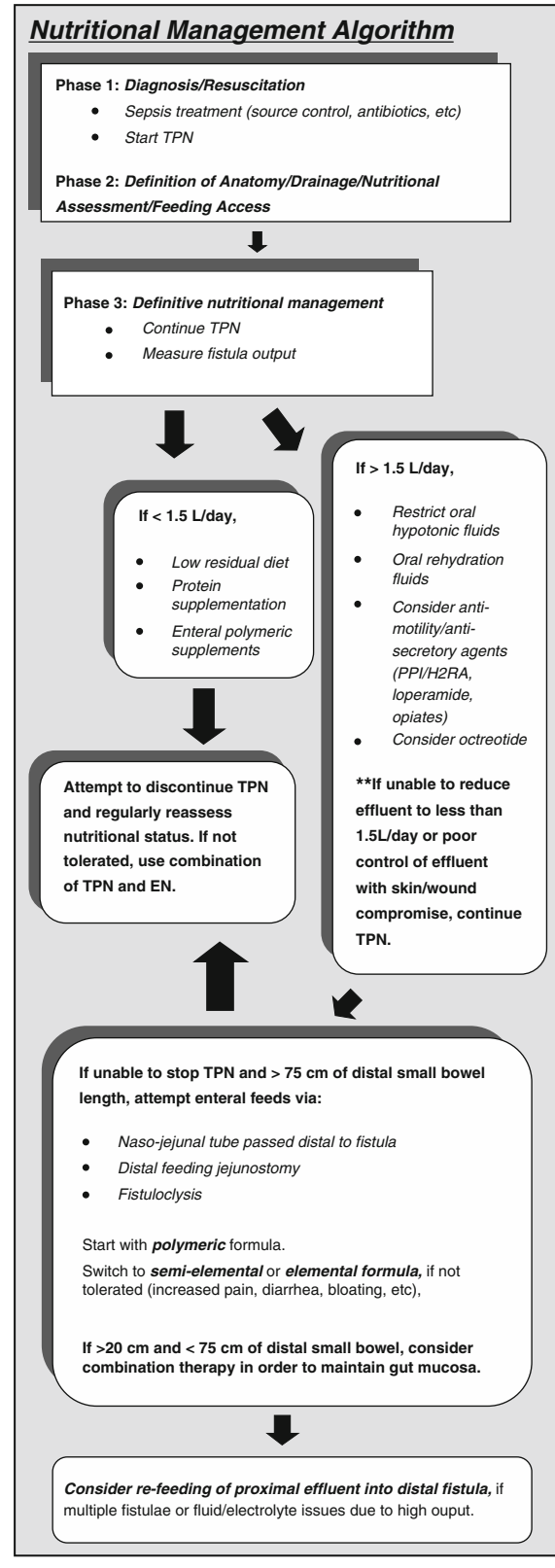

Fig. 11.2 Nutritional management of enterocutaneous fistula. From [40]; with permission

aggressive targets to goal feeding until the patient is clinically improving. Certainly, the institution of enteral feeds in sepsis is very individualized, and in those patients who improve quickly advancement to goal can be performed safely.

Complications of Enteral Nutrition

Those patients who suffer complications associated with enteral nutrition are the same who stand to benefit the most. Unfortunately, "intolerance" to enteral nutrition is poorly defined as gastroparesis, high gastric residual volumes, small bowel ileus, bowel sounds, adequate bowel movements and diarrhea have no agreed upon definitions in the intensive care patient. As well, many of these entities are not associated with documented associations with clinical outcomes such as frank aspiration and pneumonia. However, enteral nutrition is often held and the propagation of malnutrition due to feed withholding is continued. Nonetheless, we will attempt to describe some of the complications commonly associated with enteral nutrition.

Aspiration

The risk of aspiration and subsequent pneumonia is very much a concern with the patient receiving enteral feeds. Particularly when one considers the route of enteral feeding nasogastric versus nasojejunal one would intuitively think that there would be a higher risk for aspiration and subsequent pneumonias from those patients admitted to the nasogastric route. Despite several well-designed studies which attempted to demonstrate a higher risk of aspiration events in those patients fed via the nasogastric route, studies have failed to consistently demonstrate worse outcomes in gastric feed patients. Therefore, we recommend that you start enteral feeding regardless of the position of the nasal feeding apparatus. We do recommend priority be given to the nasojejunal position when placing a small bore feeding tube intraoperatively, or via endoscopic, fluoroscopic or EMPD based on the better tolerance of enteral feeds distal to the duodenum. Certainly prevention is the best medicine when dealing with ventilator-associated pneumonia. Therefore, the immune modulating benefits of early enteral feeding should be given high priority as part of any prevention strategy. The focused on the use of VAP bundles have proven highly effective to decrease the incidence of pneumonia in the ICU population. Unfortunately, those bundles do not mention early feeding.

Diarrhea

Diarrhea is common in those patients receiving enteral nutrition. While it would be easy to assume that enteral formulations are the root of most diarrhea, this is usually the least likely culprit. Diarrhea is multifactorial. When addressing the patient who has diarrhea, we perform a careful evaluation of the patient's history and physical exam, current medications, and risk factors for infection. A systematic review of all medications, antibiotic history, and nutritional plan is essential. Medications are implicated more often than not in patients receiving enteral nutrition. One of the most common findings in our population is related to bowel regimen medications. These medications are necessary for the postoperative and critically ill patients receiving narcotics, but can be culprits for diarrhea. In addition, many medications specifically elixirs contain sorbitol which can be potent inducer of loose stool.

Any assessment of loose stool in the surgical patient must include a consideration of infectious diarrhea. There should be high suspicion for *C. difficile* in patients receiving antibiotics. One must also consider other bacteria as potential pathogens in the postsurgical patient. Once infectious and medications have been ruled out one can consider changing the enteral formulation. Lactose and excessive fat or carbohydrate formulations usually are responsible for enteral induced diarrhea. However, most formulations used commonly in practice today are designed to avoid these common inducers.

There are several options for addressing diarrhea. The simple addition of dietary fiber in most

cases will suffice. Several studies have employed this strategy with success [44]. Other agents can be useful in slowing GI motility. It is crucial that enteral nutrition is not discontinued for diarrhea unless bowel ischemia or fluid/electrolyte imbalances are encountered. Careful scrutiny of medications and infections causes yield the majority of causes without interruption or alteration in the nutritional plan.

Formulas

There are multiple commercially available formulations for enteral feeding. Most formulas are similar in nature with regards to content containing about 1.0–2.0 cal/mL. Formulations are all fairly similar in the protein, carbohydrate, and fat ratios. Generally, protein content ranges from 16 to 20 %, carbohydrates 40–53 %, and fat 29–40 %. These formulations are iso-osmolar with few exceptions which include Isosource, Jevity, Osmolite, and Nutren. Numerous studies have also advocated an immunomodulating formula (containing glutamine, arginine, nucleotides, antioxidants, and omega-3 fat content) with some improved outcomes noted [45–47]. Typically though, the hospital purchasing contract drives the potential formulas available to the practitioner. The decision to choose a particular formula over the other may also include consideration of the nutritional status of the patient, electrolyte balance, absorptive capacity, disease state, and renal function. Though detailed knowledge of these formulas is often obtained by the institutions' registered dieticians, we again refer to have one or two well-known formulas known to the surgical staff. This will allow an easy prescription to be provided in the early phase of patient care associated with "early enteral nutrition provision."

Conclusion

Enteral nutrition is the preferred method of feeding and should be started early, within 24–48 h. Though this statement is mundane and stated in every nutrition text, it is probably the most important nutrition act we can perform with the greatest impact to patient care. Nuances of enteral nutrition concerning route, how much, and actual formulations used are important. However, a lack of this knowledge should not be an obstacle in accomplishing the early provision of enteral nutrition via the properly placed NGT/OGT at ~25 cc/h for almost every ICU patient who has completed a well-executed resuscitation.

References

1. Slim K, Panis Y, Chipponi J. Half of the currecnt practice of gastrointestinal surgery is against the evidence: a survery of the French Society of Digestive Surgery. J Gastrointest Surg. 2004;8(8):1079–82. Epub 2005/02/11.
2. Franklin GA, McClave SA, Hurt RT, Lowen CC, Stout AE, Stogner LL, et al. Physician-delivered malnutrition: why do patients receive nothing by mouth or a clear liquid diet in a university hospital setting? JPEN J Parenter Enteral Nutr. 2011;35(3):337–42. Epub 2011/03/09.
3. Jabbar A, Chang WK, Dryden GW, McClave SA. Gut immunology and the differential response to feeding and starvation. Nutr Clin Pract. 2003;18(6):461–82. Epub 2005/10/11.
4. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. Nutr Clin Pract. 2009;24(3):305–15. Epub 2009/06/02.
5. Miller KR, Wischmeyer PE, Taylor B, McClave SA. An evidence-based approach to perioperative nutrition support in the elective surgery patient. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):39S–50S. Epub 2013/09/18.
6. Alverdy JC, Chang EB. The re-emerging role of the intestinal microflora in critical illness and inflammation: why the gut hypothesis of sepsis syndrome will not go away. J Leukoc Biol. 2008;83(3):461–6. Epub 2007/12/28.
7. de Haan JJ, Lubbers T, Derikx JP, Relja B, Henrich D, Greve JW, et al. Rapid development of intestinal cell damage following severe trauma: a prospective observational cohort study. Crit Care. 2009;13(3):R86. Epub 2009/06/10.
8. Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. Crit Care Med. 2009;37(5):1757–61. Epub 2009/04/18.
9. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest. 2006;129(4):960–7. Epub 2006/04/13.

10. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med. 2005;33(1):213–20. discussion 60–1; Epub 2005/01/13.
11. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316. Epub 2009/04/29.
12. Jones NE, Suurdt J, Ouelette-Kuntz H, Heyland DK. Implementation of the Canadian Clinical Practice Guidelines for Nutrition Support: a multiple case study of barriers and enablers. Nutr Clin Pract. 2007;22(4):449–57. Epub 2007/07/24.
13. Jain MK, Heyland D, Dhaliwal R, Day AG, Drover J, Keefe L, et al. Dissemination of the Canadian clinical practice guidelines for nutrition support: results of a cluster randomized controlled trial. Crit Care Med. 2006;34(9):2362–9. Epub 2006/07/20.
14. Needham DM, Dinglas VD, Bienvenu OJ, Colantuoni E, Wozniak AW, Rice TW, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ. 2013;346:f1532. Epub 2013/03/21.
15. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med. 2011;39(5):967–74. Epub 2011/01/19.
16. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795–803. Epub 2012/02/07.
17. Berger MM, Chiolero RL. Hypocaloric feeding: pros and cons. Curr Opin Crit Care. 2007;13(2):180–6. Epub 2007/03/01.
18. Jeejeebhoy KN. Permissive underfeeding of the critically ill patient. Nutr Clin Pract. 2004;19(5):477–80. Epub 2005/10/11.
19. Braga M, Gianotti L, Gentilini O, Liotta S, Di Carlo V. Feeding the gut early after digestive surgery: results of a nine-year experience. Clin Nutr. 2002;21(1):59–65. Epub 2002/03/09.
20. Lee HS, Shim HJ, Lee JG, Kim KS. [The safety of early enteral feeding after emergency gastrointestinal surgery]. Korean J Gastroenterol [Taehan Sohwagi Hakhoe chi]. 2011;58(6):318–22.
21. Gianotti L, Nespoli L, Torselli L, Panelli M, Nespoli A. Safety, feasibility, and tolerance of early oral feeding after colorectal resection outside an enhanced recovery after surgery (ERAS) program. Int J Colorectal Dis. 2011;26(6):747–53. Epub 2011/02/03.
22. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS) society recommendations. Clin Nutr. 2013;32(6):879–87.
23. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010;29(4):434–40. Epub 2010/02/02.
24. Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. Crit Care Clin. 2010;26(3):527–47. Epub 2010/07/21.
25. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc. 2010;69(4):488–98. Epub 2010/06/03.
26. Han-Geurts IJ, Hop WC, Kok NF, Lim A, Brouwer KJ, Jeekel J. Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. Br J Surg. 2007;94(5):555–61. Epub 2007/04/20.
27. Wang ZH, Zhong B, Xiang JY, Zhou YB, Wang DS. [Effect of early oral enteral nutrition on clinical outcomes after colorectal cancer surgery]. Chin J Gastrointest Surg [Zhonghua wei chang wai ke za zhi]. 2013;16(8):735–8.
28. Esparza J, Boivin MA, Hartshorne MF, Levy H. Equal aspiration rates in gastrically and transpylorically fed critically ill patients. Intensive Care Med. 2001;27(4):660–4. Epub 2001/06/12.
29. Powers J, Fischer MH, Ziemba-Davis M, Brown J, Phillips DM. Elimination of radiographic confirmation for small-bowel feeding tubes in critical care. Am J Crit Care. 2013;22(6):521–7. Epub 2013/11/05.
30. Powers J, Luebbehusen M, Spitzer T, Coddington A, Beeson T, Brown J, et al. Verification of an electromagnetic placement device compared with abdominal radiograph to predict accuracy of feeding tube placement. JPEN J Parenter Enteral Nutr. 2011;35(4):535–9. Epub 2011/06/28.
31. Landzinski J, Kiser TH, Fish DN, Wischmeyer PE, MacLaren R. Gastric motility function in critically ill patients tolerant vs intolerant to gastric nutrition. JPEN J Parenter Enteral Nutr. 2008;32(1):45–50. Epub 2008/01/01.
32. Boivin MA, Carey MC, Levy H. Erythromycin accelerates gastric emptying in a dose-response manner in healthy subjects. Pharmacotherapy. 2003;23(1):5–8. Epub 2003/01/14.
33. Berne JD, Norwood SH, McAuley CE, Vallina VL, Villareal D, Weston J, et al. Erythromycin reduces delayed gastric emptying in critically ill trauma patients: a randomized, controlled trial. J Trauma. 2002;53(3):422–5. Epub 2002/09/28.
34. Boivin MA, Levy H. Gastric feeding with erythromycin is equivalent to transpyloric feeding in the critically ill. Crit Care Med. 2001;29(10):1916–9. Epub 2001/10/06.

35. Levy H, Hayes J, Boivin M, Tomba T. Transpyloric feeding tube placement in critically ill patients using electromyogram and erythromycin infusion. Chest. 2004;125(2):587–91. Epub 2004/02/11.
36. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400–15. Epub 2013/07/31.
37. Yi F, Ge L, Zhao J, Lei Y, Zhou F, Chen Z, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. Intern Med. 2012;51(6):523–30. Epub 2012/03/28.
38. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition. 2004;20(10):843–8. Epub 2004/10/12.
39. Asrani V, Chang WK, Dong Z, Hardy G, Windsor JA, Petrov MS. Glutamine supplementation in acute pancreatitis: a meta-analysis of randomized controlled trials. Pancreatology. 2013;13(5):468–74. Epub 2013/10/01.
40. Polk TM, Schwab CW. Metabolic and nutritional support of the enterocutaneous fistula patient: a three-phase approach. World J Surg. 2012;36(3):524–33. Epub 2011/10/29.
41. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis. 2012;12(12):919–24. Epub 2012/10/30.
42. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637. Epub 2013/01/29.
43. McClave SA, Chang WK. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? Nutr Clin Pract. 2003;18(4):279–84. Epub 2005/10/11.
44. Thibault R, Graf S, Clerc A, Delieuvin N, Heidegger CP, Pichard C. Diarrhoea in the ICU: respective contribution of feeding and antibiotics. Crit Care. 2013;17(4):R153. Epub 2013/07/26.
45. Pontes-Arruda A, Martins LF, de Lima SM, Isola AM, Toledo D, Rezende E, et al. Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT study. Crit Care. 2011;15(3):R144. Epub 2011/06/11.
46. Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. JPEN J Parenter Enteral Nutr. 2008;32(6):596–605. Epub 2008/11/01.
47. Pontes-Arruda A. Using parenteral fish oil to modulate inflammatory response. JPEN J Parenter Enteral Nutr. 2010;34(3):344–5. Epub 2009/11/04.

Parenteral Nutrition

12

Vivian M. Zhao and Thomas R. Ziegler

Introduction

Protein–calorie malnutrition (PCM), which encompasses major loss of lean body mass and body fat stores, with or without concomitant depletion of essential micronutrients (vitamins, minerals, trace elements) remains common in hospitalized surgical (and medical) patients in developed countries [1–8]. The prevalence of various degree of malnutrition among total hospital admissions and in intensive care unit (ICU) settings have reported to occur in 20 % to as high as 60 % of surgical and medical patients [1–4]. Generally, the majority of surgical patients will advance to oral diet shortly after operation and require minimal nutritional intervention; however, major surgery or postoperative complications can delay advancement to a full oral diet. Eventually, the degree of PCM worsens in those patients secondary to the stress of operation, increased nutritional needs for wound healing, and increased metabolic rate related to postoperative recovery, insufficient food intake and repeated catabolic insults [4, 9–11]. PCM prior to and during hospitalization are each associated with increased morbidity and mortality, length of hospital stay, and added cost of care [9, 12–17].

As early as 1936, Studley showed that preoperative weight loss significantly increased postoperative morbidity and mortality in patients undergoing gastric surgery, independent of age, impaired cardiovascular and respiratory function, and type of operation [18]. Giner et al. later confirmed that PCM is a major determinant for developing postoperative complications [3]. In highly catabolic surgical ICU patients, PCM has been associated with increased risk for infectious complications, impaired wound healing and muscle strength, and requirements for postsurgical intubation [6, 8, 12–17, 19, 20]. Various pathophysiologic factors contribute to nutritional deficiencies among patients undergoing elective or major surgery (Table 12.1) [20]. Identifying malnourished surgical patients and provision of proper nutritional support has long been a key focus of surgical patients. Research has emphasized methods of delivery to minimize surgery-associated metabolic changes. Nutrition support can be delivered safely with specialized enteral and/or parenteral nutrition [21]. This chapter will focus on parenteral nutrition (PN), which provides fluid, calories, carbohydrate, essential and nonessential amino acids, essential fats, vitamins, trace elements, and minerals.

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Table 12.1 Pathophysiologic factors that contribute to malnutrition in surgical patients

• Diminished dietary intake prior to or after surgery (e.g., anorexia, pain, altered gastrointestinal function awaiting for bowel function to return, NPO status)
• Increased catabolic hormones and cytokines concentrations (e.g., catecholamines, cortisol, interleukins, tumor necrosis factor-α)
• Decline in anabolic hormones levels (e.g., insulin-like growth factor-I, testosterone)
• Resistance to anabolic hormones with subsequent underutilization of substrate(e.g., resistance to insulin)
• Abnormal nutritional losses (e.g., diarrhea, surgical drainage, emesis, polyuria, renal replacement therapy, wounds)
• Decreased protein synthesis secondary to decreased physical activity (e.g., bed rest, deceased ambulation, chemically-induced paralysis)
• Medication–nutrient interactions (e.g., corticosteroids, diuretics, vasopressors)
• Increased requirements for calories, protein, and/or specific micronutrient (e.g., with infection, oxidative stress, trauma, large wounds)
• Iatrogenic factors (e.g., prolonged suboptimal enteral or parenteral nutrition provision in relation to metabolic requirements)

NPO nil per os

Current Clinical Practice Guideline Overview

There is limited published data from well-designed, adequately powered intent-to-treat randomized control trials (RCTs) on PN efficacy in hospital settings [5, 6, 22, 23]. Therefore, current PN utilization in hospital patients is largely based on international guidelines by major professional societies [6, 8, 9, 24–29]. A caveat regarding efficacy of current PN practices is that no rigorous RCT has featured an unfed or minimally fed control group; thus the safe duration for minimal to no feeding in surgical patients is unknown [29]. In addition, many of the earlier studies were conducted with excessive PN caloric doses and liberal blood glucose control strategies compared to current practice today, in which lower caloric doses (20–25 kcal/kg/day) and stricter blood glucose control (140–180 mg/dL) is the standard of care. Nonetheless, current research suggests that patients with moderate to severe generalized malnutrition benefit from PN in terms of overall morbidity and possibly mortality if enteral nutrition (EN) is not possible [20, 28].

Major professional societies have outlined clinical practice guidelines for calorie and protein (as amino acids in PN) intake in hospitalized adult medical and surgical patients [6, 8, 24, 25, 28]. Guidelines for pediatric patients have been published, but are beyond the scope of this chapter [26, 27]. It is important to recognize that caloric needs in hospitalized surgical patients, especially those with critical illness, can vary significantly secondary to serial changes in clinical conditions [6, 8]. Optimal caloric and protein intake in surgical patients are not well defined due to a lack of current rigorous, randomized, controlled clinical trials [6, 8, 29, 30].

Nutritional Assessment

Complete nutritional status assessment requires incorporation of medical and surgical history, current clinical and fluid status and tempo of illness, dietary intake history, body weight history, gastrointestinal and functional status, physical examination and selected biochemical tests (Table 12.2) [20]. There is no "gold standard" for nutritional assessment in surgical patients. Commonly, serum levels of albumin and prealbumin were obtained, which can be helpful in outpatient or epidemiologic settings; however, they are neither reliable nor practical postoperation because inflammation, infection, lowered hepatic synthesis, and/or increased clearance can markedly decrease blood concentrations. Plasma levels of albumin and prealbumin are also subject to fluid status (increased with hypovolemia or decreased with hypervolemia). On the other hand, serum albumin level can be an excellent prognostic indicator, with an inverse correlation between postoperative morbidity and mortality compared with preoperative serum albumin level [31, 32]. Concentrations of specific vitamin and trace elements are useful to follow in certain at-risk patients, however their levels can fluctuate secondary to volume status, inflammation, and inter-organ shifts that require serial levels to

Table 12.2 Important steps in nutritional assessment of hospitalized surgical patients

• Assess past medical and surgical history, tempo of current illness and expected hospital/perioperative course
• Evaluate dietary intake history and previous specialized nutrition support utilization
• Review body weight changes (e.g., % weight loss from usual body weight, rate of loss)
• Complete physical examination with attention to fluid status, organ functions and evidence of protein–calorie malnutrition and skin/conjunctival/tongue lesions consistent with vitamin–mineral deficiency
• Evaluate gastrointestinal tract status to assess feasibility and tolerance for enteral feeding
• Determine ambulatory capacity, mental status
• Serial evaluation of standard blood tests (organ function indices, electrolytes, pH, triglycerides, and selected vitamins and minerals if at risk for deficiency)
• Assess calorie and protein needs
• Determine enteral and parenteral access for nutrient delivery

Patients weighing less than 90 % of their ideal body weight, those with involuntary body weight loss of >5–10 % of usual body weight in the previous several weeks or months, patients, or those with a body mass index (BMI) less than 18.5 kg/m^2 should be carefully evaluated for malnutrition

guide repletion strategies. In addition, body weight often changes markedly in relation to volume status [32].

A simple and practical bedside method known as subjective global assessment (SGA) has been validated for nutritional assessment and use as prognostic indicator of clinical outcomes in stable patients without significant fluctuation in fluid status [33, 34]. The SGA integrates various components, such as history of weight loss and food intake, functional capacity, gastrointestinal symptoms that continued >2 weeks (e.g., diarrhea, nausea, and vomiting), and physical examination (e.g., muscle or fat mass wasting, edema/ascites, wounds, hair loss, skin breakdown), to categorize the degree of malnutrition (e.g., well nourished, mildly malnourished, moderately malnourished, or severely malnourished) [33, 34]. Another method commonly used in European hospitals for evaluation of nutritional risk calculates a nutritional risk score accordingly to body mass index (BMI), percent reduction in usual food intake, body weight history, age, and severity of illness [35]. New clinical practice guidelines for the identification and documentation of adult malnutrition have recently been published by the Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition that consider key elements such as percent weight loss history, dietary energy intake history, loss of skeletal muscle and fat mass, functional status, and presence of inflammation—and which disregard circulating proteins such as albumin (given their non-specificity) or BMI [36]. A detailed comprehensive nutritional assessment outline is available as an online supplement to a recent review of PN in the critically ill patient [20].

Nutrition Support Goals

Indirect calorimetry accurately measures resting energy expenditure (REE) for hospitalized patients, but its utilization is restricted by cost, availability, and inaccuracies due to technical issues [6, 37]. REE is most commonly calculated using traditional predictive equations, such as the Harris-Benedict equation, that incorporates the patient's age, gender, height, and weight [6, 20]. Unfortunately, predictive equations may over- or underestimate REE in surgical patients secondary to changes in clinical conditions and/or fluid status [20, 37]. Current American and European clinical practice guidelines suggest an approximate caloric goal of 25 kcal/kg/day for most surgical patients, which is approximately 1–1.2 times of the measured or estimated REE. For severely stressed patients, estimated caloric needs may range higher, from 25 to 30 kcal/kg/day. Ongoing RCTs are designed to better define caloric dosing guidelines in ICU patients, as data are particularly conflicting in these settings. Prehospital and preoperative body weight should be used for calculating caloric needs because measured body weight in the hospital (especially in the ICU) may be influenced by fluid status and can be much higher than recent "dry" weight. Ideal body weight (IBW) derived from routine tables or equations can be used as an alternative when recent dry weight is not available.

For the obese patient (body weight is 20–25 % above IBW), adjusted body weight should be used to estimate energy requirements [20].

Providing adequate amino acids (protein equivalents) in PN is crucial for cell and tissue function, wound healing, and to improve net protein balance, especially after major operation. In the 1980s, studies in ICU patients showed that amino acid/protein provision at a dose greater than 2.0 g/kg/day was inefficiently utilized for protein synthesis; the excess amino acids were oxidized and contributed to azotemia [38, 39]. The commonly recommended protein dose is between 1.2 and 1.5 g/kg/day for most surgical patients with normal renal and hepatic function (i.e., 50–100 % above the recommended daily allowance (RDA) of 0.8 g/kg/day); however, a dose range of 2.0–2.5 g/kg/day is currently recommended in patients with certain severely catabolic conditions such as burns, presence of large wounds, and those receiving continuous renal replacement therapy (CRRT) [6, 8, 20, 30]. Administered doses of amino acids may need to be adjusted downward to 0.6–0.8 g/kg/day in relation to the extent and progression of renal dysfunction in the absence of dialysis treatment. In the event of acute hepatic dysfunction and hyperbilirubinemia, patients are at risk for developing amino acid-induced hyperammonia and it may be prudent to administer lower doses of amino acids (0.6–1.2 g/kg/day) in relation to the degree of acute hepatic dysfunction [6, 8, 20, 30]. Protein restriction is generally not necessary in patients with stable chronic hepatic dysfunction, but clinical judgment is required.

Timing of Parenteral Nutrition Support

Although there is limited evidence to support preoperative PN overall, some data suggest that adequate feeding of severely malnourished patients for at least 7–10 days prior to surgery and continued after surgery may decrease postsurgical morbidity [32, 40]. Delaying elective surgery for preoperative nutritional support is recommended for patients with one or more of the following conditions: lost more than 10–15 % of actual body weight within 3–6 months, BMI < 18.5 kg/m^2, SGA score grade C (severe malnutrition), serum albumin <30 g/L without hepatic or renal dysfunction, or an ideal body weight <90 % [6, 9, 25].

Although most patients, in general, can tolerate advancement of oral diet within 6–9 days after surgery, this is dependent on the type of operation (e.g., gastrointestinal), minimal or no feeding for 10–14 days after major surgery can significantly increase morbidity and mortality [9, 16]. Even a short duration of starvation or insufficient oral intake was strongly correlated with worsened surgical outcome in one study [41]. Current guidelines recommend starting nutrition support immediately after operation if patients are not expected to meet their caloric need within 7–10 days (independent of their preoperative nutritional status), have developed complications impairing the resumption of dietary intake, or under conditions that affect metabolic homeostasis or increase nutrient needs such as infectious complications [9, 25].

While it may seem intuitive that early nutritional intervention is warranted for most patients, the American Society of Parenteral and Enteral Nutrition (ASPEN) ASPEN-NIH review and others consistently suggested that early postoperative PN does not improve clinical outcomes in surgical patients, except for the severely malnourished patients [42–45]. However, a major caveat is that these conclusions were developed evaluating data from studies before the current tight control of blood glucose and when overfeeding, especially of calories, was common in surgical patients. In patients with severe malnutrition requiring parenteral feeding, administration of PN for a minimum of 7–10 days has resulted in a clinically significant decrease in both infectious and non-infectious complications [42, 45–47].

Based on existing (and still limited) data, PN, either alone or as a supplement to inadequate EN, probably should not be initiated immediately during the postoperative period in well-nourished patients, but may be delayed for 3–7 days if oral dietary intake and/or enteral nutrition (i.e., tube

feeds) are not feasible or not tolerated (especially in the ICU setting) [29, 48–50]. In a recent large unblinded multicenter study of critically ill adults in Belgium (4,640 patients, largely on surgical services), supplemental PN given to achieve caloric/amino acid goals in ICU patients unable to meet needs with EN alone was associated with modestly increased infectious morbidity and renal or pulmonary dysfunction when started 2–3 days after ICU admission compared to results when supplemental PN was delayed to day 8 after admission [48]. Length of hospital and ICU stay was also shorter in those randomized to delayed PN versus early PN but mortality indices were similar [48]. Caveats of this study, however, were that differences between the two groups were small, most patients were not significantly malnourished at entry, a large proportion of patients were studied after cardiac surgery, exclusion criteria included those who had prior to the ICU admission been receiving specialized nutrition support or were ICU readmissions, and both study groups received daily intravenous mineral, vitamins, and trace elements [29]. In a subsequent smaller study of adult ICU patients from two Swiss institutions ($n = 305$; ≈25 % from surgical services), patients who achieved <60 % of their energy intake goal via early EN (day 1 of ICU admission) were randomized to supplemental PN on day 4 and continued until day 9 of ICU stay versus administration of EN alone [49]. Supplemental PN resulted in significantly lower rates of nosocomial infection compared to the EN-alone group, without a change in mortality or length of hospital or ICU stay [49].

In a more recent multicenter trial from Australia and New Zealand, 1,372 adult ICU patients were randomized to pragmatic standard nutritional care (time to begin EN and/or PN ≈3 days after admission) versus early PN initiated immediately after ICU admission, with EN advanced and PN weaned as tolerated [50]. Early PN resulted in significantly fewer days of mechanical ventilation and less muscle and fat loss, but otherwise there were no differences between groups in mortality, infections, organ function, or length of ICU or hospital stay [50]. Of note, current practice guidelines (CPGs) of ASPEN recommend delaying initiation of PN until day 8 in well-nourished ICU patients, but not to delay attempts to meet nutritional goals in patients with PN in ICU patients with preexisting significant malnutrition [6].

ASPEN CPGs recommend the following: (1) patients with moderate to severe malnutrition scheduled for major GI surgery should receive 7–14 days of preoperative nutritional support (as PN if EN not possible) if surgery can be safely delayed and (2) PN should routinely be prescribed in the "immediate" postoperative period for patients undergoing major GI surgery unable to tolerate EN and inadequate oral nutrition is anticipated for 7–10 days [9].

Indications

Perioperative PN is generally indicated only for patients who are severely malnourished and cannot be adequately fed by mouth or EN [25]. In settings when EN either not feasible or tolerated, PN is probably indicated for the following patients: (1) after major upper GI surgery when the GI tract is not accessible or not functioning (e.g., mechanical obstruction, paralytic ileus); (2) after extensive small bowel resection with or without colonic resection; (3) with perforated small bowel; (4) with high-output (>600 mL) and/or proximal fistulas that necessitate bowel rest; and (5) other conditions leading to prolonged EN intolerance (e.g., severe diarrhea, persistent emesis, significant abdominal distention, acute GI bleeding, hemodynamic instability, impaired gastric emptying, or paralytic ileus) preventing sufficient EN provision for >3–7 days [6, 8, 20]. No data to date to support withholding PN in patients with preexisting PCM who cannot tolerate EN. However, starting supplemental PN before this 7–10 day period in the patient already on EN does not improve outcome and may be detrimental if not carefully administered in light of potential metabolic and infectious complications [47]. PN is contraindicated (not evidence based) for the following patients: (1) those with functional GI tract and accessibility for EN; (2) fluid restricted patients who cannot tolerate the

intravenous fluid load provided for PN; (3) those with severe hyperglycemia or electrolyte abnormalities at the planned day of PN initiation; (4) PN therapy is unlikely to be given for >5–7 days; and (5) if new access line placement solely for PN causes unnecessary risks [6, 8, 20].

Administration

Complete PN solutions, can be administered through a peripheral or central vein. The choice of venous access and catheter type for PN mainly depends on the anticipated duration of therapy. For short-term PN needs (<14 days), peripheral intravenous IV lines can be used for 10–14 days if the patient can tolerate the required fluid load to meet amino acid and energy needs. In our service, a central vein PN is required and is deemed to be needs for 30 days or less, a percutaneous non-tunneled central venous catheter (PICC) can be used [9, 32]. When long-term PN is required, a tunneled, cuffed, silicone catheter is preferred (not evidence based). Table 12.3 outlines a comparison of peripheral and central vein PN, as well as fluid, macronutrient and micronutrient content. Due to risk of phlebitis with hypertonic central vein-type PN formulations, peripheral vein PN (PPN) provides low amount of dextrose (5 %; dextrose = 3.4 kcal/g) and amino acids (≤3 %; 4 kcal/g) and a larger proportion of calories as lipid emulsion (≤5 %; 10 kcal/g; 50–60 % of total calories) [9, 32]. PPN usually requires a 2–3 L/day fluid volume to provide adequate protein and calorie needs (based on patient body size), which limits its use for ICU patients and those require fluid restriction due to cardiac, hepatic, and/or renal dysfunction. In contrast, central venous PN (CPN) is delivered through the superior vena cava, which permits hypertonic CPN infusions. Thus, CPN can be the concentrated complete solutions (1–1.5 L/day), while meeting caloric and protein need for vast majority of patients. Non-PN hydration fluid rate should be proportionally adjusted in accordance of fluid status when PN is initiated [48–50].

Table 12.3 Parenteral nutrition (PN) indications in relation to the feasibility of enteral nutrition (EN)

Absolute contraindications for EN:
– Intestinal obstruction
– Ischemic bowel
– Acute peritonitis
Relative contraindications for EN: (use PN if EN deemed to be not feasible)
– High output fistulas
– Severe malabsorption
– Septic shock with impaired splanchnic perfusion
– Fulminant sepsis

PN electrolyte dosing is adjusted as needed to maintain normal serially measured serum levels. With high and/or low blood levels of specific electrolytes, daily dose adjustment may be required until serum levels are within the normal range. Higher dextrose concentrations in CPN may result in increased requirements for potassium, magnesium, and phosphorus. The relative percentage of sodium and potassium salts as chloride and acetate is increased to correct metabolic alkalosis and metabolic acidosis, respectively [6, 9, 32]. The most recent clinical practice guidelines recommend a glycemic goal range in hospitalized adult patients receiving nutrition support to be 140–180 mg/dL (7.8–10 mmol/L) [51]. Glycemic goals can be achieved by addition of regular insulin in PN and/or reduction of dextrose load in CPN as needed. Separate intravenous insulin drips are commonly utilized to prevent hyperglycemia in ICU settings [20, 32, 51].

Commercially available amino acid formulation used in PN provides all nine essential and several non-essential amino acids [20]. Although now controversial, European, but no American, guidelines recommend routine addition of glutamine in critically ill patients given the evidence that glutamine may become conditionally essential in certain catabolic patients [6, 8]. Although numerous small, randomized controlled trials (RCTs) suggest clinical benefits of PN supplemented with glutamine [52–54], several larger RCTs have recently shown that glutamine-containing PN does not improve clinical outcomes [55–57]. Amino acid concentration in PN may need to be adjusted downward or upward in relation to requirements as a function of the

severity of azotemia or hyperbilirubinemia in patients with renal and hepatic dysfunction, respectively. PN also contains intravenous lipid emulsions (LE) as a source of both energy and essential linoleic and α-linolenic fatty acids [32]. Soybean oil-based LE is the long-standing commercially available formulation in the USA, although a mixed lipid emulsion containing 80 % olive oil and 20 % soybean oil was recently approved for adults requiring PN. In Europe and other countries, intravenous soybean oil/medium-chain triglyceride mixtures, fish oil, olive oil/soybean oil mixtures, and combinations of oils are available for use in PN. Recent systemic reviews of alternative oil-based lipid emulsion may be associated with clinically important (but not statistically significant) reductions in mortality, ventilation days, and ICU length of stay when compared to PN containing soybean oil-based lipid emulsion in critically ill patients [58]. However, a recent double blind, randomized, controlled study in 100 mixed medical and surgical ICU patients found no differences in clinical outcomes in patients receiving PN containing soybean oil-based lipid emulsion versus the group receiving PN containing the recently approved olive/soybean oil product [59].

Lipid is typically mixed with dextrose and amino acids in the same PN infusion bag ("all-in-one" solution) and given with PN over 16–24 h [32]. Lipid emulsions may also be use as a separate infusion over 10–12 h. The maximal recommended dose of lipid emulsions infusion is 1.0–1.3 g/kg/day, with monitoring of blood triglyceride levels at baseline and then approximately weekly and as indicated to assess clearance of intravenous fat [9, 20, 28]. Triglyceride levels should be maintained below 400–500 mg/dL by lowering lipid emulsion concentration in PN to decrease risk of pancreatitis and diminished pulmonary diffusion capacity in patients with severe chronic obstructive lung disease. A typical central venous PN provides 60–70 % of non-protein calories as dextrose and 30–40 % of non-protein calories as LE [6, 8, 20, 28, 29, 32].

Specific needs for intravenous vitamins and minerals have not been rigorously defined for hospitalized patients [5, 8, 20, 28, 32]. Therefore, standardized intravenous preparations of combined vitamins and minerals have been added in PN to maintain normal blood levels in most stable patients (Table 12.3). However, several studies show that a significant proportion of critically ill patients receiving standard nutrition support may variously experience zinc, copper, selenium, vitamin C, vitamin E, and vitamin D deficiencies [5, 32]. Low micronutrient levels can be related to pre-ICU depletion; increased requirements possibly secondary to oxidative stress associated with critical illness, and increased excretion and/or tissue redistribution [5, 32]. Depletion of these essential nutrients may impair antioxidant capacity, immunity, wound healing, and other important body functions. Thus, as with electrolytes, therapy is directed at maintaining normal blood levels, with serial measurements in blood as clinically and biochemically indicated.

PN formulations can be individually compounded under a sterile hood in an IV pharmacy by trained pharmacy technicians and/or pharmacists; however, PN is available commercially as a "premixed" of the standardized solutions. An infusion pump to regulate delivery rates administers PN and the infusion catheters incorporate in-line filter to prevent microbial contamination [32].

Complications and Monitoring

Administration of PN has been associated with infectious, mechanical, and metabolic complications [20, 25, 28, 32]. Catheter-related bloodstream infections can occur. Mechanical complications are mainly related to insertion and use of central venous catheters, such as pneumothorax, hemothorax, thrombosis, and bleeding. Proper and safe administration of both peripheral and central vein PN requires strict catheter care protocols, including use of designated catheter ports for PN administration and subclavian vein insertion sites for central venous PN [9, 20, 25, 28, 32].

Potential metabolic and clinical consequences of overfeeding and refeeding syndrome during PN in critically ill patients are shown in Table 12.4 [20, 32]. High caloric, dextrose, amino acid, and fat loads ("hyperalimentation") are readily

Table 12.4 Sample formulations of typical peripheral and central parenteral nutrition

Component	Peripheral vein PN	Central vein PN
Volume (L/day)	2–3	1–1.5
Dextrose (%)	5	10–25
Amino acids (%)	2.5–3.0	3–8
Lipid (%)	2.5–5.0	2.5–5.0
Sodium (mEq/L)	50–150	50–150
Potassium (mEq/L)	20–35	30–50
Phosphorus (mMol/L)	5–10	10–30
Magnesium (mEq/L)	8–10	10–20
Calcium (mEq/L)	2.5–5	2.5–5
Multivitamins (mL/day)[a]	10	10
Trace elements/minerals (mL/day)[b]		

[a]Multivitamins are consisted of vitamins A, B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), B_9 (folate), B_{12} (cobalamin), C, D, and E, biotin, and with or without vitamin K. Specific vitamins such as vitamin B_1, B_6, B_9, B_{12}, C, and K, are available as individual supplement

[b]Trace elements/minerals consisted of chromium, copper, manganese, selenium, and zinc in various concentrations. Only copper, selenium, and zinc are available as individual supplement

Table 12.5 Potential complications of overfeeding and refeeding syndromes in patients receiving parenteral nutrition

- Intracellular shift of magnesium, phosphorus, and/or potassium (due to: excess dextrose; refeeding hyperinsulinemia)
- Immune cell dysfunction and infection (due to: hyperglycemia)
- Cardiac dysfunction or arrhythmias (due to: excess fluid, sodium and other electrolytes; intracellular/extracellular shift of electrolytes related to refeeding)
- Neuromuscular dysfunction (due to: thiamine deficiency; electrolytes shifts due to refeeding)
- Renal dysfunction or azotemia (due to: excess amino acid; inadequate caloric provision relative to amino acid dose)
- Edema or fluid retention (due to: excess fluid and/or sodium; refeeding hyperinsulinemia)
- Elevated liver function tests and/or hepatic steatosis (due to: excessive calorie, dextrose or fat content)
- Increased blood ammonia levels (due to: excessive amino acids provision with hepatic dysfunction)
- Hypercapnia (due to: excessive total caloric provision)
- Respiratory insufficiency (due to: refeeding-associated hypophosphatemia; excess fluid, calorie, carbohydrate or fat content)
- Hypertriglyceridemia (due to: excessive carbohydrate or fat provision; carnitine deficiency)

administered via central vein. While not the standard of care per current guidelines, excess dextrose, fat, and overall calorie administration remains a common practice in some centers [9, 20, 25, 28, 32]. Risk factors for PN-associated hyperglycemia include: (1) use in obese, diabetic, and/or septic patients; (2) poorly controlled blood glucose at PN initiation; (3) initial use of high dextrose concentrations (>10 %) or dextrose load (>150 g/day); (4) insufficient insulin administration and/or inadequate monitoring of blood glucose; and (5) concomitant administration of corticosteroids and vasopressor agents.

Electrolyte administration requires careful monitoring and generally day-to-day adjustment in PN to maintain normal blood levels. Overfeeding can induce several metabolic complications of varying degrees of severity affecting several organ systems (Table 12.5) [20, 32]. A recent large study found that PN use per se; overfeeding and sepsis were the major risk factors for liver dysfunction in critically ill patients [60]. Thus, PN should be advanced carefully to goal rates and the composition adjusted as appropriate based on the results of close metabolic and clinical monitoring performed daily. The calories provided by dextrose present in non-PN intravenous fluids, the soybean oil lipid emulsion carrier of propofol, a commonly used ICU sedative, and the nutrients provided in any administered EN must be taken into account in the PN prescription to avoid overfeeding [32].

Refeeding syndrome is well recognized and relatively common in at-risk patients (preexisting malnutrition or electrolyte depletion; prolonged periods of intravenous hydration therapy alone) [20, 61, 62]. Refeeding syndrome is mediated by administration of excessive intravenous dextrose (>150–250 g or 1 L of PN with 15–25 % dextrose). This markedly stimulates insulin release, which may rapidly decrease blood potassium, magnesium, and especially phosphorus concentrations due to intracellular shift and utilization in metabolic pathways. High doses of carbohydrate increase thiamine utilization and can precipitate symptoms of thiamine deficiency. Hyperinsulinemia may cause sodium and fluid

retention by the kidney. This, together with decreased blood electrolytes (which can cause cardiac arrhythmias) can result in heart failure, especially in patients with preexisting heart disease [61, 62]. Prevention of refeeding syndrome requires identification of at-risk patients, use of initially low PN dextrose concentrations (e.g., 1 L of PN with 10 % dextrose), provision of higher PN doses of potassium, magnesium, and phosphorus, based on initial and adjusted on serial blood levels within the first several days of PN administration, and renal function, and supplemental PN thiamine (e.g., 100 mg/day for 3–5 days) [20, 61, 62].

Consultation with an experienced multidisciplinary nutrition support team for recommendations regarding the PN prescription is ideal when such personnel are available. Nutrition support team daily monitoring has been shown to reduce complications, costs and to decrease inappropriate use of PN [63, 64]. Research shows that patients in need of nutritional support attain more energy, are more closely monitored and have fewer complications when treated by a multidisciplinary nutrition support team compared to non-team approach. Team approach results in improved patient care, and therapeutic and economic benefits.

Monitoring of PN therapy in the hospital setting requires daily assessment of the multiple factors outlined in Tables 12.1 and 12.2. Blood glucose should be monitored several times daily and blood electrolytes and renal function tests should be determined generally daily [20, 32]. Blood triglyceride levels should be measured at baseline and then weekly until stabile. Although guidelines are few, some centers routinely monitor periodic blood levels of copper, selenium, zinc, thiamine, vitamin B6, vitamin C, and 25-hydroxyvitamin D [20]. Liver function tests should be measured at least a few times weekly. pH should be monitored generally daily in ventilated patients when arterial blood gas pH measurements are available [20, 32].

Home Parenteral Nutrition

Home parenteral nutrition (HPN) was introduced as treatment option in 1967 primarily for patients with long-term intestinal failure [65]. HPN can be a life-saving or life-extending therapy. The goal of HPN is to prevent and/or correct malnutrition for a period of months or the rest of one's life. The HPN is commonly indicated for patients with Crohn's disease, mesenteric vascular disease, cancer, intestinal failure, and radiation enteritis who cannot meet their nutritional needs by EN, and who can be treated outside the acute care setting [66, 67]. Intestinal failure in surgical patients can be caused by obstruction, dysmotility, and surgical resection. Current practice guidelines recommend clinicians to identify a minimal expected duration of therapy before initiating HPN, and are not recommended for patients with a short life expectancy for at least 40–60 days [66]. HPN is delivered via subcutaneously tunneled catheters or implanted ports. HPN is usually given overnight (cyclic) to maintain the patients' freedom of movement during the day.

HPN therapy is not without risks. Thrombosis and catheter occlusion for occur while patients receiving HPN, but catheter-related infections are most problematic. Liver dysfunction and metabolic bone disease are also common complications related to long-term PN. The prevalence of catheter-related bloodstream infections ranges between 0.16 and 1.09 episodes per catheter years, as much as 13.2 episodes per 1,000 catheter days [56]. A PICC can be used for short-term PN, however, it has been associated with an almost twofold increased risk of infection when compared to subcutaneously tunneled catheters or implanted ports [67]. Currently there is no evidence to recommend the use of PICC for HPN [68]. To minimize these complications, several factors (e.g., medical, emotional, financial, and functional capabilities of the patients and caregivers) are considered before deciding that HPN is the appropriate treatment for patients and require careful monitoring. Recent data strongly suggest that ethanol locks, which must be administered via a silicone catheter (i.e., not via a plastic PICC), may markedly reduce PN-associated bloodstream infections, presumably by clearing microbe-containing biofilm on the catheter [69]. All available guidelines recommend routine monitoring by a multidisciplinary nutrition support team to minimize complications [66].

Conclusion

The optimal timing for EN and PN intervention in surgical patients remain major areas of uncertainty. Little prospective data is available on the clinical effects of minimal or no feeding over time (e.g., >7 days), and such data are unlikely to be forthcoming given difficulty in recruiting for such studies and in blinding [20, 29]. Rigorous RCTs are needed to define optimal caloric and protein dose regimens in subgroups of ICU patients [20, 48–50]. Some studies show that larger doses of standard soybean oil-based intravenous fat emulsions induce pro-inflammatory and pro-oxidative effects and possibly immune suppression [70]. However, conflicting results of small RCTs comparing soybean oil-based lipid emulsion with other types of lipid emulsion have not clarified optimal use. Available data suggests that the glutamine may become a conditionally essential amino acid in subsets of ICU patients, although conflicting data have been published recently [52–57]. Phase III level double-blind, intent-to-treat RCTs are needed in specific ICU patient subgroups to define clinically optimal calorie, protein/amino acid, and specific vitamin and mineral requirements, as well as efficacy of supplemental PN combined with EN to achieve caloric and protein/amino acid goals [6, 8, 20, 29, 71]. Large, multicenter RCTs are in progress and will help to define optimal use of PN in both medical and surgical over the next several years.

References

1. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system. Int J Environ Res Public Health. 2011;8(2):514–27.
2. de Luis DA, López Mongil R, Gonzalez Sagrado M, Lopez Trigo JA, Mora PF, Castrodeza Sanz J; Group Novomet. Nutritional status in a multicenter study among institutionalized patients in Spain. Eur Rev Med Pharmacol Sci. 2011;15(3):259–65.
3. Giner M, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. Nutrition. 1996;12(1):23–9.
4. Pirlich M, Schütz T, Norman K, Gastell S, Lübke HJ, Bischoff SC, et al. The German hospital malnutrition study. Clin Nutr. 2006;25(4):563–72.
5. Berger MM, Shenkin A. Update on clinical micronutrient supplementation studies in the critically ill. Curr Opin Clin Nutr Metab Care. 2006;9(6):711–6.
6. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316.
7. La Torre M, Ziparo V, Nigri G, Cavallini M, Balducci G, Ramacciato G. Malnutrition and pancreatic surgery: prevalence and outcomes. J Surg Oncol. 2013; 107(7):702–8.
8. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr. 2009;28(4): 387–400.
9. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26(1):255–9.
10. Patel MD, Martin FC. Why don't elderly hospital inpatients eat adequately? J Nutr Health Aging. 2008;12(4):227–31.
11. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNMC, Delarue J, Berger MM. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005; 24(4):502–9.
12. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L. Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. Clin Nutr. 2007;26(6): 1S–138S.
13. Chen Y, Liu BL, Shang B, Chen AS, Liu SQ, Sun W, et al. Nutrition support in surgical patients with colorectal cancer. World J Gastroenterol. 2011;17(13): 1779–86.
14. Jagoe RT, Goodship TH, Gibson GJ. The influence of nutritional status on complications after operations for lung cancer. Ann Thorac Surg. 2001;71(3): 936–43.
15. O'Brien JM, Phillips GS, Ali NA, Lucarelli M, Marsh CB, Lemeshow S. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. Crit Care Med. 2006;34(3):738–44.
16. Sandstrom R, Drott C, Hyltander A, Arfvidsson B, Scherstén T, Wickström I, Lundholm K. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. Ann Surg. 1993;217(2):185–95.
17. Schneider SM, Veyres P, Pivot X, Soummer AM, Jambou P, Filippi J, et al. Malnutrition is an independent factor associated with nosocomial infections. Br J Nutr. 2004;92(1):105–11.

18. Studley HO. Percentage of weight loss - a basic indicator of surgical risk in patients with chronic peptic ulcer. JAMA. 1936;106:458–60.
19. Zaloga GP. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes. Lancet. 2006;367(9516):1101–11.
20. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med. 2009;361(11):1088–97.
21. Seike J, Tangoku A, Yuasa Y, Okitsu H, Kawakami Y, Sumitomo M. The effect of nutritional support on the immune function in the acute postoperative period after esophageal cancer surgery: total parenteral nutrition versus enteral nutrition. J Med Invest. 2011; 58(1–2):75–80.
22. Doig GS, Simpson F, Delaney A. A review of the true methodological quality of nutritional support trials conducted in the critically ill: Time for improvement. Anesth Analg. 2005;100(2):527–33.
23. Doig GS, Simpson F, Sweetman EA. Evidence-based nutrition support in the intensive care unit: an update on reported trial quality. Curr Opin Clin Nutr Metab Care. 2009;12(2):201–6.
24. Heyland DK, Dhaliwal R, Day A, Jain M, Drover J. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27(5): 355–73.
25. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F, ESPEN. Guidelines on parenteral nutrition: surgery. Clin Nutr. 2009;28(4):378–86.
26. Koletzko B, Goulet O, Hunt J. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). 2. Energy (vol 41, pg S5, 2005). J Pediatr Gastroenterol Nutr. 2013;56(4):460.
27. Mehta NM, Compher C, A.S.P.E.N. Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr. 2009;33(3):260–76.
28. Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr. 2004;28(6):S39–70.
29. Ziegler TR. Nutrition support in critical illness–Bridging the evidence gap. N Engl J Med. 2011; 365(6):562–64.
30. Yarandi SS, Zhao VM, Hebbar G, Ziegler TR. Amino acid composition in parenteral nutrition: what is the evidence? Curr Opin Clin Nutr Metab Care. 2011; 14(1):75–82.
31. Kudsk KA, Tolley EA, DeWitt RC, Janu PG, Blackwell AP, Yeary S, King BK. Preoperative albumin and surgical site identify surgical risk for major postoperative complications. JPEN J Parenter Enteral Nutr. 2003;27(1):1–9.
32. Brown RO, Minard G, Ziegler TR. Parenteral nutrition. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, editors. Modern nutrition in health and disease. 11th ed. Philadelphia: Lippincott Williams and Wilkins; 2012. p. 1136–61.
33. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8–13.
34. Norman K, Schütz T, Kemps M, Josef Lübke H, Lochs H, Pirlich M. The subjective global assessment reliably identifies malnutrition-related muscle dysfunction. Clin Nutr. 2005;24(1):143–50.
35. Rasmussen HH, Holst M, Kondrup J. Measuring nutritional risk in hospitals. Clin Epidemiol. 2010;2: 209–16.
36. White JV, Guenter P, Jensen G, Malone A, Schofield M; Academy Malnutrition Work Group; A.S.P.E.N. Malnutrition Task Force; A.S.P.E.N. Board of Directors. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN J Parenter Enteral Nutr. 2012;36(3):275–83.
37. Anderegg BA, Worrall C, Barbour E, Simpson KN, Delegge M. Comparison of resting energy expenditure prediction methods with measured resting energy expenditure in obese, hospitalized adults. JPEN J Parenter Enteral Nutr. 2009;33(2):168–75.
38. Shaw JH, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. The response to glucose infusion and total parenteral nutrition. Ann Surg. 1987;205(3):288–94.
39. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma. 1987;27(3): 262–6.
40. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med. 1991;325(8):525–32.
41. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ. 2001;323(7316):773–6.
42. Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW. Total parenteral nutrition in the surgical patient: a meta-analysis. Can J Surg. 2001;44(2):102–11.
43. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA. 1998;280(23): 2013–9.
44. Torosian MH. Perioperative nutrition support for patients undergoing gastrointestinal surgery: critical analysis and recommendations. World J Surg. 1999;23(6):565–9.
45. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P. Nutrition support in clinical practice: review of published data and recommendations for future research directions. National Institutes of Health, American Society for Parenteral and

Enteral Nutrition, and American Society for Clinical Nutrition. JPEN J Parenter Enteral Nutr. 1997;21(3): 133–56.
46. Bozzetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L, Bonfanti G, Piacenza S. Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. JPEN J Parenter Enteral Nutr. 2000;24(1):7–14.
47. McClave SA, Martindale R, Taylor B, Gramlich L. Appropriate use of parenteral nutrition through the perioperative period. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):73S–82S.
48. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17.
49. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381(9864):385–93.
50. Doig, G,S., Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. 2013;309(20):2130–8.
51. McMahon MM, Nystrom E, Braunschweig C, Miles J, Compher C, American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), Board of Directors; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. clinical guidelines: nutrition support of adult patients with hyperglycemia. JPEN J Parenter Enteral Nutr. 2013;37(1):23–36.
52. Dechelotte P, Hasselmann M, Cynober L, Allaouchiche B, Coëffier M, Hecketsweiler B, et al. L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: the French controlled, randomized, double-blind, multicenter study. Crit Care Med. 2006;34(3):598–604.
53. Estivariz CF, Griffith DP, Luo M, Szeszycki EE, Bazargan N, Dave N, et al. Efficacy of parenteral nutrition supplemented with glutamine dipeptide to decrease hospital infections in critically ill surgical patients. JPEN J Parenter Enteral Nutr. 2008;32(4): 389–402.
54. Wernerman J, Kirketeig T, Andersson B, Berthelson H, Ersson A, Friberg H, et al. Scandinavian glutamine trial: a pragmatic multi-centre randomised clinical trial of intensive care unit patients. Acta Anaesthesiol Scand. 2011;55(7):812–8.
55. Grau T, Bonet A, Miñambres E, Piñeiro L, Irles JA, Robles A, et al. The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. Crit Care Med. 2011;39(6):1263–8.
56. Andrews PJ, Avenell A, Noble DW, Campbell MK, Croal BL, Simpson WG, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. BMJ. 2011;342:d1542.
57. Ziegler T, May A, Hebbar G, Kudsk K, Sax H, Blumberg H, Easley K, Wischmeyer P. Glutamine dipeptide-supplemented parenteral nutrition in surgical ICU patients: results of an American randomized, double-blind, multicenter trial. Clin Nutr Suppl. 2012;7(1):265.
58. Manzanares W, Dhaliwal R, Jurewitsch B, Stapleton RD, Jeejeebhoy KN, Heyland DK. Alternative lipid emulsions in the critically ill: a systematic review of the evidence. Intensive Care Med. 2013;39(10):1683–94.
59. Umpierrez GE, Spiegelman R, Zhao V, Smiley DD, Pinzon I, Griffith DP. A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. Crit Care Med. 2012;40(6):1792–8.
60. Grau T, Bonet A, Rubio M, Mateo D, Farré M, Acosta JA, Blesa A, Montejo JC, de Lorenzo AG, Mesejo A, Working Group on Nutrition and Metabolism of the Spanish Society of Critical Care. Liver dysfunction associated with artificial nutrition in critically ill patients. Crit Care. 2007;11(1):R10.
61. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr. 1990;14(1):90–7.
62. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, Lobo DN. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62(6):687–94.
63. Kennedy JF, Nightingale JM. Cost savings of an adult hospital nutrition support team. Nutrition. 2005; 21(11–12):1127–33.
64. Trujillo EB, Young LS, Chertow GM, Randall S, Clemons T, Jacobs DO, Robinson MK. Metabolic and monetary costs of avoidable parenteral nutrition use. JPEN J Parenter Enteral Nutr. 1999;23(2):109–13.
65. Shils ME, et al. Long-term parenteral nutrition through an external arteriovenous shunt. N Engl J Med. 1970;283(7):341–4.
66. Dreesen M, Foulon V, Vanhaecht K, De Pourcq L, Hiele M, Willems L. Guidelines recommendations on care of adult patients receiving home parenteral nutrition: a systematic review of global practices. Clin Nutr. 2012;31(5):602–8.
67. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F. ESPEN guidelines on parenteral nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr. 2009;28(4):467–79.
68. Zhao VM, Griffith DP, Blumberg HM, Dave NJ, Battey CH, McNally TA, et al. Characterization of post-hospital infections in adults requiring home parenteral nutrition. Nutrition. 2013;29(1):52–9.
69. Oliveira C, Nasr A, Brindle M, Wales PW. Ethanol locks to prevent catheter-related bloodstream infections in parenteral nutrition: a meta-analysis. Pediatrics. 2012;129(2):318–29.
70. Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. JPEN J Parenter Enteral Nutr. 2006;30(4):351–67.
71. Cahill NE, Murch L, Jeejeebhoy K, McClave SA, Day AG, Wang M, Heyland DK. When early enteral feeding is not possible in critically ill patients: results of a multicenter observational study. JPEN J Parenter Enteral Nutr. 2011;35(2):160–8.

Considerations in Organ Failure

13

Carlos Ortiz-Leyba

Introduction

The presence or development of dysfunction and failure of organs and systems negatively impacts the outcome among severely ill surgical patients. This unfavorable course is the clinical manifestation of an imbalance between an excessive pro-inflammatory action, the systemic inflammatory response syndrome (SIRS), and an excess in the mechanisms of anti-inflammatory regulation, the compensatory anti-inflammatory response syndrome (CARS), leading to an immunoparetic state.

Multiple-organ dysfunction syndrome or multiple-organ failure syndrome (MODS/MOF) becomes a very interesting clinical entity because it raises many questions, a lot of them without definitive answers. In this chapter, we will demonstrate the state of the art of this entity regarding its epidemiology, different physiopathology hypothesis, scoring, clinical manifestations current approach, and treatment with special attention to metabolic and nutritional management.

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The Concept of MODS/MOF

Even though concept of MODS/MOF seems easy to understand and identify, current reality is not so conclusive. Despite the fact that this entity is easily and well known, the origin has been subjected to different theories and presumed mechanisms. In a recent review from Baue identifies more than two dozen types of organ failure. The common framework used to detect MODS/MOF is based on the presence of symptoms, abnormal biochemical and/or hematologic tests, and the perturbations in mean arterial pressure and hourly urine output. Recent Surviving Sepsis Campaign guidelines describes organ failure as a state where organ function is acutely altered, such that homeostasis cannot be maintained without pharmacologic or mechanical interventions; and in its last review [1] describes the criteria to consider organ dysfunction or failure (Table 13.1). However, a conceptual dilemma remains: first, whether organ failure is a consequence of microcirculatory disturbances leading to an imbalance in organ metabolism and oxygen utilization, with severe damage, even death, in cellular structures, as it was initially described [2]; or secondly, if organ failure is due to an adaptive mechanism that allows cells protect organ function by diminishing their metabolism, and allowing a presumable recovery [3] (Fig. 13.1).

This dualism regarding the origin or *primus movens* in the development of MODS/MOF may be partially the result of the chronology and the

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Table 13.1 Definition of organ dysfunctions (Surviving Sepsis Campaign [2])

Organ dysfunction	Variables	Criteria
Pulmonary	Arterial hypoxemia	$PaO_2/FiO_2 < 300$
Renal	Acute oliguria	Output <0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation
		Creatinine increase >0.5 mg/dL or 44.2 μmol/L
Hematological/coagulation	Coagulation abnormalities	INR >1.5 or aPTT > 60 s
		Platelet count <100,000 μL^{-1}
Gastrointestinal	Ileus	Absent bowel sounds
Hepatic	Hyperbilirubinemia	Plasma total bilirubin >4 mg/dL or 70 μmol/L
Tissue perfusion		
	Hyperlactatemia	>1 mmol/L
	Decreased capillary refill or mottling	

PaO_2/FiO_2 partial pressure arterial oxygen/fraction of inspired oxygen, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time

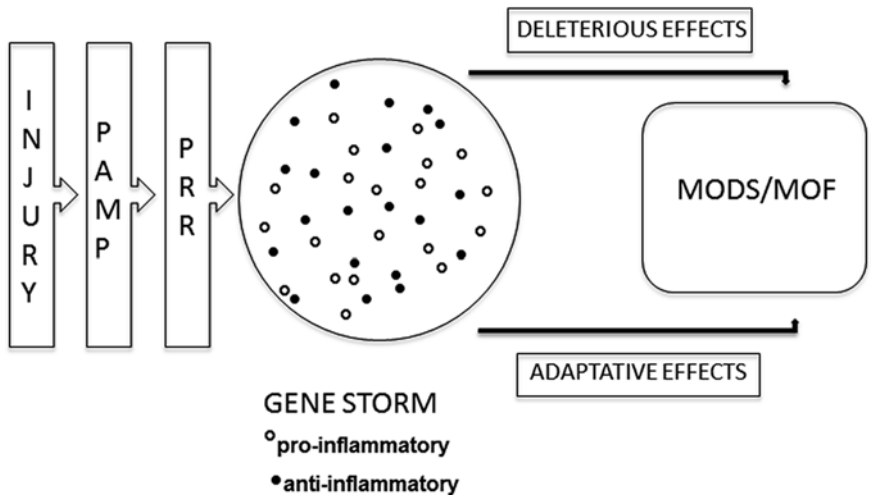

Fig. 13.1 Current organ failure development hypothesis

clinical profile of this entity. Moore et al. [4] were the first authors to refer a biphasic course in the presentation of MOF among trauma patients. They described an early-onset MOF on days 0–3 after the initial trauma, and a late-onset MOF appearing on day 4. Moreover, others authors supported the hypothesis that affected organs in early MOF were lung, heart, and kidney, while on late MOF, liver, nervous system or gastrointestinal tract (GIT) were involved. This resulted in the concept of two-hit theory of MOF, considering GIT as an engine of the second "hit" resulting in the successive failure of organs [5]; according to other authors, the motor would be a nosocomial infection [6]. This theory is now under revision due to observations of different host responses after injury and the universal application of resuscitation protocols to prevent the potential failure of organs and systems.

Another issue to consider is the role of MODS concept as a precursor to MOF, allowing the clinician to apply therapies that would minimize organ damage and potentially restore function. Different prognosis scores around MODS concept have been created, as we will develop later in this review.

Epidemiology and Outcome

Controversy exists around the epidemiology of MOF. Its incidence ranges between 15 and 61 %. Reasons for this variation include differences in patient populations, scoring systems [7], and the clinical period where observations were made. Early observations demonstrated a very high incidence [8], but the latest studies exhibit a trend to a better outlook. Trauma patients have the lowest incidence of MOF ranging from 15 [9] to 25 % [10], in contrast to burn patients where the incidence can reach 40 % [11]. A recent observational, multicenter study performed in 79 ICUs in Spain, and in Latin America, on 7,615 trauma, medical, surgical, and cardiac critically ill patients over a 2-month period noted an incidence of 17.6 % [12].

MOF associated mortality among trauma patients is six- to eightfold higher than in trauma patients without MOF [9, 13]. Morbidity closely parallels mortality as patients with MODS/MOF have more days of mechanical ventilation, longer ICU and hospital lengths of stay and a higher number of nosocomial infections. Mortality is closely related to the number of organs systems that fail, hence a patient with four or more affected organs has a predicted mortality of 100 % [14, 15].

Patients who survive MODS/MOF exhibit greater mortality over time, even after been discharged. In a cohort study of 545 medical-surgical ICU patients with MODS followed for 1 year, global mortality was 52.9 %, 29.5 % in ICU, and 14.8 % at the hospital. Variables associated with delayed mortality include decreased functional condition and the need for readmission at the hospital [16]. In a recent multicenter Scottish study on 872 patients from ten ICUs, authors described a 5-year mortality of 58.2 %, 34.4 % of which were within 28 days. They concluded that cardiovascular, respiratory, and liver failure during their stay were potent independent factors associated with this adverse prognosis [17]. This data supports previous reports demonstrating that patients who suffered MOF had 3.9 times greater odds for assistance in daily activities than those without MOF.

Scoring Systems

As there is no concise definition for MOF different MOF scores systems have been developed to stratify grades of organ dysfunction, and to predict outcome.

The four commonly accepted and applied scoring systems are: the Denver postinjury multiple-organ failure score; the Marshall score, the logistic organ dysfunction system (LODS) score (more commonly utilized in Europe) [18], and the sequential organ failure assessment (SOFA) score [19]. Differences exist among them regarding number of organs and systems to be checked and the grades of severity and limits for each step in each organ system (Table 13.2). The Denver score

Table 13.2 Main differences among organ dysfunction scores

	Denver[5]	Marshall[8]	SOFA[23]	LODS[22]
Grades	0–3	0–4	1–4	Not applicable
Points	0–12	0–24	0–24	0–22
Pulmonary	PaO_2/FiO_2	PaO_2/FiO_2	PaO_2/FiO_2	PaO_2/FiO_2
Renal	Creatinine	Creatinine	Creatinine/urine output	Blood urea nitrogen/ creatinine/urine output
Hepatic	Bilirubin	Bilirubin	Bilirubin	Bilirubin/prothrombin time
Cardiac/cardiovascular	Inotrope dose	PHR	MAP/vasopressor/ inotrope doses	Heart rate/SAP
Coagulation/hematology	No	Platelets	Platelets	Leucocytes/platelets
CNS	No	GCS	GCS	GCS

PaO_2/FiO_2 partial pressure arterial oxygen/fraction of inspired oxygen, *PHR* pressure adjusted rate (Heart rate × Central venous pressure/Mean arterial pressure), *MAP* mean arterial pressure, *SAP* systolic arterial pressure, *CNS* central nervous system, *GCS* Glasgow Coma Scale

considers four organs and four grades; meanwhile LODS, Marshall, and SOFA scores accept six organs or systems and five grades. The definition of grade varies among the former three, moreover the weight of each dysfunction is different. A parameter very useful in these scores is the value *delta*, which means the maximum difference between the initial value and the highest score obtained during the patient's stay; thus it is common to use *delta* SOFA or *delta* MODS.

The Marshall score was validated on surgical ICU patients, and has been found to be a predictive of mortality using both raw score and a delta MODS [8]. These findings were confirmed in a prospective observational cohort study on 1,200 mechanically ventilated patients performed in Canada [20]. The SOFA score has been validated in medical-surgical ICU patients and multiple patient populations (sepsis, cardiovascular, trauma, peritonitis, burns) [21, 22]. Although not designed for prognosis, a SOFA greater than 15 has been correlated with a mortality rate of 100 % according to a multicenter prospective study in 1,449 ICU patients. Furthermore, among the patients who remained in ICU more than 1 week, an increase of the SOFA score was associated with worse outcome [23]. In another multicenter prospective observational study on 1,340 ICU patients with MODS, those with SOFA score 10 or higher for 5 or more and an age greater than 60, had a mortality rate of 100 %.

The LODS score has been developed through a multiple logistic regression on 13,152 ICU patients in 12 countries [18]. The LODS allows the determination of the degree of organ dysfunction, as well as the prediction of mortality. In one French multicenter prospective study on 1,685 ICU patients comparing daily LODS vs. SOFA scores during the first 7 days of stay, both scores displayed good accuracy for both prognosis and the prediction of mortality.

Sauaia et al. [24], in a validation of the Denver and Marshall scores, concluded that both were useful tools but that the Denver score showed a greater specificity for mortality and ventilator free days (higher than 70 %). However, the sensitivity and specificity for days of mechanical ventilation and ICU length of stay in the intensive care unit were under 70 %.

Peres-Bota et al. [25] compared LODS and SOFA scores, and concluded that both were accurate predictors of outcome; nevertheless, patients in shock or with cardiovascular dysfunction, the SOFA score was a better predictor. This difference has also been found in patients with severe traumatic brain injury. In a prospective cohort study, the SOFA scoring system better discriminates both mortality and neurologic outcome [26].

Since MODS/MOF scores have been developed using different modalities (literature reviews, panel of experts, logistic regression), and on varied patient populations (trauma, surgery, mixed ICU, medical), it seems evident that their strength is their stratification of organ dysfunction in general, but their weakness there is a loss of accuracy in specific populations [27]. This is the reason for the development of disease-specific scoring systems.

Disease-specific scoring systems include the Glasgow Coma Scale (GCS) for evaluation of central nervous system dysfunction; risk injury failure end stage renal disease (RIFLE) [28] and acute kidney injury network (AKIN) [29] classification of renal involvement; Child-Pugh score for liver failure [30, 31]; and lung injury score (LIS) for patients with acute respiratory distress syndrome (ARDS) [32].

At this point it should be clear that organ dysfunction scores are not designed for outcome prediction. The Acute Physiology and Chronic Health Evaluation (APACHE) scale, the simplified acute physiology score (SAPS), or mortality probability model (MPM) are better able to predict outcome.

Pathophysiology

General Mechanisms

Dysfunction and/or failure of organs and systems are following multiple different types of injury. Despite this, a detailed and definite knowledge about the pathophysiology remains incomplete, even in the bimodal model proposed by Moore.

However, general mechanisms that uncouple in the presence of MODS/MOF after any of these

entities are quite well known. The inciting event could either be septic or non-septic; nevertheless, both trigger a common inflammatory response through activator molecules, coming from microorganisms or their products, damaged tissues, denatured proteins from dying cells, or even foreign bodies. Those activators, known as PAMP (pathogen-associated molecular patterns), accomplish their activity either directly or through the activation of cytokines and other inflammatory mediators, generating biologic and metabolic effects resulting in the clinical syndrome of MOF.

PAMPs may be divided into microbial origin and non-microbial origins. The best known microbiologic PAMPs are lipopolysaccharide (LPS), lipoteichoic acid, peptidoglycan, phenol-soluble modulin. Non-microbiologic PAMPs include allergens, toxic compounds, and lipoproteins.

Immunologic identification of damaged tissues is mediated by intracellular proteins or by other mediators coming from damaged cells called alarmins. For some authors alarmins and PAMPs together are called damage-associated molecular patterns (DAMP), although for some others DAMP are synonymous with alarmins. Characteristics of alarmins include release from necrotic cells (not apoptotic), or release from living immune cells by means of endoplasmic reticulum or Golgi apparatus. The ability to recruit and activate of other immune cells where receptors are expressed and the capacity to restore lost hemostasis to injured tissues are also characteristics of DAMPs.

DAMPs such as alarmins are recognized by immune cells receptors identified as pattern-recognition receptors (PRR) resulting in activation of innate immunity and a generalized inflammatory response. Many receptors have been described, including triggering receptor expressed on myeloid cells (TREM 1), receptor of advanced glycation end products (RAGE), macrophage scavenger receptor (MSR), K+ channels, CD11/CD18 receptors, CD55, CXCR4 chemokine receptor, CD180, heat shock protein 70/90 Receptor (Hsp70/Hsp90), but the best known are TOLL-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLR), formerly named NOD. PRRs trigger changes in transcription factors; the best known of which is NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), the control of transcription of nuclear DNA, and resulting in altered regulation of genes responsible for both innate and adaptive immune responses.

Activation of host response to injury is independent of the type of stimulus. Adaptive immunity occurs concurrently, once B-cell receptors are activated. Activation and ultimate cellular recruitment are performed by cytokines and some of the alarmins. Cytokine production tends to be brief and time-limited in response to a stimulus. Cytokines can be divided in two big groups, pro-inflammatory (e.g., TNF-a, IL-1b, IL-6, IL-12, IL-17, INF-c) and anti-inflammatory (e.g., IL-1ra, IL-4, IL-6, IL-10, IP10, IL-13, TGF-b, sTNFR p55, p75, sIL-6R), though some of them (e.g., IL-6) can share both characteristics according the inflammatory milieu. In addition to the large constellation of cytokines involved in the inflammatory response, different alarmins have been recognized as active clinical agents [33], including S100 proteins, calcium pyrophosphate dihydrate (CPPD); spliceosome-associated protein 130 (SAP130), uric acid and monosodium urate crystals, DNA, mitochondrial DNA, RNA, ATP, hyaluronan, biglycan, heparin sulfate, formylpeptides, and cholesterol crystals. Among alarmins, it is also worth highlighting heat shock proteins (HSP), high mobility group box 1 (HMGB1), and macrophage migration inhibitory factor (MIF).

Some members of the HSP family, HSP60 and HSP70, can be detected in serum. As signal molecules, they have a global pro-inflammatory activity, but may also attenuate ischemia-reperfusion injury (oxidative injury) and protect endothelial cells from neutrophil mediated necrosis.

HMGB1 is a nuclear protein that binds DNA and modulates transcription and chromatin remodeling, and facilitates the binding of transcription factors and nucleosomes. It is produced by injured, dying, or stressed cells, as well as by macrophages and other immune cells. It is involved in the stabilization of nucleosomes and the facilitation of gene transcription through the modulation of the activity of steroid hormone receptors. MHBGN1 also induces maturation of

dendritic cells and has activity as chemokine, since its effects are also exerted in the endothelium. It binds to TLR4, increasing the release of pro-inflammatory mediators, and interacts with RAGE receptors. It mediates fever and anorexia, and is considered a late mediator of sepsis (8–32 h). High concentrations have been associated with clinical deterioration. HMGB1 can also be considered a trigger in the stimuli which activate innate immunity [34]. In experimental studies, blocking HMGB1 with polyclonal antibodies protects from lethal entodoxinemia and from acute lung injury (ALI). HMBG1 blocking agents may be considered as a therapeutic target.

MIF protein is constitutively expressed in large quantities by epithelial cells of the lung and kidney, immune cells (macrophages, eosinophils), and endocrine cells (pituitary), and is released by following exposure to inflammatory cytokines or bacterial products. It modulates the immune response through TLR4, allowing quick response of macrophages [35]. In situations of severe sepsis and septic shock, high levels of MIF have been detected, activating a pro-inflammatory response and increasing the secretion of cytokines by the upregulation TLR4 expression. MIF represents a putative biomarker and potential molecular target in ALI [36] and is detectable in the alveolar airspaces of patients with sepsis-induced ARDS [37].

MODS/MOF presentation is also related to imbalance in humoral responses. Complement system is clearly involved in this process [38]. Complement may be activated in three different pathways: the classic, mannose-binding lectin, and alternative pathways. All converge at the crossroads C3 to continue the cascade activation. The process releases large amounts of anaphylatoxin C5a. This is a central molecule in the inflammatory response, and exerts its effects through interactions with the C5AR and C5a-like receptor 2 (C5L2) receptors, which are upregulated during sepsis. The synergistic action of C5a and its receptors contributes, at an early state, to the inflammatory activity that turns into expression of tissue factor, and triggers the release of MIF and HMGB1. On the other hand, it facilitates an immunosuppression reaction through an induction of neutrophil dysfunction, and apoptosis of thymocytes and medullary adrenal cells. In animal model of sepsis, the blockade of C5a improved outcome and prevented MOF [39]. In a baboon model of sepsis, the use of the C5a inhibitor compstatin decreased the coagulopathic response by down-regulating tissue factor and PAI-1, reduced fibrinogen, fibrin-degradation products, and APTT, and preserved the endothelial anticoagulant properties [40]. Those findings might have implications on future complement-blocking approach in the clinical treatment of MODS/MOF.

Neural Regulation

The active participation of autonomic nervous system (ANS) in the control of inflammatory response opens new fields and perspectives for the understanding of MODS/MOF physiopathology. Stimulation of the adrenergic system leads to an amplification in pro-inflammatory behavior, particularly during the first steps of injury and organ dysfunction, whereas the activation of cholinergic system prompts an anti-inflammatory trend. Catecholamines released in adrenal glands and in neurons of the sympathetic system act through α and β-adrenergic receptors expressed on different types of cells. In the other hand, anti-inflammatory effects of cholinergic pathway are mediated through α7 nicotinic acetylcholine (ACh) receptors (α7nAChRs) [41]. Vagal nerve stimulation releases acetylcholine that inhibits pro-inflammatory molecules such as HMGB1 and TNF. Activation of the α-7 receptors with nicotine in an animal model of sepsis has shown an improvement of inflammation and an increase on survival [42].

Microvascular Milieu

The molecular storm triggered by host response to injury occurs in the microvascular environment. Normal endothelium performs two essential roles. It regulates blood vessel tone and it actively participates in leucocytes recruitment,

directing them to sites where the cellular damage and inflammation occur. This process is mediated through the expression of adhesion molecules (ICAM, VCAM, ELAM) that are able to bind to leucocyte integrins CD11/CD18 and initiate leukocyte diapedesis and migration through endothelial wall. This process results in high levels of nitric oxide (NO) by monocytes inducible NO synthase (iNOS), which converts L-arginine to L-citrulline. NO acts as free radical and is a modulator of the vascular tone, causing vasodilatation, increased vascular permeability and organ dysfunction. Free radical formation is a result of inhibition of mitochondrial function, leading to a decrease in TPA synthesis and an increase of reactive oxygen species (ROS), generating peroxynitrite. Action of ROS on cells contributes to important changes in release of lipid substrates such as series 2 prostaglandins (PG2) and series 4 leukotrienes (LT4) with additional pro-inflammatory and pro-aggregate activities.

Alterations in the coagulation and fibrinolytic cascades also occur at the level of the endothelium. Pro-coagulant activity is upregulated, mediated by thromboxan A2, plasminogen activator inhibitor (PAI), platelet activating factor (PAF), and von Willebrand factor. There is also an associated downregulation of anticoagulant activity factors, including thrombomodulin, protein C receptor, and tissue plasminogen activator (t-PA).

Metabolic changes at the level of the endothelium, combined with hypoxia leads to intravascular platelet aggregations and microvascular thrombosis, manifesting clinically as fever, chills, tachycardia, tachypnea, agitation, and a subsequently organ dysfunction if homeostasis cannot be restored [43]. The association between organ failure and endothelial cell damage has been established by Shapiro et al. [44] in septic patients, who measured levels of vascular endothelial growth factor (VEGF), a stimulator of permeability, and its receptor sFLT. They concluded that sFLT levels correlated with measured initial SOFA and SOFA at 24 h; VEGF and sFLT levels also correlated with inflammatory cascade activation. A second study by the same investigators, performed in patients with sepsis further supports the strong role of the microcirculation in the genesis to MODS/MOF. They measured a broad panel of endothelial activation markers including sVCAM-1, sICAM-1, sE-selectin, PAI, VEGF and sFLT-1, and found an association between endothelial activation and subsequent organ dysfunction and mortality. sFLT-1 was the marker with the strongest association with SOFA score [45]. Animal models also demonstrate a relationship between high levels of angiopoietin-2 (Angpt-2), an endothelial protein released upon inflammatory stimulation, and SOFA measurements [46]. Sakr et al. [47] measured microcirculatory perfusion on 46 patients with septic shock and noted that decreased microcirculatory flow was associated with the development of multiorgan failure and death. With the same methods, Trzeciak et al. [48] stated that an increase of microcirculatory flow during resuscitation was associated with reduced organ failure.

Consequently, derangement of microcirculation seems to play a very important role, as the first hit in the presence of multiple-organ failure, while late multiple-organ dysfunction may be associated with mitochondrial failure [49].

Mitochondrial Role

Mitochondrial function has emerged as one of the cornerstones of MODS/MOF genesis. Release of pro-inflammatory cytokines and other mediators, together the release of great amounts of NO and ROS, and a maldistribution of macrovascular and microvascular blood flow, affects the mitochondrial function and energy production. If the inciting stimulus continues, mitochondrial energy is severely compromised, a situation which may be reversed by regeneration of new mitochondria as the patient enters in a recovery state [50].

The classic interpretation of decreased mitochondrial function is that cells die and organs fail due to a lack of energy, but an alternative hypothesis has been postulated by Singer [51], based in the observation that cell necrosis is not a key feature of the response to sepsis. Singer proposed that the decline in mitochondrial function is a protective response, with cells entering

a hibernation-like state, and MODS/MOF would be a manifestation of the "physiologic shutdown." This process could be reversed with the generation of new functional mitochondria and a recovery of energy, subsequent metabolic restoration, and clinical improvement. This regeneration, called biogenesis, seems to be triggered by NO production and mitochondrial DNA oxidative damage [52]. In the other hand, if sepsis persists, hibernation stops being playing an adaptive and potentially protective role, and shifts to a pathologic and harmful situation.

Others have supported this hypothesis. Haden et al. [53], in a murine model of peritonitis, found during recovery an increase in the mitochondrial biogenesis with restoration of oxidative metabolism. Brealey et al. [54], in a study based on skeletal muscle biopsies on 28 septic ICU patients, reported an association between NO overproduction, antioxidant depletion, mitochondrial dysfunction, and decreased ATP concentrations related to organ failure and outcome.

Carré et al. [55] studied biogenesis responses in muscle biopsies on 16 critically ill patients with MOF, at their admission to ICU, vs. 10 patients submitted to elective hip surgery as control group. Their study showed that muscle mitochondrial capacity was decreased soon after ICU admission, especially among non-survivors. However in the group of ICU survivors, early mitochondrial biogenesis and antioxidant defense responses were found. These authors conclude that an over-exuberant response to sepsis could increase susceptibility to mitochondrial damage, cellular energetic dysfunction, and would prevent the recovery of normal function.

However, criticism has arisen due to the heterogeneity of the body of evidence. Diversion among the methodology of different studies on mitochondrial dysfunction has prompted criticism of the proposed theories and interpretation of the conclusions. As has been pointed out by Jeger et al. [56], a consensus definition for "mitochondrial dysfunction" seems to be missing. Even in human studies, only the musculoskeletal and circulatory systems have been studied, although MOF affects numerous other organ systems. Answers to these questions need new tools for mitochondrial function assessment such as dynamic and biological tests providing new and complementary information.

Genomics

Recent genomic studies have contributed to a new understanding to physiopathology and timing of MOF. The generally accepted biphasic "two hit" model, fueled by gastrointestinal tract dysfunction (GITD), by nosocomial infection, or by new surgery, must be revisited due to new insights related to the expression of pro and anti-inflammatory genes.

Xiao et al. [57] studied a cohort of 167 adult severe blunt trauma patients who presented in shock requiring transfusion and evaluated the leukocyte transcriptome at several time points over 28 days. The authors found the expression of more than 80 % of leucocyte transcriptome was significantly altered in a way described as "genomic storm," changes that occurred rapidly (4–12 h) and continued for days and weeks. The "genomic storm" included both inflammatory and anti-inflammatory gene upregulation and was independent of inciting stimulus (trauma, burns, low dose of endotoxin). Moreover, the gene profile showed similar behavior despite patient outcome (complicated and uncomplicated recovery). These authors propose a new paradigm for the inflammatory response where changes in the expression of systemic inflammatory genes, and anti-inflammatory and adaptive genes, occur early and concurrently, not sequentially. Interestingly, complicated recovery is not related to a different leucocyte transcriptome pattern, but with a prolongation in this gene expression profile [58]. This paradigm reappraises the classical diagram of two curves explaining SIRS, CARS, MOF and outcome, and substitutes it by a new model. Partially based in this concept, Gentile et al. [59] have coined a new clinical entity they called "persistent inflammation-immunosuppression catabolism syndrome" (PICS), encompassing those ICU patients who remain with manageable organ dysfunctions but usually do not meet established criteria for late

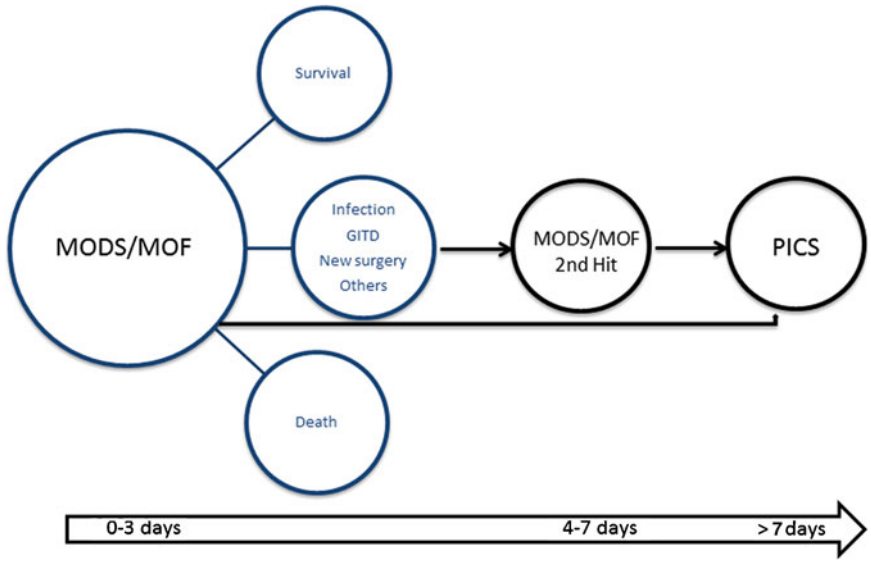

Fig. 13.2 Proposed timeline in organ failure outcomes. Abbreviations in the text.

MOF (Fig. 13.2). Poor nutritional status, poor wound healing, immunosuppression, and recurrent infections characterize their clinical course.

Clinical Presentation

Lung

The lung is one of the most frequently affected organs in the course of MODS/MOF. Pulmonary dysfunction has been well studied since the study of Asbaugh et al. in 1967 [60]. Its incidence has reached approximately 190,000 cases per year in the United States [61], and mortality in the more severe forms is 40–60 %. Its clinical presentation was formerly classified by the American-European Consensus Conference Committee [62] as ALI if $PaO_2/FiO_2 < 300$, and ARDS if $PaO_2/FiO_2 < 200$. Nevertheless, this definition has been very recently changed. However these definitions have been revised by the European Society of Intensive Care Medicine, the American Thoracic Society, and the Society of Critical Care Medicine [32] in order to improve case recognition and better match treatment options to severity, in both research trials and clinical practice [63]. In the new classification ALI concept disappears and ARDS is classified as: mild ($200 < PaO_2/FiO_2 \leq 300$ with positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cm H_2O); moderate ($100 < PaO2/FiO2 \leq 200$ with PEEP ≥ 5 cm H_2O); and severe ($PaO_2/FiO_2 \leq 100$ with PEEP ≥ 5 cm H_2O).

The inflammatory response and resultant increase in lung vascular permeability promote an alveolar invasion of activated neutrophils, red blood cells, and fibrin-rich fluid, resulting in damage to alveolar epithelium and a denuded alveolar basement membrane with loss of type I cells [64]. This drives the formation of hyaline membranes, inactivation of surfactant, and finally collapse of the alveoli [65].

Clinically, ARDS is manifested as a rapid onset of respiratory failure due to arterial hypoxemia that is refractory to treatment with supplemental oxygen. Radiological findings include bilateral infiltrates described as patchy or asymmetric, with or without including pleural effusions, consolidation, and atelectasis. If ARDS progresses, an increased alveolar dead space and a decrease in pulmonary compliance result.

Kidney

The kidney is a commonly affected organ in MODS/MOF. The prevalence of acute kidney injury/failure is approximately 60 % in patients with MODS/MOF [28], with associated mortality rates between 26 and 64 % [66].

A previous definition for acute renal failure (ARF) was developed following RIFLE criteria [67]. Recently, a newer definition of AKI has been coined [68], and finally, a new consensus from the kidney disease: improving global outcomes (K-DIGO) group [69] has been issued to address the entire spectrum of ARF. Diagnostic criteria for AKI are a reduction (within 48 h) in kidney function currently defined as an absolute increase in serum creatinine of greater than or equal to 0.3 mg/dL (≥26.4 μmol/L), an increase in serum creatinine of greater than 50 % (1.5-fold from baseline), or documented oliguria of less than 0.5 mL/kg/h for more than 6 h. The Consensus Conference has also proposed a three grade staging system based on quantitative changes in serum creatinine and urine output (based on RIFLE criteria).

The pathophysiology of AKI is uncertain and factors such as hypovolemia, inflammatory response, neuronal mechanisms, coagulopathies, renal arterial vasoconstriction have been implicated. Sepsis, major surgery (especially open heart surgery), and acute decompensated heart failure are also common triggers of acute kidney injury [70].

As AKI is often a result of renal hypoperfusion, rapid resuscitation is best first step in the treatment of AKI. Ideally, one or more biomarkers would exist to aid in the early identification of AKI Biomarkers under study include urinary neutrophil gelatinase-associated lipocalin (uNGAL), urinary hepatocyte growth factor (uHGF), urinary cystatin C (uCystatin C), kidney injury molecule-1 (KIM-1), *N*-acetyl-β-D-glucosaminidase (NAG), monocyte chemotactic peptide (MCP-1), Il-18, liver-type fatty acid-binding protein (L-FABP), and netrin-1. According to early results, these markers can identify patients with a renal dysfunction prior to the development of a high creatinine level [71] and they may increase the possibility for recovery [72]. Moreover, it has been suggested that they could reflect different etiologies of AKI. Cystatin C can predict changes in glomerular filtration rate, whereas neutrophil gelatinase-associated lipocalin is related to tubular stress or injury [73]. At present, it is necessary to better understand these biomarkers before adopting them in current clinical practice [73].

Cardiovascular System

The cardiovascular system can be affected via myocardial dysfunction, refractory peripheral vasodilatation, or a combination of the two.

Septic injury often results in cardiovascular derangement, and neural mechanisms may be implicated as cardiac autonomic dysfunction, clinically displayed as rhythm disturbances. Cardiac myocytes may be also directly damaged by PAMP such as endotoxin [74] and by NO and its substrate peroxynitrite which induce mitochondrial impairment and a diminished cardiac contractility. This septic cardiomyopathy is characterized by a global cardiac enlargement with biventricular contractility impairment, and a striking reduction in left ventricular (LV) ejection fraction and stroke work index [75]. A good biomarker for diagnosis and for assess the degree of ventricular dysfunction are troponins.

Vascular dysfunction is characterized by microvascular and endothelial impairment, decreased vasoconstrictor tone and a vascular hyporesponsiveness to vasopressor agents [76] resulting in resistant hypotension. Involved mechanisms seem to be the same as in cardiac dysfunction, with a preponderant role for NO and its metabolites. However, adrenal insufficiency, anomalous catecholamine signaling, damaged potassium channels, even hyperglycemia are factors that could be also implicated [77].

Nervous System

Neurological dysfunction in MODS/MOF is represented by two different entities, residing each

one in different zones in the nervous system. Disturbances in mental status, confusion, delirium, even coma are very frequent in severe sepsis and septic shock [78]. Sepsis-associated encephalopathy (SAE) occurs in up to 87 % of septic patients, and is of unknown pathophysiology. Putative etiologies include aromatic amino acids and cytokines crossing blood–brain barrier, oxidative stress, or decrease of cerebral blood flow. Electroencephalogram is a sensitive test for the diagnosis of SAE when the patient is sedated and mechanically ventilated, while biomarkers such as S100B protein could be also useful but need more study prior to widespread clinical use. SAE is potentially reversible, but its presence is a poor prognostic indicator [79].

The other great complication in neural dysfunction axonal polyneuropathy named critical illness polyneuropathy (CIP), resulting in generalized weakness and difficulty weaning from mechanical ventilation. As in the case of SAE, its origin and pathophysiology remain unknown, although hyperosmolality, parenteral nutrition, non-depolarizing neuromuscular blockers, and neurologic failure are associated with its development. CIP is significantly associated with an increase in the mortality [80], duration of mechanical ventilation and in the lengths of intensive care unit and hospital stays [81].

Gastrointestinal Tract

The gastrointestinal tract (GIT) is a commonly affected organ in MODS/MOF, caused variably by compromised blood flow, structure damage, inappropriate cell function, alteration of metabolic activity, and impairment of the gastrointestinal barrier itself [82]. The effects of MODS/MOF on intestinal absorption are not fully understood.

Intestinal absorption of amino acids is regulated by three mechanisms: quantity of intraluminal substrate, capacity of the transport systems, and ability of the enterocyte to metabolize the substrates. This absorption is impaired as demonstrated by Gardiner & Barbull [83] in a model of septic rats, where a decrease in the intraluminal concentration of amino acids (arginine, leucine, and proline) occurred. Intestinal transport of amino acids has been studied in septic patients by analyzing the vesicles on the edge of the intestinal lining [84], and the release of glutamine, alanine, and leucine were considerably decreased with respect to the control group. The transport of substrates through intestinal wall is also inhibited as a result of the decrease of mesenteric blood flow and subsequently, owing to an increase of anaerobic metabolism, there may be decreased stores of ATP and reduced active transport of intraluminal substrates.

Both mechanisms reduce the ability of the intestinal lumen to absorb nutrients, and this event can limit the availability of intracellular substrates for the maintenance of metabolic functions and the enterocyte barrier [85]. Consequently, the reduced intestinal absorption in MODS/MOF may limit the use of enteral feeding. If we also consider the fact that malnutrition is common in these patients and that there is often a gastrointestinal paresis or dysfunction, it is clear that nutritional requirements often cannot be met and it is necessary to resort to total or supplementary parenteral feeding [86], even though this type of mixed feeding has been criticized by some researchers [87].

A very interesting controversy is to consider gastrointestinal failure (GIF) as a motor for development of secondary MOF since GIT lumen is loaded with a great number of bacteria and an increase of permeability would allow a massive translocation of bacterial products. This hypothesis, raised by Marshall et al. [5], considered gut as an “undrained abscess” and bacterial translocation is supported by different experimental studies [88]. Although inflammatory GIT damage, bacterial translocation, and development of subsequent failure of other organs become a frequent clinically found association, causality has not been proven. It is possible that the increase of the GIT permeability and translocation are epiphenomenons that occur alongside to other organ dysfunctions and not its motor. In a recent study, aiming to develop a GIF score for 28-day mortality prediction of ventilated patients [89], authors concluded GIF is often secondary and not the primary cause of other organ failure.

This conclusion leads to another important issue in GIF, the need of a definition and the development of a specific score for stratifying and, if possible, predicting this organ dysfunction. The search for accurate markers has not yielded satisfactory results, although plasma citrulline, an amino acid mainly synthesized from glutamine by enterocytes, has been studied as possible marker for small bowel function [90]. Their clinical utility in diagnosis and management of GI dysfunction (GITD) remains to be verified. Currently, two types of GITD are seen in MOF, intra-abdominal hypertension (IAH) [91] defined by a sustained increase in intra-abdominal pressure equal to or above 12 mmHg as measured by bladder pressures; and the presence enteral feeding (EF) intolerance. Malbrain and De Laet [92] coined the term Acute Intestinal Distress Syndrome based on IAH measurements. Reintam et al. [93] elaborated a GIF score based upon the occurrence of feeding intolerance and IAH, ranging from level 0 (normal gastrointestinal function) to level 4 (abdominal compartment syndrome) based on a prospective, single-center, study on 264 mechanically ventilated. They concluded that mean GIF score during the first 3 days had a prognostic value for ICU mortality. Nevertheless, since feeding intolerance is a subjective measurement, an expert panel published of the results of a Conference Report defining terminology, definitions, and management of GI function in ICU setting [94]. In this consensus of the ESICM Working Group on Abdominal Problems, acute gastrointestinal injury (AGI) has been scored with four grades of severity: grade I = increased risk of developing GI dysfunction or failure (a self-limiting condition); AGI grade II = GI dysfunction (a condition that requires interventions); AGI grade III = GI failure (GI function cannot be restored with interventions); and AGI grade IV = dramatically manifesting GI failure (a condition that is immediately life-threatening). They also defined Primary AGI as associated with primary disease or direct injury to organs of the GI system, and Secondary AGI when developed as the consequence of a host response in critical illness without primary pathology in the GI system. Feeding Intolerance syndrome (FI) defined as a failure to tolerate at least 20 kcal/kg BW/day via enteral route within 72 h of feeding attempt or if enteral feeding had to be stopped for whatever clinical reason. Finally definitions for GI symptoms, and their respective managements, have been delineated: vomiting, gastric residual volume, GI bleeding, diarrhea, lower GIT paralysis, abnormal bowel sounds, and bowel dilatation.

An attempt to test the hypothesis that symptoms of GI dysfunction could be used as predictors separately and/or as part of SOFA was unsuccessful [69] as a valid GI dysfunction score does not improve its accuracy.

Liver

Liver dysfunction in MODS is less frequent than pulmonary, cardiovascular, or renal dysfunction. This is in some way surprising because crucial metabolic and immunological pathways occur in the liver. Moreover, it produces and releases high amounts of inflammatory substrates such as cytokines, bioactive lipids, and acute phase proteins [95].

Early dysfunction occurs within hours after injury and, produced by hepatosplanchnic hypoperfusion, resulting in acute increases in transaminases, lactate dehydrogenase, and bilirubin, and is often reversible with adequate resuscitation. Late dysfunction is caused by inflammatory molecules and/or sterile DAMP, and characterized by structural and functional injury [96]. The liver is an organ with large populations of Kupffer cells and natural killer (NK) cells that are able to induce a high rate of expression of endothelial adhesion molecules [97]. It is remarkable that late hepatic failure has increased production of inflammatory cytokines in the hepatosplanchnic area, despite increased hepatic blood flow [98]. Dysfunction in the GI tract is also a putative mechanism of liver dysfunction. Contributing agents for this gut-liver axis [99] would be intestinally induced cytokines.

Hematological System

Imbalance in the pro-coagulant and anti-fibrinolytic states may lead to the development of disseminated intravascular coagulation (DIC), resulting in increased mortality due to microvascular thrombosis and resultant end-organ ischemia. Fortunately, DIC is much less frequent than isolated thrombopenia or abnormal clotting times, but its diagnosis may be influenced by the different scores used by clinicians (JMHW DIC [100], ISTH overt DIC (ISTH DIC) [101], and JAAM DIC [102]). The three scoring systems have been evaluated [103] in a prospective study on 413 patients with different underlying diseases of DIC, and results displayed a high sensitivity with JAAM score, and high specificity ISTH overt-DIC diagnostic criteria. The three DIC scores may prognosticate poor patient outcome depending on the studied population [104].

Metabolic Disturbances

Metabolic disturbances in MODS/MOF are highly dependent on timing, the inflammatory status, and organs affected. The ebb and flow proposed by Cuthbertson [105] may not be relevant to the early resuscitation of patients. Metabolic derangements are characterized by the hypermetabolic response defined by Cerra [106] composed of hyperglycemia, increased protein catabolism, hyperlactacidemia, increased lipolysis, and hypertriglyceridemia. Hyperglycemia requires careful management and has gained significant attention due to its recognized association with increased mortality and morbidity [107]. Hypoglycemia, associated with hepatic failure, is a poor prognostic indicator.

Protein catabolism is fueled by the needs for gluconeogenesis, substrates for wound repair, acute phase reactants production, and substrates for enterocytes and immune cells. Urinary urea nitrogen excretion is greatly augmented in the first days of injury, especially in burns and trauma where catabolic daily losses higher than 25 g. are not uncommon.

Increased pro-inflammatory cytokines, mainly TNF, block some enzymes such as lipoprotein-lipase and contribute to a decrease of free fatty acids and a hypertriglyceridemia in a direct proportion to the severity of injury.

Resting energy expenditure (REE) is strikingly elevated at the initial phases of MODS/MOF [108], but as dysfunction progress, REE requirements decline [109]. In the same manner, albumin and hepatic protein synthesis are down-regulated. These observations determine nutritional support, as we shall detail below.

Treatment

General Management

Treatment of MODS/MOF is based on three arms: prevention of its appearance, adequate resuscitation to avoid progression if present, and selective organ support.

For prevention, an adequate fluid and oxygen support optimize oxygen delivery to tissues are mandatory. At the same time, any potential or real source of injury has to be addressed in a rapid fashion. According to Surviving Sepsis Campaign[2] intervention has to be undertaken within the first 12 h after the diagnosis, if feasible, including, necrotizing soft tissue infection debridement, any emergency surgical procedure, burn wound excision, removal of suspected intravascular access devices, etc. If severe sepsis is present, appropriate empiric antibiotic treatment needs to be administered within the first hour of the recognition. Moreover, selective decontamination of the digestive tract (SDD) reduces the number of patients with multiple-organ dysfunction syndrome [110], although this treatment is controversial and no consistent improvement in mortality has been demonstrated. Blood transfusions should be avoided and a restrictive transfusion policy established [111]; even among critically ill non-bleeding patients with moderate anemia, red blood cell transfusion has no demonstrable benefits [112]. Glucose control is imperative since hyperglycemia has been associated to MODS/

MOF through a mechanism of mitochondrial damage [113].

Once organ dysfunction is present, adequate resuscitation to preserve microcirculation and cellular metabolism is necessary. Careful hemodynamic monitoring, judicious use of vasopressors and fluids, and an approach minimizing the initial metabolic derailment are cornerstones in the management in this phase. The use of algorithms and criteria for early identification in organ disorder may be useful [114].

There have been several recent criticisms about routine interventions in the setting of MOD/MOF. A meta-analysis of Marik & Cavallazzi [115] has categorically disqualified the use of central venous pressure (CVP) as a guide for fluid therapy. The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee concluded that solutions containing hydroxyethyl starch (HES) are associated to a greater risk of kidney injury requiring dialysis and had a greater risk of mortality and recommended suspension of marketing authorizations for these solutions [116]. Norepinephrine is preferred over dopamine as the first-choice vasopressor, based on evidence that dopamine in septic shock is associated with an increased risk development of arrhythmias and death compared to norepinephrine [117]. β-2 agonist treatment in patients with ARDS should be limited to the treatment of important reversible airway obstruction but not in routine therapy; a multicentre, placebo-controlled, parallel-group, randomized trial on ARDS patients treated with intravenous salbutamol vs. a control group (BALTI-2 study), was stopped after the second interim analysis because an increased 28-day mortality. These results were concordant with previous where aerosolized albuterol in ALI was used [118].

Individual organ support is important and is restricted to pulmonary, cardiovascular, and renal support. Hematological failure can be restored with blood product administration. Recent recommendations about mechanical ventilation of ARDS have been issued regarding recommended tidal volume, plateau pressure, PEEP, recruitment manoeuvres, and patient positioning [2]. Renal replacements therapy can be instituted either by continuous renal replacement therapies or by conventional hemodialysis but the first issue is preferred in hemodynamically unstable patients [2]. Extracorporeal Membrane Oxygenation (ECMO) is only suggested for children with refractory respiratory failure of septic origin but it is not recommended for adults. Intra-aortic balloon pump (IABP) counterpulsation and left ventricular assist devices (LVAD) have rare indications in cardiac support for patients with secondary MODS/MOF and are reserved for primary and isolated refractory cardiac failure.

Nutritional and Tailored Substrates Support

Metabolic and nutritional support of these patients is one most complex challenge in the field of critical care. Strategies must take in account at least two considerations, the current inflammatory state and how many organs and at what extent are at failure or dysfunction. These considerations discourage the use of so-called "nutrients soup" formulations commercially labeled for injury or sepsis or MODS/MOF, and they justify the rationale for tailored substrates support.

The clinician's approach nutritional repletion needs to consider if patient is in a pro-inflammatory state or in an immunoparetic period. At the first situation, substrates and formulations that are associated with a decrease of the inflammation have to be used; in the other hand, if patient is under CARS, immunostimulating formulas are appropriated (Table 13.3) as substrates can act as pharmaconutrients instead of simple nutrients [119]. For example, arginine may be appropriate early in the course of inflammation, inappropriate at the peak of systemic inflammation, and again appropriate in the recovery phase [120].

There is however a lack of studies on this topic of isolated substrates, as the great majority has been performed with commercially mixed formulations, and to extrapolate those results for the behavior of one particular substrate is difficult.

Table 13.3 Conditioning factors in the administration of nutritional support in organ dysfunction

Limitations	Consequences
Phase of inflammatory response	Immunoregulators/immunostimulants
Available commercial formulations	Lack of studies with isolated nutrients
Prominence in organ dysfunction	Tailored pharmaconutrition according to clinical situation

Other challenges include directing nutritional support to address single vs. multiple-organ systems in failure.

Finally, and as an added problem for this issue, the presence of hyperglycemia requires careful control and may sometimes impact caloric support.

Arginine

Data regarding arginine repletion is conflicting. Some authors proposed that arginine should be avoided in infected critically ill patients, based on a meta-analysis [121] which concluded in infected critically ill patients immunonutrition may be harmful. The theory was based on the hypothesis of an overproduction of NO through arginine negatively impacts outcome. Other studies have demonstrated that plasma concentrations of arginine are clearly decreased in patients with sepsis in the absence of trauma or surgery [122].

Glutamine

Glutamine has long been well regarded in the nutritional support of injury, not only because it is an essential amino acid, but because its use has been associated with good outcomes in critical illness. Low plasma glutamine concentration is an independent predictor of poor. Wernerman et al. [123] in a multicenter, controlled, randomized, double-blind placebo-controlled study of intravenous glutamine administration tested the hypothesis that this support could improve SOFA scores and mortality. This study demonstrated lower mortality in the treatment arm, without significance when they were studied by intention to treat. Glutamine administration did not alter serial SOFA scores.

In another randomized, controlled, and double-blind study, glutamine supplementation did not reduce appearance of new infections, 6 months mortality, length of stay, SOFA score, nor the use of antibiotics [124].

However, a recent study demonstrated that glutamine repletion was associated with a reduced rate of infectious complications and a better glycemic control than the control group. However, there were no changes in SOFA, ICU and hospital length of stay, or mortality [125].

A recent multicenter, randomized, 2-by-2 factorial trial was performed on multiple-organ failure patients receiving mechanical ventilation who received nutrition supplemented with glutamine, antioxidants, both, or placebo (REDOXS) [126]. The primary outcome was 28-day mortality. Results were striking in that there was a trend toward increased mortality at 28 days among patients in the study group vs. control group (32.4 % vs. 27.2 %; adjusted odds ratio, 1.28; 95 % confidence interval [CI], 1.00–1.64; $P=0.05$). Hospital morbidity and mortality at 6 months were significantly higher among those who received glutamine. They did not find any effect of glutamine on rates of organ failure or infectious complications. This study has aroused great controversy among scientific community. Criticism is mainly directed at the potential toxicity of the amount in glutamine support (60 % of total dietary protein), and in a presumed bias in allocation of patients according to the number of failing organs at baseline. According to REDOXS study, recommendations about glutamine support are maintained in EN in burn and trauma patients but a caution in patients with shock and MOF, given the possibility of increasing mortality.

Lipids

Omega-6 polyunsaturated fatty acids (ω-6 PUFA) are essential and required in the inflammatory response. In a recent study on patients with sepsis compared to healthy controls, arachidonic acid (AA) concentrations were more reduced among septic patients [127]. Gene expression studies confirmed a reduction of the induction of the expression of messenger RNA of cyclo-oxygenase 2 (COX-2). Likewise, authors concluded that reduction in the release of AA, and its metabolites, 11-HETE, PGE2, and TXB2 was associated with worse outcome.

Monounsaturated fatty acids (ω-9MUFA) and oleic acid metabolites are generally considered as less active than ω-6 PUFA in the setting of injury and organ failure. In a study of 100 critically ill mostly surgical patients receiving PN, and were randomly assigned to receive emulsions of soybean oil (ω-6) or olive oil-based fat emulsion (ω-9), did not demonstrate significant effects on mortality, length of stay, rates of infectious and noninfectious complications, glycemic control, oxidative stress markers, immune function and inflammatory markers [128].

These results confirm a previous, observational and prospective study [129], on a smaller number of critically ill patients receiving to PN, without differences between the control group (soybean oil) and the study group (olive oil-based fat emulsion), with regard to infection rate, variations on the protein levels of acute phase, clinical variables (stay, mortality), and leukocytosis. In fact, the study group had a trend toward greater leukocytes, challenging the assumptions that ω-9 have either a presumed anti-inflammatory or neutral effect.

Polyunsaturated fatty acids (ω-3 PUFA) have been studied in patients in MOF with ALI or ARDS. In a recent multicenter, controlled and randomized phase II trial patients received either enteral fish oil (9.75 g Eicosapentaenoic acid + 6.75 g Docosahexaenoic acid) or saline in EN. Outcome measures were the quantification of interleukin-8 levels in bronchoalveolar lavage. Authors concluded that fish oil did not reduce biomarkers of pulmonary or systemic inflammation in patients with ALI.

Rice et al. performed a randomized, double-blind, and multicenter placebo-controlled OMEGA study on patients with respiratory failure [130], to determine if the supplementation of the diet with ω-3 PUFA, γ-linolenic acid, and antioxidants would increase mechanical ventilation-free days. The study was stopped for futility and the authors concluded that supplementation did not improve the clinical outcomes of patients with ALI and may be harmful.

Another randomized, multicenter study examined the effects of an enteral diet enriched with Eicosapentaenoic acid, γ-linolenic acid, and antioxidants on the incidence of organ dysfunction and nosocomial infections in patients with respiratory, against a control group with standard enteral nutrition [131]. Results showed that there were not differences in PO_2/FiO_2 ratio, mechanical ventilation days or nosocomial infection rate.

Future Options

After more than a decade searching a magic bullet to block the inflammatory process has generated plenty of conflicting results, research is being directed to new approaches and new targets.

Inhibition of C5a in MODS/MOF of septic origin is promising, with preliminary results in rheumatoid diseases [132]. Mesenchymal stem cells may have an application due to the large number of studies supporting an immunosuppressive function of these cells [133] through production of activated molecules that enhance repair [134, 135].

Regulation of neural pathways is other promising strategy. ACE-inhibitors [ACEI] are known to ameliorate depressed autonomic function (heart rate variability [HRV]) and improve endothelial function; in an retrospective study on 178 MODS patients, ACEI treatment was associated with lower short- and longer-term mortality compared with patients without ACEI [136].

On the side of mitochondrial therapies, different therapies have been proposed targeting membrane stabilization, mitochondrial ROS scavenger, mitochondrial antioxidants, substrate

and/or cofactor provision, with promising results in different [137] experimental studies.

The horizon for MODS/MOF therapy could be altered by advances in gene therapy [138], tissue regeneration and molecular reprogramming, in the term health engineering proposed by Cobb [139], where a joint approach of critical care, systems sciences, molecular engineering, computational biology, and applied mathematics would work for improving prognosis issues.

Conclusion

The appearance of MODS/MOF in the outcome of surgical patients is always a concern for clinician. Its presence is clearly associated with a worse prognosis and a heavy burden for hospital costs, although frequency and mortality are fortunately decreasing. MODS/MOF has been always contemplated to be initiated by an inflammatory response, but a different approach considering it as an adaptive mechanism mediated by mitochondrial switch off against the initial injury is gaining ground. Both may be present in the timeline of the process, and it could explain, together with the recent advances in genomic response, the revisited concept of late MOF and a new consideration for PICS. All the scoring systems lack sensitivity and specificity and are poor tools for prognosis. Several studies have produced an important advance in the knowledge of pro and anti-inflammatory pathways and their modulation. Potential therapeutic implications have been demonstrated, such as neural regulation or mitochondrial role, and new attempts have been made to evaluate the behavior of the microcirculation and tissue perfusion. In the clinical setting, a renewed interest in the validation of diagnosis criteria is taking place with new definition for ARDS, GIT failure, and AKI; and a searching for biomarkers that may detect dysfunction at early phase is underway. Regarding to treatment, search for a magic bullet has been abandoned and the efforts are directed to prevention and resuscitation. Several therapeutic postulates have been challenged, affecting not only resuscitative fluids but also metabolic and nutritional support. Fortunately, new targets for future therapies are emerging, as is the case for gene modulation, mesenchymal stem cells application, or different lines on mitochondrial therapies.

References

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal S, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165–228.
2. Eiseman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet. 1977;144:323–6.
3. Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet. 2004;364(9433):545–8.
4. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40:501–10.
5. Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract. The "undrained abscess" of multiple organ failure. Ann Surg. 1993;218(2):111–9.
6. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med. 2012;40(4):1129–35.
7. Brattstrom O, Granath F, Rossi P, Oldner A. Early predictors of morbidity and mortality in trauma patients treated in the intensive care unit. Acta Anaesthesiol Scand. 2010;54:1007–17.
8. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, et al. Epidemiology of trauma deaths: a reassessment. J Trauma. 1995;38(2):185–93.
9. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. J Trauma Acute Care Surg. 2013;74(3):774–9.
10. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Arch Surg. 2005;140(5):432–8.
11. Kallinen O, Maisniemi K, Böhling T, Tukiainen E, Koljonen V. Multiple organ failure as a cause of death in patients with severe burns. J Burn Care Res. 2012;33(2):206–11.
12. Cabré L, Mancebo J, Solsona JF, Saura P, Gich I, Blanch L, et al. Multicenter study of the multiple organ dysfunction syndrome in intensive care units: the usefulness of Sequential Organ Failure Assessment scores in decision making. Intensive Care Med. 2005;31:927–33.
13. Ulvik A, Kvale R, Wentzel-Larsen T, Flaatten H. Multiple organ failure after trauma affects even

long-term survival and functional status. Crit Care. 2007;11(5):1–8.
14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. Ann Surg. 1985;202(6):685–93.
15. Zimmerman JE, Knaus WA, Sun X, Wagner DP. Severity stratification and outcome prediction for multisystem organ failure and dysfunction. World J Surg. 1996;20(4):401–5.
16. Hortigüela-Martín VA, Sanchez-Casado M, Rodríguez-Villar S, Quintana-Díaz M, Marco-Schulke C, Gómez-Tello V, et al. Post-Intensive Care Unit mortality and related prognostic factors in a cohort of critically ill patients with multi-organ dysfunction. Med Clin. 2013;140(11):479–86.
17. Lone NI, Walsh TS. Impact of intensive care unit organ failures on mortality during the five years after a critical illness. Am J Respir Crit Care Med. 2012;186(7):640–7.
18. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D. ICU Scoring Group. The logistic organ dysfunction system: a new way to assess organ dysfunction in the intensive care unit. JAMA. 1996;276:802–10.
19. Vincent JL, Moreno R, Takala J, Willatts S, de Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–10.
20. Cook R, Cook D, Tilley J, Lee KA, Marshall J. Multiple organ dysfunction: baseline and serial component scores. Crit Care Med. 2001;29(11): 2046–50.
21. Giannoni C, Chelazzi C, Villa G, Raffaele De Gaudio A. Organ dysfunction scores in ICU. Trends Anaesth Crit Care. 2013;3(3):89–96.
22. Lorente JA, Vallejo A, Galeiras R, Tómicic V, Zamora J, Cerdá E, et al. Organ dysfunction as estimated by the sequential organ failure assessment score is related to outcome in critically ill burn patients. Shock. 2009;31(2):125–31.
23. Vincent JL, De Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med. 1998;26(11): 1793–800.
24. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438–47.
25. Peres-Bota D, Melot C, Ferreira FL, Ba VN, Vincent JL. The multiple organ dysfunction score (MODS) versus the sequential organ failure assessment (SOFA) score in outcome prediction. Intensive Care Med. 2002;28(11):1619–24.
26. Zygun D, Berthiaume L, Laupland K, Kortbeek J, Doig C. SOFA is superior to MOD score for the determination of non-neurologic organ dysfunction in patients with severe traumatic brain injury: a cohort study. Crit Care. 2006;10(4):R115.
27. Vincent JL, Moreno R. Scoring systems in the critically ill. Crit Care. 2010;14:207–15.
28. Hoste EAJ, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10(3):1–10.
29. Molitoris BA, Levin A, Warnock DG, Joannidis M, Mehta RL, Kellum JA, et al. Improving outcomes of acute kidney injury: report of an initiative. Nat Clin Pract Nephrol. 2007;3(8):439–42.
30. Child CG. Surgery and portal hypertension. In: Child CG, editor. The liver and portal hypertension. Philadelphia, PA: WB Saunders; 1964. p. 50–72.
31. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646–9.
32. ARDS Definition Task Force. Acute respiratory distress syndrome. JAMA. 2012;307(23):2526–33.
33. Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol. 2010;10(12):826–37.
34. Andersson U, Tracey KJ. HMGB1 is a therapeutic target for sterile inflammation and infection. Annu Rev Immunol. 2011;29:139–62.
35. Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. Nat Rev Immunol. 2003;3(10):791–800.
36. Gao L, Flores C, Fan-Ma S, Miller EJ, Moitra J, Moreno L, et al. Macrophage migration inhibitory factor in acute lung injury: expression, biomarker, and associations. Transl Res. 2007;150(1):18–29.
37. Donnelly SC, Bucala R, Metz CN, Grant IS, Robertson CR, Haslett C. Macrophage migration inhibitory factor and acute lung injury. Chest. 1999;116 Suppl 1:111S.
38. Rittirsch D, Redl H, Huber-Lang M. Role of complement in multiorgan failure. Clin Dev Immunol. 2012;2012:962927.
39. Rittirsch D, Flierl MA, Nadeau BA, Day DE, Huber-Lang M, Mackay CR, et al. Functional roles for C5a receptors in sepsis. Nat Med. 2008;14(5):551–7.
40. Silasi-Mansat R, Zhu H, Popescu NI, Peer G, Sfyroera G, Magotti P, et al. Complement inhibition decreases the procoagulant response and confers organ protection in a baboon model of Escherichia coli sepsis. Blood. 2010;116(6):1002–10.
41. Rosas-Ballina M, Tracey KJ. The neurology of the immune system: neural reflexes regulate immunity. Neuron. 2009;64(1):28–32.
42. Tracey KJ. Reflex control of immunity. Nature. 2002;420:853–9.
43. Doerschug KC, Delsing AS, Schmidt GA, Haynes WG. Impairments in microvascular reactivity are related to organ failure in human sepsis. Am J Physiol Heart Circ Physiol. 2007;293(2):H1065–71.
44. Shapiro NI, Yano K, Okada H, Fischer C, Howell M, Spokes KC, et al. A prospective, observational study of soluble FLT-1 and vascular endothelial growth factor in sepsis. Shock. 2008;29(4):452–7.

45. Shapiro NI, Schuetz P, Yano K, Sorasaki M, Parikh SM, Jones AE, et al. The association of endothelial cell signaling, severity of illness, and organ dysfunction in sepsis. Crit Care. 2010;14(5):R182.
46. David S, Mukherjee A, Ghosh CC, Yano M, Khankin EV, Wenger JB, et al. Angiopoietin-2 may contribute to multiple organ dysfunction and death in sepsis. Crit Care Med. 2012;40(11):3034–41.
47. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med. 2001;32(9):1825–31.
48. Trzeciak S, McCoy JV, Dellinger RP, Arnold RC, Rizzuto M, Abate NL, et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med. 2008;34(12):2210–7.
49. Trzeciak S, Cinel I, Dellinger RP, Shapiro NI, Arnold RC, Parrillo JE, et al. Resuscitating the microcirculation in sepsis: the central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. Acad Emerg Med. 2008;15(5):399–413.
50. Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. Crit Care Med. 2007;35(9):S441–8.
51. Singer M. Mechanisms of sepsis-induced organ dysfunction and recovery update in intensive care and emergency medicine. Crit Care Emerg Med. 2007;44:299–310.
52. Harrois A, Huet O, Duranteau J. Alterations of mitochondrial function in sepsis and critical illness. Curr Opin Anaesthesiol. 2009;22(2):143–9.
53. Haden DW, Suliman HB, Carraway MS, Welty-Wolf KE, Al AS, Shitara H, et al. Mitochondrial biogenesis restores oxidative metabolism during Staphylococcus aureus sepsis. Am J Respir Crit Care Med. 2007;176:768–77.
54. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360:219–23.
55. Carré JE, Orban JC, Re L, Felsmann K, Iffert W, Bauer M, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Resp Crit Care Med. 2010;182(6):745–51.
56. Jeger V, Djafarzadeh S, Jakob SM, Takala J. Mitochondrial function in sepsis. Eur J Clin Invest. 2013;43(5):532–42.
57. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, et al. A genomic storm in critically injured humans. J Exp Med. 2011;208(13):2581–90.
58. Leavy O. Inflammation: trauma kicks up a storm. Nat Rev Immunol. 2011;12(1):3.
59. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
60. Ashbaugh D, Boyd BD, Petty T, Levine B. Acute respiratory distress in adults. Lancet. 1967; 290(7511):319–23.
61. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Nef M, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353:1685–93.
62. Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, et al. Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. Crit Care Med. 2000;28(1):232–5.
63. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012;38(10):1573–82.
64. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342:1334–49.
65. Tsushima K, King LS, Aggarwal NR, De Gorordo A, D'Alessio FR, Kubo K. Acute lung injury review. Intern Med. 2009;48:621–30.
66. Bagshaw SM, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G, et al. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med. 2009;35:871–81.
67. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, The Acute Dialysis Quality Initiative Workgroup. Acute renal failure definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative Group. Crit Care. 2004;8:R204–12.
68. Mehta RL, Kellum JA, Shah SV, The Acute Kidney Injury Network. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
69. The Kidney Disease Improving Global Outcomes (KDIGO) Working Group. Definition and classification of acute kidney injury. Kidney Int. 2012; Suppl 2:19–36.
70. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380:756–66.
71. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54:1012–24.
72. Srisawat N, Wen X, Lee M, Kong L, Elder M, Carter M, et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol. 2011;6(8):1815–23.
73. Obermüller N, Geiger H, Weipert C, Urbschat A. Current developments in early diagnosis of acute kidney injury. Int Urol Nephrol. 2014;46(1):1–7. doi:10.1007/s11255-013-0448-5 [Epub ahead of print].
74. Werdan K, Schmidt H, Ebelt H, Zorn-Pauly K, Koidl B, Hoke RS, et al. Impaired regulation of cardiac function in sepsis, SIRS, and MODS. Can J Physiol Pharmacol. 2009;87(4):266–74.

75. Hunter JD, Doddi M. Sepsis and the heart. Br J Anaesth. 2010;104(1):3–11.
76. Matsuda N, Hattori Y. Vascular biology in sepsis: pathophysiological and therapeutic significance of vascular dysfunction. J Smooth Muscle Res. 2007; 43(4):117–37.
77. Levy B, Collin S, Sennoun N, Ducrocq N, Kimmoun A, Asfar P, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. In: Pinsky MR, Brochard L, Mancebo J, Antonelli M, editors. Applied physiology in intensive care medicine 2. Berlin: Springer; 2012. p. 251–61.
78. Lamar CD, Hurley RA, Taber KH. Sepsis-associated encephalopathy: review of the neuropsychiatric manifestations and cognitive outcome. J Neuropsychiatry Clin Neurosci. 2011;23:237–41.
79. Chelazzi C, Consales G, De Gaudio AR. Sepsis associated encephalopathy. Curr Anaesth Crit Care. 2008;19(1):15–21.
80. Garnacho-Montero J, Madrazo-Osuna J, García-Garmendia JL, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero-Almodóvar A, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med. 2001;27(8):1288–96.
81. Garnacho-Montero J, Amaya-Villar R, García-Garmendía JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. Crit Care Med. 2005;33(2):349–54.
82. Ortiz-Leyba C, Ortiz-Moyano C, Jiménez-Jiménez FJ, Garnacho-Montero J, García-Garmendia JL. Nutritional support in severe sepsis. Clin Pulm Med. 2003;10(1):26–33.
83. Gardiner K, Barbull A. Intestinal amino acid absorption during sepsis. JPEN. 1993;17:277–83.
84. Salloun RM, Copeland EM, Souba WW. Brush border transport of glutamine and other substrates during sepsis and endotoxemia. Ann Surg. 1991; 213:401–10.
85. Groeneveld ABJ. Gastrointestinal exocrine failure in critical illness. In: Rombeau JL, Takala J, editors. Gut dysfunction in critical illness, Update in intensive care and emergency medicine, vol. 26. Berlin: Springer; 1996. p. 297–306.
86. Heidegger CP, Berge MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381(9864):385–93.
87. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17.
88. Louis K, Netea MG, Carrer DP, Kotsaki A, Mylona V, Pistiki A, et al. Bacterial translocation in an experimental model of multiple organ dysfunctions. J Surg Res. 2013;183(2):686–94.
89. Reintam A, Poeze M, Malbrain ML, Björck M, Oudemans-van Straaten HM, Starkopf J, Gastro-Intestinal Failure Trial Group. Gastrointestinal symptoms during the first week of intensive care are associated with poor outcome: a prospective multicentre study. Intensive Care Med. 2013;39(5):899–909.
90. Piton G, Manzon C, Cypriani B, Carbonnel F, Capellier G. Acute intestinal failure in critically ill patients: is plasma citrulline the right marker? Intensive Care Med. 2011;37(6):911–7.
91. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. Intensive Care Med. 2006; 32(11): 1722–32.
92. Malbrain ML, De Laet I. AIDS is coming to your ICU: be prepared for acute bowel injury and acute intestinal distress syndrome. Intensive Care Med. 2008;34(9):1565–9.
93. Reintam A, Parm P, Kitus R, Starkopf J, Kern H. Gastrointestinal failure score in critically ill patients: a prospective observational study. Crit Care. 2008;12:R90.
94. Reintam A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012;38(3):384–94.
95. Dhainaut JF, Marin N, Mignon A, Vinsonneau C. Hepatic response to sepsis: interaction between coagulation and inflammatory processes. Crit Care Med. 2001;29:S42–7.
96. Spapen H. Liver perfusion in sepsis, septic shock, and multiorgan failure. Anat Rec. 2008;291:714–20.
97. Olanders K, Sun Z, Borjesson A, Dib M, Andersson E, Lasson Å, et al. The effect of intestinal ischemia and reperfusion injury on ICAM-1 expression, endothelial barrier function, neutrophil tissue influx, and protease inhibitor levels in rats. Shock. 2002;18(1):86–92.
98. Poeze M, Ramsay G, Buurman WA, Greve JWM, Dentener M, Takala J. Increased hepatosplanchnic inflammation precedes the development of organ dysfunction after elective high-risk surgery. Shock. 2002;17:451–8.
99. Soeters PB, Luyer MS, Willem J, Greve M, Buurman WA. The significance of bowel permeability. Curr Opin Clin Nutr Metab Care. 2007;10:632–8.
100. Kobayashi N, Maekawa T, Takada M, Tanaka H, Gonmori H. Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. Bibl Haematol. 1987;49:848–52.
101. Taylor Jr FB, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation: on behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of

the International Society on Thrombosis and Haemostasis (ISTH). Thromb Haemost. 2001;86: 1327–30.
102. Gando S, Iba T, Eguchi Y, Ohtomo Y, Okamoto K, Koseki K, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. Crit Care Med. 2006;34:625–31.
103. Takemitsu T, Wada H, Hatada T, Ohmori Y, Ishikura K, Takeda T, et al. Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. Thromb Haemost. 2011;105: 40–4.
104. Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, Kurosawa S, Stepien D, Valentine C, et al. Sepsis: multiple abnormalities, heterogeneous responses, and evolving understanding. Physiol Rev. 2013;93(3):1247–88.
105. Cuthbertson DP. Post-shock metabolic response. Lancet. 1942;239(6189):433–7.
106. Cerra FB. Hypermetabolism, organ failure, and metabolic support. Surgery. 1987;101:1–14.
107. Van Den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
108. Frankenfield DC, Oniert LA, Badellino MM, Wiles CE, Bagley SM, Goodarzi S, et al. Correlation between measured energy expenditure and clinically obtained variables in trauma and sepsis patients. JPEN. 1994;18(5):398–403.
109. Dickerson RN. Optimal caloric intake for critically ill patients: first, do no harm. Nutr Clin Pract. 2011;26(1):48–54.
110. Silvestri L, van Saene HK, Zandstra DF, Marshall JC, Gregori D, Gullo A. Impact of selective decontamination of the digestive tract on multiple organ dysfunction syndrome: systematic review of randomized controlled trials. Crit Care Med. 2010; 38(5):1370–6.
111. Leal-Noval SR, Muñoz M, Asuero M, Contreras E, García-Erce JA, Llau JV, et al. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the "Seville Document". Blood Transfus. 2013;11(4):1–25.
112. Leal-Noval SR, Muñoz-Gómez M, Jiménez-Sánchez M, Cayuela A, Leal-Romero M, Puppo-Moreno A, et al. Red blood cell transfusion in non-bleeding critically ill patients with moderate anemia: is there a benefit? Intensive Care Med. 2013;39(3):445–53.
113. Gunst J, Derese I, Aertgeerts A, Ververs EJ, Wauters A, Van den Berghe G, et al. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. Crit Care Med. 2013;41(1):182–94.
114. Levitt JE, Calfee CS, Goldstein BA, Vojnik R, Matthay MA. Early acute lung injury: criteria for identifying lung injury prior to the need for positive pressure ventilation. Crit Care Med. 2013;41(8): 1929–37.
115. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. Crit Care Med. 2013;41(7):1774–81.
116. European Medicines Agency. Recommendation to suspend marketing authorisations for hydroxyethyl-starch solutions to be re-examined. 12 July 2013. EMA/349341/2013.
117. De Backer D, Aldecoa C, Hassane H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. Crit Care Med. 2012;40(3):725–30.
118. Home AJRCCM, Home AJRCMB, By Subject CME. Randomized, placebo-controlled clinical trial of an aerosolized β 2-agonist for treatment of acute lung injury. Am J Resp Crit Care Med. 2011;184(5): 561–8.
119. Jones NE, Heyland DK. Pharmaconutrition: a new emerging paradigm. Curr Opin Gastroenterol. 2008;24(2):215–22.
120. Ortiz-Leyba C, Montejo-González JC, Vaquerizo-Alonso C, Metabolism and Nutrition Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus SEMICYUC-SENPE: septic patient. Nutr Hosp. 2011;26 Suppl 2:67–71.
121. Heyland DK, Novak F, Drover JW, Jain M, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA. 2001;286:944–53.
122. Davis J, Anstey N. Is plasma arginine concentration decreased in patients with sepsis? A systematic review and meta-analysis. Crit Care Med. 2011; 39(2):380–5.
123. Wernerman J, Kirketeig T, Andersson B, et al. Scandinavian glutamine trial: a pragmatic multicentre randomised clinical trial of intensive care unit patients. Acta Anaesthesiol Scand. 2011;55:812–8.
124. Andrews PJ, Avenell A, Noble DW, Campbell MK, Croal BL, Simpson WG, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. BMJ. 2011;342:d1542.
125. Grau T, Bonet A, Miñambres E, Piñeiro L, Irles JA, Robles A, et al.; for the Metabolism, Nutrition Working Group, SEMICYUC, Spain. The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. Crit Care Med. 2011;39(6):1263–8.
126. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368:1489–97.
127. Bruegel M, Ludwig U, Kleinhempel A. Sepsis-associated changes of the arachidonic acid metabolism and their diagnostic potential in septic patients. Crit Care Med. 2012;40(5):1478–86.

128. Umpierrez GE, Spiegelman R, Zhao V, Smiley DD, Pinzon I, Griffith DP, et al. A double-blind, randomized clinical trial comparing soybean oil–based versus olive oil–based lipid emulsions in adult medical–surgical intensive care unit patients requiring parenteral nutrition. Crit Care Med. 2012; 40:1792.
129. Mateu-de Antonio J, Grau S, Luque S, Marín-Casino M, Albert I, Ribes E. Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. Br J Nutr. 2008;99(4):846–54.
130. Rice TW, Wheeler AP, Thompson BT, de Boisblanc BP, Steingrub J, Rock P, NIH NHLBI Acute Respiratory Distress Syndrome Network of Investigators. Enteral omega-3 fatty acid, γ-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA. 2011;306(14):1574–81.
131. Grau-Carmona T, Morán-García V, García-de-Lorenzo A, Heras-de-la-Calle G, Quesada-Bellver B, López-Martínez J, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. Clin Nutr. 2011;30(5):578–84.
132. Wagner E, Frank MM. Therapeutic potential of complement modulation. Nat Rev Drug Discov. 2010;9:43–56.
133. Ghannam S, Bouffi C, Djouad F, Jorgensen C, Noël D. Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. Stem Cell Res Ther. 2010;1:2.
134. Groeneveld KM, Leenen LP, Koenderman L, Kesecioglu J. Immunotherapy after trauma: timing is essential. Curr Opin Anaesthesiol. 2011;24(2): 219–23.
135. Gotts JE, Matthay MA. Mesenchymal stem cells and acute lung injury. Crit Care Clin. 2011;27(3):719–33.
136. Schmidt H, Hoyer D, Rauchhaus M, Prondzinsky R, Hennen R, Schlitt A, et al. ACE-inhibitor therapy and survival among patients with multiorgan dysfunction syndrome (MODS) of cardiac and non-cardiac origin. Int J Cardiol. 2010;140(3):296–303.
137. Dare AJ, Phillips AR, Hickey AJ, Mittal A, Loveday B, Thompson N, Windsor JA. A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. Free Radic Biol Med. 2009;47(11):1517–25.
138. Teoh H, Quan A, Creighton AK, Bang KA, Singh KK, Shukla PC, et al. BRCA1 gene therapy reduces systemic inflammatory response and multiple organ failure and improves survival in experimental sepsis. Gene Ther. 2012;20(1):51–61.
139. Cobb JP. MORE for multiple organ dysfunction syndrome: Multiple Organ REanimation, REgeneration, and Reprogramming. Crit Care Med. 2010;38(11): 2242–6.

Endocrine Perturbations in Critical Illness

14

Grace S. Lee, Silvio E. Inzucchi, and Elizabeth H. Holt

Disorders of Glucose Control

Diabetes Management in the Intensive Care Unit

Background

Acute illness results in an increase in circulating concentrations of stress hormones, including adrenaline and cortisol, which impair insulin action, thereby leading to hyperglycemia [1]. Extensive evidence from observational studies reveals a strong correlation between hyperglycemia during critical care and patient outcomes, including mortality [2]. Even when controlling for other markers of severity of illness, the degree of blood glucose elevation appears to be independently associated with adverse events. Importantly, the relationship between glucose and mortality appears to be more tightly linked in patients without a prior history of diabetes—i.e., in those with newly identified hyperglycemia [3]. It remains debated, however, as to whether hyperglycemia during critical illness is a marker for or a mediator of patient outcomes.

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Evidence

Clinical trials of tight glycemic control using intensive insulin therapy in the critical care setting, including the surgical intensive care unit (ICU), have had conflicting results. Older studies employing historical controls suggested that moderate control of blood glucose (to the 150–199 mg/dL range) using intravenous (IV) insulin infusion in the cardiothoracic ICU reduced deep sternal wound infection rates in patients undergoing cardiac surgery [4]. In the landmark randomized clinical trial by van den Berghe and Belgian colleagues involving 1,548 surgical ICU patients, reducing blood glucose levels to 80–110 mg/dL with an intensive IV infusion protocol (mean blood glucose 103 mg/dL) was associated with a 42 % relative reduction in ICU mortality and a 34 % relative reduction in hospital mortality, when compared to conventional care (mean blood glucose 153 mg/dL) [5]. These data, however, have not been confirmed by other groups. In fact, in the NICE SUGAR study, a multicenter randomized clinical trial involving 6,104 critically ill medical and surgical patients, intensive glucose management using a similar protocol and target (mean blood glucose 118 mg/dL) resulted in a puzzling 14 % *increase* in mortality as compared to conventional therapy (mean blood glucose 145 mg/dL) [6]. Follow-up analyses have linked increased mortality in NICE SUGAR to the development of severe hypoglycemia (blood glucose <40 mg/dL), occurring in 6.8 % of patients in the intensive group and 0.5 % in the conventional group. However a cause and effect

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relationship remains unproven. Other investigators have found that iatrogenic hypoglycemia in the hospital does not carry with it the same negative implications as *spontaneous* hypoglycemia (i.e., that due to malnutrition, sepsis, liver failure.) [7]. Accordingly, it may be those patients who are at risk for developing low blood glucose with or without insulin therapy may simply be sicker, and higher risk individuals.

A meta-analysis has shown no overall benefit from intensive insulin therapy in the ICU, although a possible benefit in surgical ICUs was raised [8]. It should be pointed out, however, that this finding was mainly driven by the van den Berghe surgical ICU cohort.

Guidelines

Based on these data, the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) and, in their 2009, consensus statement encouraged good but not necessarily overly stringent blood glucose control in all critical care settings. Insulin infusion was deemed the most appropriate and flexible form of therapy in this setting, to be used when the blood glucose exceeds 180 mg/dL, with a glucose target of 140–180 mg/dL [9]. The Society for Critical Care Medicine (SCCM) in their 2012 guidelines statement recommends a similar range (<150 mg/dL) [10], although the SCCM's own Surviving Sepsis Campaign's 2012 *International Guidelines for Management of Severe Sepsis and Septic Shock*, endorses a somewhat more conservative blood glucose target of ≤180 mg/dL [11]. SCCM also advises the use of IV insulin in the critical care setting.

Insulin Infusions

When IV insulin is administered, validated infusion protocols should be used, either "paper" algorithms or computerized devices, the latter simplifying implementation for nursing staff. The ideal protocol should reduce blood glucose gradually (within several hours) and safely into the target range. In most protocols, hourly blood glucose determinations are necessary for safe implementation, with frequent infusion dosing adjustments. Infusion rates are typically range between 1 and 5 U of insulin per hour, but can exceed this in highly insulin-resistant individuals. Continuous parenteral feeding and, particularly, total parenteral nutrition (TPN) can also markedly increase insulin requirements. The best protocols adjust the rate based on the blood glucose, rate of changes, and prevailing insulin infusion rates. At our institution, the ICU insulin infusion protocol targets 120–160 mg/dL and has been associated with a median blood glucose of 150 mg/dL (IQR 127–180 mg/dL), achieved after a median of 7 h, with an exceedingly low severe hypoglycemia rate of 1/5,000 blood glucose determinations [12]. This rivals the background rate of hypoglycemia in the control/conventional therapy arms of most clinical trials of intensive glucose management.

Plasma venous or arterial blood glucose samples are ideal, but only if rapid result turnaround is ensured, such as with point-of-care analyzers. Most institutions, however, continue to use bedside, capillary blood glucose meters in this setting. These are adapted versions of home-use meters, and it should be acknowledged that the accuracy of these devices is only ±15–20 % vs. plasma glucose samples. In critically ill patients, with anemia, acidosis, and peripheral vasoconstriction, even wider discrepancies can be observed. There is some interest in the potential use of continuous glucose monitoring (CGM) in the ICU [13]. These devices measure interstitial glucose concentrations from subcutaneous tissues and provide readings every 5 min. They appear to be reasonably accurate in the hospital but it is not clear if they are reproducible and reliable enough to be used for adjusting insulin infusions, particularly in the low-normal glycemic range. More studies will be necessary before we can consider the use of CGM in the critically ill.

Subcutaneous Insulin Regimens

Upon transfer from the surgical ICU, if substantial insulin requirements persist (i.e., >1 U/h) or in patients on insulin prior to admission (especially in Type 1 diabetics), smooth transitioning to a subcutaneous regimen is important to prevent

post-infusion hyperglycemia. Several transition protocols are available, most using initial doses estimated from the terminal hours of the insulin infusion [14]. For example, if a patient has required 2 U/h over the 6 h prior to transition, an estimated need of 48 U can be estimated for the day. Some protocols then take this entire amount (whereas others use 80 % of this amount), dividing by 2. Thus, 50 % of the daily requirement is administered as a dose of basal insulin (e.g., 24 U QD of insulin glargine or detemir, or 12 U BID of NPH). The balance is administered as a rapid-acting insulin analogue, further divided into three pre-meal doses of (e.g., 8 U TID AC of insulin lispro, aspart, or glulisine.) If the patient is not yet eating, the mealtime dose is held and correction insulin is instead administered ever 4–6 h (regular insulin or a rapid analogue) to correct for hyperglycemia. If substantial short- or rapid-acting insulin coverage is required, a portion of this (classically, 50 %) can be incorporated into the next day's basal insulin dose.

In the non-ICU setting, most organizations (AACE-ADA, Society of Hospital Medicine, the Endocrine Society) [9, 15, 16] recommend that pre-prandial blood glucose be maintained <140 mg/dL and that all blood glucose levels be kept <180 mg/dL. Focusing on safety and the avoidance of hypoglycemia is important, particularly in the less supervised setting of a general surgical ward. The frequent changes in a patient's nutritional status must be considered on a daily or even more frequent basis such that insulin doses are nimbly adjusted to anticipate the patients' requirements. In addition, the patient's trajectory of illness (and, therefore, stress response) and other medications that might impact metabolic control (e.g., glucocorticoids) must be considered as well. Using endocrine consultants or hospital diabetes management teams has been demonstrated to improve glycemic control and clinical outcomes.

As the patient's nutritional status improves and calorie intake normalizes outside of the ICU, the so-called *basal-bolus* insulin strategy is endorsed as the most physiologic, especially in type 1 diabetes and the more severely insulin-deficient patients with type 2 diabetes [15]. Here, a *basal* insulin (glargine, detemir, NPH) once or twice per day suppresses hepatic glucose production, controlling glucose levels overnight and in between meals. It is given in conjunction with a pre-meal *bolus* of rapid acting insulin analogue to blunt postprandial glycemic excursions, in an attempt to recapitulate normal insulin secretory dynamics. Furthermore, the mealtime dose is ideally adjusted (i.e., increased) for preprandial hyperglycemia with correction doses of the same type or rapid-acting insulin (e.g., +2 additional units added to the planned nutritional dose, when the pre-meal blood glucose ≥150 mg/dL, +4 U for ≥200 mg/dL) The optimal ratio between basal and the sum of the bolus components is classically 1:1.

Such a complex glucose control strategy will necessitate careful coordination between medical assistants who are charged with obtaining and reporting blood glucose readings, dietary staff who provide the meals, nurses who administer the insulin, and the surgeon or other physician who orders and adjusts the insulin doses. In patients who are made NPO, in preparation of surgery or other procedures, or in whom nutritional intake is in doubt, mealtime boluses will obviously need to be omitted. As noted previously, basal insulin alone (reduced by 20 % for a safety margin, unless the patient has remained hyperglycemic), along with "coverage" involving correction rapid analogue every 4–6 h or regular human insulin every 6 h, should be sufficient to control glycemia. When calorie intake improves, fixed mealtime boluses can be resumed.

Transitioning the Patient to Discharge

Upon discharge, the patient's at home glucose control requirements will need to be determined. Those on insulin prior to hospitalization will require resumption of that strategy if it was resulting in acceptable blood glucose control (i.e., HbA1c in or near the targeted range of <7 %) [15]. If not, a more intensified strategy will be required (higher dose, more injections, different insulin formulations, etc.) In those who were previously treated with oral agents (or an injectable GLP-1 receptor agonists), those drugs can also be

resumed upon discharge, as long as the patient has not developed a prevailing contraindication (e.g., renal insufficiency in someone previously treated with metformin) and if the preadmission control was acceptable. If not, an adjustment in the regimen or the use of insulin at home will be necessary. Such changes are usually optimally made using medical consultants or after conversation with the patient's primary care physician or endocrinologist.

In those individuals with newly identified hyperglycemia, not all will require antihyperglycemic therapy upon discharge. This decision should be based on the patients' blood glucose levels toward the end of the hospitalization, the in-hospital treatment required, and measurement of HbA1c, which will reflect blood glucose levels in the 2–3 months prior to admission. In those with normal or near-normal HbA1c levels, so long as blood glucose is not significantly elevated (>180–200 mg/dL), discharge off antihyperglycemic therapy is acceptable, but early outpatient follow-up is necessary so that the patients' glycemic status can be reassessed. Importantly, the patients' capacities for self-care need to be incorporated into the decision to treat with insulin, which can be a dangerous medication when used inappropriately or without proper patient and family education.

Diabetic Emergencies

Epidemiology

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two major acute complications of diabetes mellitus (DM). The rate of hospital admissions for DKA has been rising and in 2009 it reached 4.6 per 10,000 population, which is about a 44 % increase since 1988 [17]. Fortunately, the death rate due to all hyperglycemic crises has been declining since the 1990s, with an age-adjusted death rate of 7.5 per 1,000,000 population in 2009, which is less than half the rate in 1980 [18]. Due to the magnitude of these conditions, it is vital to understand how to diagnose and treat these conditions appropriately.

Definitions of DKA and HHS

DKA is present when the following criteria are met: plasma glucose >250 mg/dL, arterial pH ≤7.30, serum bicarbonate ≤18 mEq/L, positive urinary and serum ketones, and an anion gap <10 mEq/L [19]. The degree of acidemia, measured by arterial pH, determines if it is categorized as mild (pH 7.25–7.30, bicarbonate 15–18), moderate (pH 7.00–7.24, bicarbonate 10 to <15), or severe DKA (pH < 7.00, bicarbonate <10) [19]. That being said, it has been suggested that these categories should apply only to patients with a simple metabolic acidosis [20–22]. Clinicians should be mindful of the possible presence of mixed acid–base disorders as well, which can be seen in 43–50 % of DKA cases [20–22]. HHS is present when the following criteria are met: plasma glucose >600 mg/dL, an arterial pH > 7.30, serum bicarbonate >18 mEq/L, an effective osmolality of >320 mOsm/kg [19, 23]. Small urinary and serum ketones may be seen in HHS, while it is always seen in DKA [19]. In addition, it is important to note that about 33 % of patients may have characteristics of both disorders and thus these conditions are not mutually exclusive [24, 25].

Although we typically think of DKA occurring in patients with type 1 DM, there is also an entity known as ketosis-prone type 2 DM [26, 27]. The initial clinical presentation of DKA in these patients is similar to that of patients with type 1 DM, but ketosis-prone type 2 DM patients differ because they may recover β-islet cell function after a few months [26]. In fact, 10 years after their initial presentation with DKA, up to 40 % of these patients do not require insulin therapy [26, 27]. Interestingly, in about 50 % of unprovoked DKA in ketosis-prone type 2 DM patients, one cannot determine a precipitating factor for the DKA [28]. In this subset of patients who develop unprovoked DKA, a male predominance has been observed [28]. Common characteristics in patients with ketosis-prone type 2 DM include obesity, low prevalence of autoimmune markers, lack of genetic HLA association, and male predominance [26, 28]. It has also been noted that a significant proportion of these patients are African-American or Hispanic

although this entity has also been reported in other populations such as Asians, Caucasians, and Native Americans [28].

Pathophysiology

DKA occurs due to relative insulin deficiency along with an increase in counter-regulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone [19, 23]. The hyperglycemia results from increased gluconeogenesis, increased glycogenolysis, and decreased peripheral glucose utilization in the liver, muscle, and adipocytes [23]. Both insulin deficiency and increased cortisol levels lead to increased proteolysis and lipolysis. Proteolysis creates amino acid substrates that fuel gluconeogenesis and lipolysis creates glycerol, which also fuels gluconeogenesis, and free fatty acids (FFA). These FFA undergo beta-oxidation in the liver to generate ketones (beta-hydroxybutyrate and acetoacetate) and thus result in an anion gap metabolic acidosis [Anion gap $= Na^+ - (Cl + HCO_3)$] [23]. In addition, increased glucagon relative to insulin decreases malonyl CoA, which results in the disinhibition of carnitine palmitoyl acyltransferase I (CPT I), which is known to transport FFA into the mitochondria for oxidation and thus contributes to this ketogenesis [29]. Furthermore, hyperglycemia itself leads to volume depletion with resulting impaired renal function, which decreases the patient's ability to excrete glucose and ketoanions [30]. In concert, these processes result in hyperglycemia and ketoacidosis.

Interestingly, patients with hyperglycemic crisis may also demonstrate inflammation and hypercoagulability as evidenced by increased levels of proinflammatory cytokines, reactive oxygen species, cardiovascular risk factors, coagulation markers, fibrinolysis, and platelet activity [29, 31, 32]. Clinically, these patients may thus also present with thrombosis, myocardial infarction, and disseminated intravascular coagulation [29, 31].

Similar to DKA, the pathophysiology of HHS involves a relative insulin deficiency but unlike DKA, the amount endogenous insulin secretion in HHS is usually greater [19]. This amount of insulin prevents lipolysis and thus explains why ketone bodies are not typically seen in HHS [19, 33]. HHS also results in an osmotic diuresis resulting in an even greater free water deficit, which can be greater than 9 L, than is present in DKA, which is usually about 6 L [24]. Patients with HHS develop hyperosmolarity, hypovolemia, and intravascular and extravascular dehydration. This leads to an increase in counter-regulatory hormones thereby exacerbating the existing hyperglycemia and insulin resistance [23, 29].

Clinical Presentation

The clinical presentation of DKA and HHS include symptoms of fatigue, weakness, polyuria, polydipsia, weight loss, and even altered mental status if the presentation is severe [19]. Patients with DKA often also have nausea, vomiting, and abdominal pain that parallels the degree of acidemia present [34]. This pain may be severe enough to prompt a work-up for an acute abdomen 50–75 % of the time [23, 34]. One distinguishing feature between DKA and HHS is the duration of symptoms prior to presentation. DKA is an acute process that typically develops within 24 h, whereas HHS is a process that develops over several days to weeks [19].

Physical exam findings in both conditions may include tachycardia, hypotension, dry mucous membranes, and poor skin turgor. Findings present in DKA may also include Kussmaul respirations, breath with a fruity odor due to ketones, nausea, vomiting, and abdominal tenderness to palpation [19, 34]. Altered mental status may be present in both conditions but tends to be more common and more severe in HHS because of the degree of hyperosmolarity [Effective Serum Osmolality $= 2 \times$ (measured) Na + [mEq/L] + Glucose (mg/dL)/18] present [24, 35]. Obtundation and coma usually occur when the effective osmolality is greater than 330 mOsm/kg [23]. If the patient's osmolality does not reach this threshold and altered mental status is present, it is essential to broaden the differential diagnosis for the neurologic change [19, 23]. In addition to the above, patients with HHS may have other neurologic changes such as hemiparesis, hemianopia, and seizures [19].

Evaluation

The initial evaluation of the patient presenting in hyperglycemic crisis should include an immediate fingerstick glucose and urinalysis to look for ketones. Initial labs should include a plasma glucose, serum ketones, an arterial blood gas to check the degree of acidemia, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, calcium, magnesium, phosphate), BUN, Cr, lactic acid, osmolality [19]. Based on the patient's clinical picture and the above labs, one can make a diagnosis based on the definitions of DKA and HHS mentioned above.

This evaluation often reveals pseudohyponatremia resulting from the shift of water to the extracellular space. The traditional teaching is that a corrected sodium value should be calculated to account for this shift. To do this, for every 100 mg/dL of glucose greater than 100, 1.6 mEq/L is added to the measured serum sodium level [24]. That being said, in HHS, where the plasma glucose is greater than 400 mg/dL, a factor of 2.4 mEq/L may be more appropriate [36].

Although the patient's serum potassium level may be normal or elevated on presentation, the patient's total body potassium level is usually low [24]. This is a result of relative insulin deficiency, which causes an extracellular shift of potassium [29]. It is for this reason that one must watch for the development of hypokalemia when insulin treatment is started [29].

The patient should be admitted to the ICU if there is worsening level of consciousness, airway compromise, hemodynamic instability, or severe acidemia. Recently, Huang et al. reported the use of the "PHD Score" in order to assess mortality risk in patients presenting with hyperglycemic crises in Taiwan [37]. This tool was only studied in a single center, was in part based on retrospective data, and its use not yet been validated in other populations.

In addition to the above, a simultaneous evaluation for a precipitating factor should be done. Since the most common precipitant for hyperglycemic crises is infection, labs should include a complete blood count (CBC) with differential, urinalysis with urine culture, sputum culture, viral nasal swab, blood cultures, and imaging should include a chest X-ray [19]. Although leukocytosis is usually seen in DKA even in the absence of infection, a white blood cell count of greater than $25 \times 10^3/mm^3$ or bandemia ≥ 10 % should raise the concern for the presence of an infection [19, 38].

Other precipitants include accidental or intentional insulin noncompliance, myocardial infarction, cerebrovascular accident, pancreatitis, and medications (e.g., corticosteroids, diuretics, beta blockers, calcium channel blockers, cimetidine, diazoxide, phenytoin, sympathomimetic agents, pentamidine, typical or atypical antipsychotics) [19, 24, 39]. Of note, pancreatitis cannot be diagnosed based on the values of amylase and lipase alone because these values may be significantly elevated in up to 25 % of DKA patients without pancreatitis [40]. Additional risk factors for DKA also include psychological illness, eating disorders, and cocaine use [19, 41]. If the patient presents with recurrent DKA, a urine toxicology panel and an overdose panel should be considered [35, 41]. Endocrine disorders that are associated with hyperglycemia and should be kept in mind include Cushing's syndrome, acromegaly, pheochromocytoma, thyrotoxicosis, and hyperaldosteronism [39].

Management

In DKA and HHS, the aims of therapy are to treat the patient's dehydration, hyperglycemia, and electrolyte abnormalities. It is also important to treat the precipitant of the hyperglycemic crisis, if one is found [19]. The treatment is described in detail below and it is important to note that the patient's fingerstick should be checked hourly and electrolytes, BUN, and creatinine should be checked every 2–4 h until the patient's hyperglycemic crisis has resolved.

Treatment begins with intravenous fluids (IVF) to restore intravascular, interstitial, and intracellular volume [19]. If hyperosmolarity is present, IVF can also help to correct it and thereby lead to an improved response to insulin therapy [42]. Typically, normal saline is started at a rate of 15–20 mL/kg body weight/h or 1–1.5 L

in the first hour [19]. The patient's hemodynamics, volume status, electrolyte status, urine output, and corrected serum sodium value determine the next type of IVF that is given [19]. If the patient remains hypovolemic, normal saline is continued. Half normal saline (0.45 % NaCl) should be used if the corrected serum sodium is normal or elevated [19]. Of note, if cardiac or renal dysfunction is present, one must be watched carefully for signs of volume overload. If the patient develops cardiogenic shock, pressor support is necessary.

Next, insulin therapy should only be started when the patient is hemodynamically stable and the serum potassium level is greater than 3.3 [19, 29]. The reason is that insulin both (1) causes water to move from the extracellular to the intracellular space leading to further hypotension and (2) causes an intracellular shift of potassium leading to worsening hypokalemia [19, 29]. In order to ensure that the patient's serum potassium remains adequate, it should be repleted when it is at the upper limit of normal [19]. Insulin therapy may begin with a 0.1 U/kg body weight bolus followed by an infusion of 0.1 U/kg/h or as an infusion of 0.14 U/kg/h without an initial bolus [19, 43]. The goal is to decrease plasma glucose at a rate of 50–75 mg/dL/h and the insulin infusion should be titrated to this goal using hourly fingersticks [19]. Of interest, although an insulin infusion is used in many hospitals, it has been demonstrated that for the treatment of mild to moderate DKA, subcutaneous rapid-acting insulin use every 1–2 h is as effective as regular IV insulin therapy [44, 45].

Total body phosphate depletion is also present in patients with DKA but is typically only repleted if the serum phosphate is less than 1 mEq/L or if the patient has comorbidities such as cardiac or respiratory compromise or anemia [19, 46]. The reason is that evidence is lacking that aggressive phosphate repletion improves patient outcomes in DKA and repletion carries the risk of developing hypocalcemia [46, 47].

Bicarbonate therapy is controversial and is typically only used in severely acidemic patients because they are at risk for developing cerebral vasodilatation and coma, decreased myocardial contractility, and gastrointestinal complications [19, 48]. At pH levels between 6.9 and 7.1, studies have not shown any benefit in morbidity or mortality when bicarbonate is used to treat DKA patients [19, 49]. In DKA, the patient's ketoacidosis improves as ketone bodies are metabolized in the citric acid cycle [29]. Since there are no randomized controlled trials in DKA patients with a pH < 6.9 and there are serious complications that may occur with severe acidemia, bicarbonate therapy is given in these patients. The typical dose is 100 mmol of bicarbonate in 400 mL H_2O + 20 mEq KCl infused over 2 h. This is repeated every 2 h until the pH is ≥7. In addition, the serum potassium is monitored every 2 h [19]. The potential complications of bicarbonate therapy include worsening hypokalemia, intracellular acidosis, cerebral edema, and paradoxical central nervous system acidosis [19].

When the patient's plasma glucose reaches 200 mg/dL in DKA, dextrose should be added to the IVF and the insulin infusion rate is decreased to 0.02–0.05 U/kg/h. This is done to achieve a plasma glucose between 150 and 200 mg/dL and avoid hypoglycemia while further insulin therapy is required to close the anion gap and prevent more lipolysis and ketoacid production [19]. Insulin and dextrose therapy are continued in this manner until the DKA has resolved, which is defined by achieving a plasma glucose of <200 mg/dL and two of the following: serum bicarbonate ≥15 mEq/L, venous pH > 7.3, and/or anion gap ≤12 mEq/L. In HHS, dextrose is added and the insulin infusion rate decreased when the plasma glucose reaches 300 mg/dL. In HHS, this is continued with a goal plasma glucose of 200–300 mg/dL until the patient's HHS has resolved, which is defined by the normalization of osmolality and mental status [19].

When both conditions have met criteria for resolution, transition from IV to subcutaneous insulin may start with 1–2 h of overlap in order to prevent relapse of hyperglycemia or ketoacidosis. If the patient was already on insulin prior to this crisis, then the patient's home doses may be used if the patient's glycemic control was adequate prior to admission. If this is a new diagnosis of diabetes, then dosing may begin at

0.5–0.8 U/kg/day. A basal-bolus-correction (BBC) regimen may be used where 50 % of the total daily dose is given as a basal insulin (e.g., glargine or detemir), the remainder is divided into three equal doses given as rapid-acting insulin (e.g., aspart, glulisine, or lispro) at mealtimes, and a correction scale of rapid-acting insulin is also used [19]. Recently, it has been demonstrated that in patients with type 2 DM, the use of a "basal-plus correction" regimen, which uses a long-acting insulin (e.g., glargine) and a correction scale of rapid-acting insulin at mealtimes, achieves similar glycemic control as the BBC regimen [50].

Complications

Complications that may occur in DKA and HHS include hypoglycemia, hypokalemia, hyperchloremic metabolic acidosis, and cerebral edema [19, 51]. Cerebral edema is more common in pediatric patients but quite rare in adults with DKA. Possible contributors to its development may include increased cerebral blood flow, inflammatory mediators, cerebral ischemia, hypoxia, and a quick decrease in osmolality in the setting of IVF repletion [19, 51]. A patient with cerebral edema may have a headache, worsening level of consciousness, papilledema, bradycardia, hypertension, seizures, or respiratory compromise and even respiratory arrest. If this occurs, it is vital to treat with mannitol and mechanical ventilation [51].

Adrenal Disorders

Adrenal Insufficiency

Background

Any critical illness is associated with activation of the hypothalamic–pituitary–adrenal (HPA) axis, stemming from the release of corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary [52]. This, in turn, activates the adrenal cortex to augment its production of glucocorticoids, mainly cortisol. Recent evidence also suggests that decreased cortisol metabolism in critical illness may also increase circulating cortisol concentrations in critical illness [53]. Irrespective of cause, the hypercortisolemia that results has myriad effects on metabolic processes (mainly insulin counter-regulatory effects), vascular responsiveness to catecholamines, and modulation of the immune response. In the surgical ICU, occasional patients are admitted with preexisting adrenal insufficiency, either due to primary or secondary adrenal disease. In addition, dysfunction in the HPA axis should be considered in patients who exhibit suspicious feature of adrenal failure, particularly hypotension without known cause or when it hypotension becomes refractory to usual therapies.

Adrenal insufficiency is distinguished into primary and secondary causes. In *primary adrenal failure*, both adrenal glands are themselves dysfunctional, resulting in deficiency in both glucocorticoids (i.e., cortisol), mineralocorticoids (i.e., aldosterone), and adrenal androgens (i.e., DHEA, androstenedione), the first two being critical for survival. When deficient, and unless these hormones are replaced, patients rapidly develop hypotension, electrolyte imbalance (hyperkalemia, hyponatremia, metabolic acidosis), and hypoglycemia. Over time, due to the effects of increased pituitary ACTH secretion, the skin hyperpigments. This condition may result from autoimmune adrenalitis, bilateral adrenalectomy, the use of adrenolytic medications, or from glandular destruction from infectious or infiltrative diseases or, rarely, bulky tumor metastases. In contrast those with *secondary* (*or central*) *adrenal insufficiency* (from hypothalamic or pituitary dysfunction) experience loss of glucocorticoids and androgens only, with preserved mineralocorticoid secretion, the latter of which is under the predominate control or the renin-angiotensin system. Accordingly, the maintenance of vascular volume (through the effects of aldosterone) remains unimpaired. Hypotension still occurs (due to cortisol's effects on enhancing catecholamine action), but is usually not as severe as occurs in patients with primary adrenal failure.

Hyperkalemia is also absent, although hyponatremia, which is of multifactorial origin in adrenal insufficiency, still occurs. Individuals with this form of adrenal failure often have had a prior history of pituitary tumor, cranial irradiation, or have had longer-term suppression of the HPA axis from chronic high- or moderate-dose glucocorticoid therapy.

Symptoms of acute adrenal insufficiency ("adrenal crisis"), in addition to vascular collapse, hypoglycemia, and electrolyte disorders, also include profound fatigue, nausea, vomiting, abdominal pain, myalgias, low-grade fever, and mental status changes. Adrenal crisis may share some features of a surgical abdomen, although, typically, signs of peritoneal irritation, lactic acidosis and marked leukocytosis are lacking. Adrenal insufficiency should be suspected in any critically ill patient who presents with one or more of these features, particularly the persistent hemodynamic instability persisting after adequate fluid resuscitation. Of course, in the critically ill, such signs and symptoms are common may be difficult to attribute solely to hypoadrenalism. Accordingly, the clinic laboratory plays a critical role in diagnosis and must be used as an important part of the comprehensive clinical assessment of the patient.

Assessing Adrenal Function in the ICU

Laboratory investigation of adrenal function in the critically ill patient is controversial. In most circumstances in the ICU, obtaining a single measurement of serum or plasma cortisol concentration should suffice to rule out a diagnosis of adrenal insufficiency. The stress from critical illness will maximize adrenal steroid output and a random cortisol level should usually suffice as, essentially, a dynamic test to assess the integrity of the entire HPA axis. It should be noted, however, that "normal values" for the cortisol response to acute illness have not been fully defined, although most experts agree that an ambient level above 20–25 mg/dL indicates adequate adrenal response. This is, however, to some degree dependent on the severity and acuity of illness. Most authorities also agree that cortisol levels below 10 μg/dL raises the likelihood of at least partial adrenal insufficiency in this setting; the lower the level, the more secure one may be in this assessment. Making interpretation of measured cortisol levels more challenging is the realization that the *total* cortisol concentration (which includes that bound to cortisol-binding globulin [CBG]) may not fully reflect the adequacy of circulating free (i.e., unbound) cortisol, particularly in those with malnutrition and protein deficiency.

When in doubt, the adrenal response to 250 μg of IV bolus of cosyntropin, a synthetic ACTH analogue, should be performed, with a 30 min cortisol value of ≥18–20 μg/dL widely viewed as an acceptable response, although some authors prefer to see an increase of at least 9 μg/dL. It should also be noted, that the response to cosyntropin merely assess the *adrenal* response toto a pharmacological stimulus, but mail fail to detect secondary adrenal insufficiency, particularly if it is acute. Of course, the "gold standard" test the integrity of the entire HPA axis remains the insulin tolerance test to precipitate hypoglycemia. This is obviously both impractical and potentially dangerous in the critically ill and is not advised.

A related topic pertains to the diagnosis and management of *relative* or *functional* adrenal insufficiency, which has seen evolving definitions, diagnostic strategies, and opinions over the past decade. This condition is defined as subnormal adrenal steroid production in the absence of any anatomic or structural defects of the HPA axis and implies "exhaustion" of the secretory adrenocortical reserve in the context of near-maximal stimulation. Proposed contributing factors include the suppression of cortisol and/or ACTH production by circulating inflammatory cytokines, the development of tissue resistance to glucocorticoid action, and resistance of the adrenal cortex resistance to ACTH. Despite years of study, however, there remains lack of agreement on both the clinical significance and the biochemical definition of this state [54]. The clinical question relative hypoadrenalism may be appropriately raised when refractory hypotension occurs, despite fluid resuscitation or conventional doses of pressors, in the setting of sepsis.

One older, but frequently cited, multicenter, randomized, controlled clinical trial from France

involved 300 patients with septic shock unresponsive to fluid resuscitation. The investigators showed a significant reduction in mortality rate (hazard ratio (HR) 0.67, $p=0.02$) in patients with a post-cosyntropin cortisol augmentation of ≤9 μg/dL who were randomized to a stress steroid regimen of 200 mg of IV hydrocortisone and 50 μg of fludrocortisone per day. However, the larger ($N=499$) multicenter Corticosteroid Therapy of Septic Shock (CORTICUS) [55] trial in 2008, was not able to confirm any benefit on mortality (HR 1.09, p 0.51) in those subjects randomly assigned to IV hydrocortisone, although quicker reversal of shock was found in the hydrocortisone group (3.3 days vs. 5.8 days in the placebo group, $p<0.001$). There were, however, more superinfection events, including new septic shock episodes in those randomized to the steroid regimen. Importantly, the pre-randomization response to cosyntropin did not at all predict the response to hydrocortisone. Accordingly, this test is no longer routinely recommended by the SCCM in its Surviving Sepsis Campaign [56]. Moreover, the CCS advises that IV hydrocortisone at a dose no higher than 300 mg/day be given only to adult septic shock patients after blood pressure is documented to be poorly responsive to fluid resuscitation and vasopressor therapy (see Table 14.1).

Table 14.1 Society of Critical Care Medicine (SCCM) guidelines for corticosteroid use in patients with septic shock

1. Do not use intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. In case this is not achievable, suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C)
2. Do not use the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B)
3. In treated patients hydrocortisone should be tapered when vasopressors are no longer required (grade 2D)
4. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock (grade 1D)
5. When hydrocortisone is given, use continuous infusion (grade 2D)

Adapted from [11]

When the diagnosis of adrenal insufficiency is suspected in a patient whose condition is deteriorating rapidly, treatment with 50–100 mg of hydrocortisone IV every 6–8 h is reasonable until the diagnosis can be confirmed. Of course, such therapy will make the subsequent evaluation of cortisol levels difficult. Any steroid with glucocorticoid activity, including dexamethasone, will interfere with normal adrenal function. Accordingly, measured cortisol concentrations, once steroid therapy has begun, must be interpreted cautiously. That is, cortisol levels will be low when any steroid is given that has suppressive effects on adrenocortical function, whereas most glucocorticoid medications will additionally interfere with laboratory cortisol assays as well. Consultation with a laboratory medicine expert and/or an endocrinologist can be very helpful when such questions are raised.

We would underscore that the question of *relative* adrenal insufficiency is an entirely separate clinical consideration from the management of patients with previously diagnosed hypoadrenalism or in patients with overt, newly identified hypoadrenalism. Examples of the latter include patients with first presentation of primary (autoimmune adrenalitis, bilateral adrenal hemorrhage, etc.) or secondary adrenal failure (post-transsphenoidal pituitary surgery, pituitary apoplexy, etc.) In these individuals, prompt therapy with stress doses of glucocorticoids is critical for successful patient outcomes (see below).

Management of Established Adrenal Disease in the ICU

Patients with a history of either primary or secondary adrenal insufficiency will require special attention to hormonal needs in the setting of critical illness. Oral glucocorticoids (hydrocortisone, cortisone acetate, prednisone or methylprednisolone) and instead provided IV, either with intermittently or by continuous infusion. The standard of care to is provide the so-called stress doses of steroids, equivalent to 200–300 mg of hydrocortisone per day (usual strategies involved 50–75 mg IV every 6 h or 100 mg IV every 8 h). If fluid overload and sodium retention is a concern, the patient can be treated with a steroid with less

Table 14.2 Relative potencies of steroid hormones

	Glucocorticoid potency	Mineralocorticoid potency
Hydrocortisone	1	1
Cortisone acetate	0.8	0.8
Prednisone	4	0.8
Methyl-prednisolone	5	0.5
Dexamethasone	30	0
Fludrocortisone	15	150
Aldosterone	0	400+

Adapted from [59]

mineralocorticoid effects at equivalent doses (see Table 14.2). These include methylprednisolone or dexamethasone, the latter having essentially no sodium retentive properties. The dose is maintained for 1–3 days until the patient experiences improvement in his or her clinical status, and then gradually reduced (over several days to 1–2 weeks) to the baseline dose and transition to oral dosing, as allowed by the patient's condition [57].

In patients with primary adrenal disease who are critically ill, fludrocortisone is typically held when IV hydrocortisone is given, since the latter has substantial activity at the mineralocorticoid receptor when given at doses exceeding 50–100 mg/day. In addition, the extracellular fluid space is usually being repleted and sustained by IV crystalloid (0.9 % NaCl or Lactate Ringer's) solutions. The reinstitution of fludrocortisone will be required when IV fluids are reduced to maintenance requirements and when hydrocortisone doses are reduced to below 50–100 mg/day. If glucocorticoids are used that have less mineralocorticoid effect, fludrocortisone may need to be continued, especially when dexamethasone is used. The development of mild hyperkalemia may be used as a sign of inadequate aldosterone-like activity, along with clinical assessment of intravascular volume. Plasma renin activity is a more sensitive marker for mineralocorticoid insufficiency, but this may be difficult to interpret in the critically ill. More importantly, most hospital laboratories do not measure this hormone with sufficient frequency to allow for practical use in the acute setting [58, 59].

Pheochromocytoma

Preoperative Preparation

Proper preoperative preparation of the pheochromocytoma patient is of the utmost importance as surgery on an unprepared patient may lead to hypertension, stroke, and death. In addition, other triggers for worsening hypertension in the pheochromocytoma patient should be avoided. These include CT scan contrast, metoclopramide and glucagon. The rationale behind the preparation of the pheochromocytoma patient is to control hypertension safely and to expand intravascular volume. In addition, agents given preoperatively prepare the vasculature for high levels of catecholamines that may be released at the time of surgery as the adrenal gland is manipulated. The mainstays of preparation include alpha blockade, beta blockade, and in some cases metyrosine.

- *Alpha blockade*: Traditionally this is done with phenoxybenzamine (or phentolamine for IV administration). Phenoxybenzamine is a long-acting, nonspecific alpha blocker. Other alpha blockers such as prazosin [60] or doxazosin may also be used, as phenoxybenzamine is not always tolerated or available. Treatment should start about 2 weeks preoperatively. Phenoxybenzamine may be started at 10 mg QHS and titrated up over several days to 2 weeks as symptoms and blood pressure will allow. The goal is a mildly orthostatic patient. During the time of dose titration, it is important to expand intravascular volume by encouraging oral salt and water intake in order to make up for the vasodilatory properties of the alpha blockade. In the hospital setting intravascular volume expansion can also be accomplished with infusion of saline. It should be noted that labetalol is not a substitute for alpha blockade in patients with pheochromocytoma, as it has insufficient alpha blocking properties relative to its beta blocking properties.
- *Beta blockade*: Patients who are already on alpha blockers and are tachycardic may be treated with beta blockers as well. Beta blockade should be started at a low dose and titrated to give a heart rate in the normal range. Beta

blockade should not be started prior to alpha blockade in pheochromocytoma patients. The blockade of peripheral beta receptors which mediate vasodilation, in the presence of unopposed alpha-mediated vasoconstriction, can lead to more severe elevation in blood pressure.

- *Metyrosine*: In individuals who cannot tolerate alpha and beta blockade, or where tumor burden is considerable, metyrosine therapy should be considered [61]. Metyrosine is an inhibitor of the tyrosine hydroxylase enzyme. It therefore inhibits production of catecholamines from tyrosine, resulting in a lowering of catecholamine levels systemically. It may be started at 250 mg PO BID and titrated up as tolerated a few days before surgery in addition to alpha and beta blockade, to lower catecholamines preoperatively and minimize catecholamine release during the surgical exploration. Side effects of metyrosine include crystalluria (at high doses) so adequate fluid intake must be ensured. In addition metyrosine may cause extrapyramidal side effects and sedation.
- *Volume expansion*: As noted above, volume expansion is an important part of the preparation with alpha blockade. In addition, volume expansion should be emphasized the night before surgery so that the patient's intravascular volume is adequate to withstand the drop in catecholamines that will occur after the adrenal vasculature is ligated.
- Management of hypertensive crisis, both in the operating room and prior to surgery can be accomplished with phentolamine, sodium nitroprusside, or nicardipine. Esmolol may be of use if the patient is tachycardic.

Postoperative Management

- It is not uncommon for patients to develop hypotension after surgery for pheochromocytoma. This is due to a combination of the acute decline in catecholamine levels, as well as residual effects of blood pressure-lowering agents administered preoperatively. This can be managed with fluid resuscitation; rarely pressors are needed as well.
- It should be noted that individuals with pheochromocytoma and diabetes often experience an improvement in their insulin sensitivity postoperatively. Therefore, reintroduction of oral diabetes medications and insulin should be done cautiously as it is best to err on the side of inadequate therapy rather than causing hypoglycemia.

Cushing Syndrome

Patients with Cushing syndrome are occasionally encountered in the surgical ICU, typically after an infectious complication requiring surgery. In this circumstance, prompt control of hypercortisolism, to enhance previously suppressed immune function and deranged wound healing are of critical importance. The standard method to permanently control elevated plasma cortisol concentrations in patients with Cushing syndrome is to address the underlying cause. Cushing syndrome is classically divided into ACTH-dependent and ACTH-independent etiologies. Patients with ACTH-dependent disease usually harbor an ACTH-secreting pituitary adenoma. When possible, transsphenoidal resection of the tumor, usually a microadenoma, is advisable. The other ACTH-dependent cause is an ectopic hormone syndrome, classically from a pulmonary neoplasm, either a small cell carcinoma or a bronchial carcinoid. Outside of the lungs other ectopic ACTH tumors include a variety of neuroendocrine tumors, including thymic carcinoids, medullary carcinoma of the thyroid and pancreatic islet cell tumors. Very often in ectopic ACTH syndrome, the disease is metastatic at diagnosis and cannot be cured surgically. ACTH-independent causes of Cushing syndrome are primary adrenal diseases, such as adrenal adenomas, carcinomas, and, rarely, either micronodular or macronodular adrenal hyperplasias. Surgical resection is key to cure in these conditions, although adrenocortical carcinoma is an aggressive tumor that is often already quite advanced, potentially incurable, at diagnosis. The diagnostic evaluation of these syndromes is beyond the

scope of this chapter. Importantly, however, in the setting of critical illness, irrespective of cause of Cushing syndrome, the patient is not an optimal surgical candidate. Accordingly, medical therapy of hypercortisolism is required.

When urgent control of hypercortisolism is needed, options include adrenolytic therapy. Potential oral medications include ketoconazole, metyrapone, aminoglutethamide, and mitotane [62]. Each has significant side effects which may mitigate their utility in the setting of critical illness. Moreover, for maximal effectiveness, these drugs usually require several weeks of dose titration. Newer options include the oral cortisol (and progesterone) receptor antagonist, mifepristone, and the injectable somatostatin receptor antagonist, pasireotide. The former may be used in any form of Cushing syndrome whereas the letter is approved only for ACTH-secreting pituitary adenomas. Other neuroendocrine tumors associated with ectopic ACTH syndrome, including carcinoid, may also respond to other somatostatin receptor antagonists, including octreotide and lanreotide. Pasireotide has the disadvantage of being frequently associated with hyperglycemia, which itself is associated with adverse outcomes in the ICU.

One agent that could be considered in the rare case of severe, uncontrolled Cushing syndrome requiring prompt control in a critically ill patient is etomidate [63]. This IV anesthetic agent has been found to have potent anti-adrenal effects. It blocks two enzymes involved in glucocorticoid biosynthesis, 11β-hydroxylase and 17α-hydroxylase. When properly titrated, it can achieve a eucortisolemic state within several hours. Of course, careful assessment of ventilatory status is crucial when using this agent, although subhypnotic doses (0.1 mg/kg/h) have also been successfully employed [64]. When used, the dose should be titrated to achieve a plasma cortisol level in the high-normal range (15–25 mg/dL). Relative hypocortisolism should, of course, be avoided in the critically ill.

The complex, critically ill patient with Cushing syndrome requires a comprehensive, multidisciplinary approach to optimize outcomes. They frequently presented with perturbations of electrolytes (particularly hypokalemia), hyperglycemia, hypertension, and fluid overload. Ideally, an endocrinologist should be consulted to assist in patient evaluation and management.

Thyroid Disorders

Hypothyroidism

Epidemiology

The prevalence of hypothyroidism is known to depend on the variables of age, race, sex, and iodine intake. Based on National Health and Nutrition Examination Survey (NHANES) 1999–2002, the prevalence of hypothyroidism (Thyroid-stimulating hormone, TSH > 4.5 mIU/L; overt hypothyroidism with T4 < 4.5 μg/dL; mild hypothyroidism with T4 ≥ 4.5 μg/dL) in the general US population was 3.7 % (0.3 % overt and 3.4 % mild) [65]. Its prevalence increases with age and was found to be more common in women and non-Hispanic whites (compared to non-Hispanic blacks) [65].

Definition and Clinical Presentation

Hypothyroidism refers to a state where there is a reduced production of thyroid hormone in the body [66, 67]. Overt hypothyroidism is defined biochemically as an elevated serum TSH and a reduced serum-free thyroxine (FT4) concentration [68, 69]. Subclinical hypothyroidism is defined as an elevated TSH with a normal FT4 level [68, 69]. The majority (99 %) of hypothyroidism is due to primary hypothyroidism, which is due to permanent loss or destruction of the thyroid gland, and it may be congenital or acquired [66]. Acquired causes include Hashimoto's thyroiditis, Iodine deficiency, drugs (e.g., lithium, amiodarone, ipilimumab), infiltrative diseases, surgical resection, or radioactive iodine [66]. Central or secondary hypothyroidism occurs when there is a defect in TSH production [66].

Clinically, hypothyroidism may affect all organ systems and its symptoms may include fatigue, weight gain, reduced appetite, cold intolerance,

constipation, myalgias, and depression [66]. Common physical exam features include puffy appearance periorbitally, dorsa of hands and feet, and in the supraclavicular fossa, coarse skin, typically pale and cool, hair loss, thinning of the lateral eyebrow, brittle nails, hoarse voice, bradycardia, and reflexes with a delayed relaxation phase [66]. Cardiovascular effects include a decreased stroke volume, inotropy, and chronotropy, increased systemic vascular resistance, and pericardial effusion. Pulmonary effects include hypoventilation, carbon dioxide retention, and obstructive sleep apnea [66]. In addition, impaired renal excretion of water and water retention from hydrophilic deposits in tissues result in increased total body water and thus leads to hyponatremia [66]. Overt hypothyroidism is treated with thyroid hormone supplementation, which is typically based on weight-based dosing of 1.7 μg/kg once daily [70]. That being said, lower doses (e.g., 25 μg PO once daily) are used initially when treating elderly patients or patients with coronary artery disease due to the risk of increasing myocardial oxygen demand [70].

Myxedema coma is a rare but severe complication of long-standing hypothyroidism that is an endocrine emergency. It has a high mortality rate of 20–60 % and for that reason these patients require ICU care [71]. It usually occurs in the winter and in elderly patients. Clinically, it may be characterized by hypothermia, myxedematous appearance, bradycardia, severe hypotension, carbon dioxide retention, and altered mental status that may present as disorientation, confusion, psychosis, or rarely coma [71]. Dilutional hyponatremia may also be present and thus one must watch for seizures as well. Gastrointestinal complications such as ileus and megacolon may occur as well. Precipitants may include cold exposure, infection, trauma, stroke, surgery, or the use of central nervous system depressants or anesthetics [66, 71, 72]. Of note, infection may be present in the absence of fever due to the hypothyroid state.

Treatment of myxedema coma requires intravenous (IV) levothyroxine administration due to unpredictable absorption from the gut. Due to rare occurrence of myxedema coma, controlled studies on its treatment regimens are lacking. Typically, 500 μg of levothyroxine is administered intravenously in a single dose followed by daily doses of 100 μg IV [66]. Alternatively, some recommend a combination of levothyroxine 200–300 μg IV and liothyronine 25 μg IV, each given as a single dose initially, followed by one dose of levothyroxine 100 μg IV 24 h later, and then levothyroxine 50 μg IV daily until the patient regains consciousness [66]. Due to the possibility of concomitant adrenal insufficiency, stress dose hydrocortisone (e.g., 100 mg IV every 8 h) should be given simultaneously to prevent adrenal crisis while the metabolic rate increases [66, 72]. In addition, mechanical ventilation may be required if hypercapnia or hypoxia are present [71]. One should avoid active external warming with heating pads due to the resulting peripheral vasodilatation that can lead to vascular collapse [66]. Instead, internal warming by gastric perfusion may be considered. Hypotension should be treated with fluids and vasopressor agents if necessary [71]. Due to the dilutional hyponatremia, hypotonic fluids should be avoided to prevent worsening hyponatremia. Some patients may require hypertonic saline and glucose to improve severe hyponatremia and hypoglycemia that may be present [66]. For the possibility of infection, empiric broad spectrum antibiotics should be given until the infectious work-up is complete.

In general, hypothyroid patients requiring surgery may be categorized into one of the three groups: Patients with (1) known hypothyroidism that are on thyroid supplementation and are currently euthyroid, (2) mild to moderate hypothyroidism, and (3) severe hypothyroidism (myxedema coma) [72].

In the first group, surgery should not be delayed since they are euthyroid. The physician should just be aware of the diagnosis and the need for levothyroxine supplementation, whose half-life is 6–7 days in a euthyroid patient and thus it may be held for a day while the patient is NPO the night prior to the procedure [70, 73]. Of note, the elimination half-life of levothyroxine in hypothyroid patients is approximately 9–10 days [70]. Alternatively, levothyroxine may be given intravenously as about 50–75 % of the patient's oral dose while the patient is NPO [74].

Regarding the second group, unfortunately, there are no randomized controlled studies looking at outcomes in hypothyroid patients undergoing surgery. The largest are two retrospective case control studies that have been done looking at surgical outcomes. Weinberg et al. looked at 59 patients with hypothyroidism compared with euthyroid controls and found that there were no differences in surgical outcome, perioperative complications, or length of stay in the hospital [75]. This study suggested that for patients with mild to moderate hypothyroidism, there was no evidence to delay surgery. A study by Ladenson et al. looked at 40 patients with hypothyroidism and found that the hypothyroid patients had more intraoperative hypotension in noncardiac surgery and more heart failure in cardiac surgery [76]. The combined group of hypothyroid patients undergoing any surgery also had more postoperative gastrointestinal (e.g., prolonged constipation and ileus) and neuropsychiatric complications. That being said, there were no differences in perioperative arrhythmia, hypothermia, hyponatremia, impaired wound healing, postoperative infection, pulmonary complications, or death [76]. That being said, airway obstruction has been reported in hypothyroid patients in the postoperative period and thus airway patency should be monitored [77]. Thus, if patients with mild to moderate hypothyroidism need urgent surgery, it should be performed but the patient should be closely monitored for possible postoperative complications as described above.

A controversial area is whether patients with mild to moderate hypothyroidism who present for cardiac catheterization or cardiac surgery should be treated with thyroid hormone replacement [72, 78]. The reason is that thyroid hormone therapy can increase the myocardial oxygen demand thereby causing ischemia [72]. A prospective study by Drucker et al. looked at ten untreated hypothyroid patients with mild to moderate hypothyroidism and ischemic heart disease who underwent coronary artery bypass surgery and found that all of these patients tolerated this surgery well without any thyroid hormone supplementation [78]. Thus, it is felt that if patients with mild to moderate hypothyroidism require urgent cardiac revascularization, in many cases this procedure may be performed prior to starting thyroid supplementation [72]. If it is safe to delay the cardiac surgery, then another approach would be to start a low dose (e.g., 25 μg PO daily) to at least partially correct the hypothyroidism prior to surgery [72]. Most of all, it is important to make a decision based on the individual patient's risks and benefits.

In summary, limited evidence suggests that surgery may be performed in patients with mild to moderate hypothyroidism without delay but that one must be watchful for complications as noted above. That being said, these studies did not include many patients with severe hypothyroidism or myxedema coma and thus in these patients, we recommend delaying surgery until their clinical condition has improved. If, however, the surgery is emergent and must be performed in a patient with severe hypothyroidism, treatment with intravenous T3 or T4 and stress dose glucocorticoids as detailed above should be given perioperatively [73].

Thyrotoxicosis

Epidemiology

Based on National Health and Nutrition Examination Survey (NHANES) 1999–2002, the prevalence of hyperthyroidism (Thyroid-stimulating hormone, TSH < 0.1 mIU/L) in the general US population was 0.5 % [65]. Hyperthyroidism is more common in females, nonwhites, and the elderly.

Definitions and Clinical Presentation

Thyrotoxicosis refers to a state of excess thyroid hormone whereas hyperthyroidism specifically refers to overproduction and release of thyroid hormone [66]. Causes of hyperthyroidism include Graves' disease, toxic multinodular goiter, toxic adenoma, type 1 amiodarone-induced thyrotoxicosis, or rarely metastatic functioning thyroid carcinoma [66]. The most common is Graves' disease, which is a disorder where autoimmune antibodies stimulate the TSH receptors and lead to an increase in thyroid hormone production [66].

Thyrotoxicosis with transient hormone excess includes thyroiditis, which may be autoimmune, viral, or drug-induced (e.g., type 2 amiodarone-induced thyrotoxicosis, lithium, interferon-α, IL-2, GM-CSF) in etiology [66].

Clinically, hyperthyroidism may affect all organ systems and its symptoms may include fatigue, weight loss, increased appetite, heat intolerance, palpitations, nausea, emesis, hyperdefecation, and irregular or absent menses in women [66, 71]. Insomnia, anxiety, and emotional lability may also be seen. Physical exam findings may often include fever, tachycardia, atrial fibrillation, proptosis, exophthalmos, a stare, lid lag, goiter, proximal muscle weakness, tremor, and hyperkinesia [66]. Onycholysis may also be seen. In addition to abnormal thyroid function tests, additional lab findings may include elevated alanine aminotransferase (ALT) and alkaline phosphatase (AP) levels, which may be due to decreased splanchnic blood flow, and hypercalcemia, which is due to increased bone resorption relative to bone formation [66].

Thyroid storm is a rare but severe complication of hyperthyroidism that has a mortality rate of 20–50 % and is considered an endocrine emergency [79, 80]. It is most commonly seen in Graves' disease and precipitants may include infection, trauma, surgical emergencies, or planned operations. Other less common precipitants may include radiation thyroiditis, parturition, or DKA [66]. In this condition, the patient cannot tolerate the metabolic stress present. Similar to other patients with thyrotoxicosis, they may have fever, diaphoresis, tachycardia, arrhythmias, and tremor but these features are typically much greater in magnitude. In addition, these patients may also have emesis, pulmonary edema, high-output congestive heart failure (CHF), hypotension, agitation, delirium, psychosis, and even coma [66]. Thyroid storm is a clinical diagnosis but there is a scoring system that can aid with its diagnosis. This score takes into account features of the patient's presentation including temperature, central nervous system effects such as agitation, delirium, psychosis, extreme lethargy, seizure, and coma, gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal pain, and jaundice, cardiovascular complications including tachycardia, CHF, atrial fibrillation, and the presence of a precipitant [81].

Due to the severity of thyroid storm, the patient should be placed in the ICU. The goals in the treatment of thyroid storm are to achieve a euthyroid state, treat the intercurrent illness if one is present, and provide supportive care [66]. Propylthiouracil (up to 400 mg every 4–6 h) is the preferred thionamide choice because it inhibits both thyroid hormone synthesis and thyroidal and peripheral conversion from T4 to T3 [66]. Saturated solution of potassium iodide (SSKI; 50 mg iodide per drop; 5 drops every 6 h) or Lugol's solution (8 mg iodine per drop; 5–10 drops three times per day) is given to decrease the release of preformed thyroid hormone from the gland and this is called the Wolff–Chaikoff effect [66]. These should be administered at least 1 h after the patient is given thionamide therapy to prevent the use of that iodide as substrate for more thyroid hormone production. Stress dose steroids (hydrocortisone 100 mg IV every 8 h or dexamethasone 8 mg once daily) should be given to inhibit the release of thyroid hormone and decrease peripheral conversion from T4 to T3. Beta blockers should be used to control the patient's tachycardia unless asthma or cardiac failure is present. Due to the risk of high-output heart failure in these patients, a short acting beta-blocker such as esmolol or labetalol may be used [66]. That being said, propranolol has more commonly been used. If there is a contraindication to using beta blockade, a calcium channel blocker such as diltiazem is an alternative rate control agent. After an infectious work-up including blood and urine cultures are sent, empiric broad-spectrum antibiotics may be given. Supportive care includes treating the fever with acetaminophen and ice packs. Salicylates worsen free thyroid hormone levels by displacing T3 and T4 from TBG and transthyretin and thus are not recommended [82].

In general, hyperthyroid patients requiring non-thyroidal surgery may be categorized into one of the three groups: Patients with (1) known hyperthyroidism that are on antithyroid medications and are currently euthyroid, (2) mild to moderate hyperthyroidism, and (3) severe hypo-

thyroidism (thyroid storm). In the first group of patients, surgery does not need to be delayed. They should take their antithyroid medications on the morning of surgery [72, 83]. For those who have uncontrolled hyperthyroidism that is mild or moderate, surgery should not be performed unless it is urgent or emergent [72]. If surgery must be performed despite the presence of uncontrolled hyperthyroidism, the anesthesiologist must be aware of the patient's condition and anticipate the likely need for antithyroid medications (thionamides such as propylthiouracil or methimazole), beta blockers, corticosteroids, and iodine (SSKI; Lugol's solution) [72]. In patients with thyroid storm, surgery should be avoided unless it is emergent and therapy has been initiated.

Indications for thyroidectomy include thyroid malignancy, refractory thyrotoxicosis from amiodarone, toxic MNG, toxic adenoma, or Graves' disease [84, 85]. In these patients, a euthyroid state should be achieved before the thyroidectomy is performed in order to decrease the risk of complications such as thyroid storm. The appropriate treatment should be given, which may include antithyroid medications, steroids, and beta blockers for the reasons described above. In addition, SSKI drops may be used to decrease the vascularity of the gland preoperatively [72, 86].

Nonthyroidal Illness Syndrome

Nonthyroidal illness syndrome (NTIS) is also known as "low T3 syndrome" or "euthyroid sick syndrome." NTIS refers to the thyroid function testing abnormalities that are found in patients with nonthyroidal illness. It may be seen in up to 75 % of hospitalized patients and although the lab abnormalities are variable, it is typically characterized by a low triiodothyronine (T3), elevated reverse T3 (rT3), low or low normal TSH, and sometimes a low free thyroxine (fT4) [87]. The degree of these changes is more profound in patients who are critically ill and lower T4 levels in ICU patients have been associated with increased mortality [39, 61]. Some believe that these changes in thyroid hormone levels are protective to patients who are ill by decreasing overall metabolism [66, 88].

The majority of circulating T3 is made peripherally in the liver and kidney by 5′-deiodination of T4 and the remainder is secreted by the thyroid [66, 89]. This is performed by D1 and D2 5′-monodeiodinases [66]. T4 may also be converted to rT3, which is thought to be hormonally inactive, by the D3 5′-deiodinase. The mechanisms that are believed to lead to the above thyroid test abnormalities include: (1) ow T3 level due to inhibition of 5′-monodeiodination, (2) elevated rT3 due to inhibition of 5′-monodeiodinase activity resulting in less rT3 to diiodothyronine (T2) conversion (less clearance), and (3) low T4 level due to decreased T4 binding and transient central hypothyroidism [66, 90–92]. The mechanisms that lead to inhibition of 5′-monodeiodinase activity leading to low T3 include: (1) exogenous glucocorticoids or elevated endogenous serum cortisol levels, (2) FFA, (3) cytokines (e.g., IFN-α, TNF, IL-6, NF-kB), and (4) drugs such as amiodarone, propranolol, and propylthiouracil [91, 93–97].

In the recovery phase of illness, patients with NTIS may develop a temporary rise in their TSH but typically these patients eventually show normalization of their TSH within 1–2 months [66]. Treatment of patients with NTIS is controversial, but there is no evidence that treatment of NTIS patients with thyroid supplementation is beneficial [98, 99]. Thus, in acutely ill patients, thyroid function tests are not generally recommended unless the patient's clinical presentation is felt to be due to hypothyroidism or thyrotoxicosis.

Calcium Disorders

Serum Calcium in Normal Conditions

Careful regulation of calcium balance in the body is essential because calcium is the main mineral component of the skeleton, calcium plays important roles in neuronal transmission, muscle contraction, and blood clotting, and calcium is a key intracellular signal that controls numerous processes throughout the body.

A typical normal range for serum total calcium concentration is between 8.8 and 10.5 mg/dL. Of this calcium, 50–60 % of the calcium is bound to plasma proteins or is complexed with anions such as citrate and phosphate. The remaining ionized or "free" calcium is responsible for its physiologic actions. The concentration of ionized calcium is normally maintained in a very tight range: 4.5–5.3 mg/dL.

The body maintains normal serum calcium by regulating its entry through the intestine, its exit via the kidney, and its storage in bone. These processes are controlled by parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$]. PTH is produced by the parathyroid glands. 1,25-$(OH)_2D_3$ is made by a sequence of events beginning when cholecalciferol (vitamin D_3) is produced by exposure of the skin to UV light; it is also derived from dietary sources or supplements. In the liver, vitamin D_3 is converted to 25-(OH) vitamin D_3, which in turn is hydroxylated in the kidney to produce the active form, 1,25-$(OH)_2D_3$ (calcitriol). The effect of PTH and 1,25-$(OH)_2D_3$ is to keep plasma-ionized calcium concentration under tight control, despite variations in calcium supply.

Fluctuations in plasma-ionized calcium concentration are monitored by parathyroid cells via the cell membrane calcium-sensing receptor (CaSR) [100]. Binding of calcium ions to the extracellular domain of the CaSR activates a series of intracellular signaling events, ultimately controlling PTH secretion. Plasma-ionized calcium levels above normal lead to down-regulation of PTH secretion, while low ionized calcium causes an increase in PTH secretion. PTH activates bone resorption and distal nephron calcium resorption. PTH also increases renal production of calcitriol, which stimulates calcium absorption by the small intestine.

Hypercalcemia

Hypercalcemia is a frequently encountered metabolic abnormality. Presenting signs and symptoms may be absent or subtle, except in cases where calcium is significantly elevated or has risen rapidly. The diagnostic work-up of hypercalcemia is straightforward [101]. Identifying the cause of hypercalcemia requires a complete history, physical examination, laboratory tests, and diagnostic imaging studies.

History and Physical Examination

Most patients with mild hypercalcemia (serum calcium level <11 mg/dL) do not have symptoms, although they may have mild fatigue, changes in cognition, depressed mood, or constipation. In individuals with serum calcium values between 12 and 14 mg/dL, there may be anorexia, nausea, abdominal pain, muscle weakness, and depressed mental status. Dehydration may be seen caused by decreased urine concentrating ability due to high urinary calcium levels. At calcium levels above 14 mg/dL, there may be progressive lethargy and coma.

A review of the medical record may help determine the duration of the hypercalcemia and its cause. Prescription medications, food, and dietary supplements should be considered possible causative agents. A family history should be performed to identify evidence of any related endocrinopathies. Patients who have hyperparathyroidism associated with multiple endocrine neoplasia (MEN) may show evidence of the other conditions that make up these syndromes. Patients with sarcoidosis may have fever, lymphadenopathy, rashes, or pulmonary manifestations. Hypercalcemia of malignancy typically develops only when a significant tumor burden is present; thus, most of these patients have an established cancer diagnosis.

On physical exam, evidence for dehydration should be sought. Aside from depressed mental status and signs of dehydration, physical exam findings are generally normal in hypercalcemic patients, particularly if calcium levels are only modestly elevated.

Laboratory Studies

The first step in evaluating hypercalcemia is to rule out spurious hypercalcemia caused by an increase in concentrations of the plasma proteins that bind calcium. This may be seen in HIV infection, chronic hepatitis, and multiple myeloma.

The ionized calcium concentration in these situations remains normal. To correct the measured serum calcium for elevations in plasma protein, the serum calcium level should be lowered by 0.8 mg/dL for every 1 g/dL of albumin above the normal range. When performed under optimal conditions, ionized calcium measurement is more accurate than adjusted total serum calcium.

Once hypercalcemia is confirmed, the next step is measurement of the serum PTH concentration [102]. The results of PTH measurement indicate whether hypercalcemia is mediated by PTH and thus help identify the cause of hypercalcemia. The hypercalcemia is considered PTH mediated if serum calcium is high and the PTH level is elevated or inappropriately normal. When PTH levels are low in the face of high serum calcium, the hypercalcemia is said to be non-PTH mediated, or PTH independent.

Serum creatinine should be measured as hypercalcemia that may be seen in the setting of renal failure, and renal function may be impaired in the setting of dehydration or nephrocalcinosis. Levels of 25-(OH) vitamin D should be measured to rule out supplemental vitamin D intoxication. High 1,25-$(OH)_2$D levels may be seen in granulomatous disease and some lymphomas. Inorganic phosphorus measurement may be helpful as low serum phosphate is often seen in primary hyperparathyroidism, while high phosphate may occur in vitamin D intoxication.

Other diagnostic studies may be dictated by clinical circumstances. Electrocardiography is recommended for patients with severe hypercalcemia to detect shortening of the QTc interval or atrioventricular block.

Causes of Hypercalcemia

Primary hyperparathyroidism: High serum calcium and PTH concentrations [in the absence of lithium use or familial hypocalciuric hypercalcemia (FHH)] is evidence of primary hyperparathyroidism. PTH levels are usually increased to no more than five times the upper limit of normal. More significant elevations should raise suspicion for parathyroid carcinoma. In 75–80 % of patients, a solitary parathyroid adenoma is present, hyperplasia involving multiple parathyroid glands is found in 15–20 % of patients, and parathyroid carcinoma is present in less than 1 %. On occasion, double adenomas are found [103]. Patients with multiple endocrine neoplasia type I (MEN I) or MEN II typically have parathyroid hyperplasia involving all parathyroid glands [104].

Familial hypocalciuric hypercalcemia: FHH, also referred to as benign familial hypercalcemia, is a rare genetic condition caused by inactivating mutations in the CaSR. This results in insensitivity of the parathyroid cell to serum calcium, a higher set point for the extracellular ionized calcium concentration and inappropriately normal to mildly elevated PTH levels. Patients with FHH have chronic asymptomatic hypercalcemia associated with relatively low urinary calcium excretion. This is usually a benign condition requiring no treatment.

Tertiary hyperparathyroidism: Diseases that result in a low serum calcium or a high serum phosphate typically will be associated with an elevation in PTH as a compensatory measure. This increase of PTH is termed secondary hyperparathyroidism. Common causes of secondary hyperparathyroidism include vitamin D deficiency, intestinal malabsorption of calcium or vitamin D, renal calcium wasting, severe dietary calcium insufficiency, and hyperphosphatemia from chronic renal insufficiency.

In patients with long-term secondary hyperparathyroidism, hyperplasia or neoplasia of the parathyroid glands may develop. This results in autonomous parathyroid function, with the production of excess PTH at all times, resulting in hypercalcemia. This is most often seen in patients with chronic kidney disease. More than one parathyroid gland is usually affected.

Once the diagnosis of primary hyperparathyroidism is made, additional testing may be necessary to determine whether the condition is severe enough to warrant parathyroidectomy [105]. If MEN II is in the differential diagnosis, medullary thyroid cancer should be excluded, and pheochromocytoma must be ruled out before the patient can safely go to surgery.

Malignancy-associated hypercalcemia: If the serum calcium is elevated and the PTH is low, the patient has PTH-independent hypercalcemia. Malignancy is the most common cause of PTH-independent hypercalcemia and is usually to blame when an acutely elevated calcium level is discovered. When the PTH is low and the patient is not known to have a malignancy, other diagnostic options should include thyrotoxicosis, vitamin D intoxication, sarcoidosis, immobilization, certain endocrine disorders, and drugs and supplements.

Hypercalcemia of malignancy has two forms: humoral hypercalcemia of malignancy (HHM) and local osteolytic hypercalcemia (LOH). HHM results from production by the tumor of a circulating factor that affects calcium metabolism, either at the level of skeletal calcium release, renal calcium handling, or intestinal calcium absorption. Occasionally it can be caused by the unregulated production of calcitriol (usually by B cell lymphomas) or other mediators that interfere with calcium homeostasis. The best-recognized cause of HHM is parathyroid hormone-related protein (PTHrP) [106]. The PTHrP peptide is homologous with PTH, and they have a common receptor. When PTHrP circulates at supraphysiologic concentrations, it causes similar metabolic effects to PTH, inducing osteoclasts to resorb bone, reducing renal calcium output, and increasing renal phosphate clearance [106].

Tumors that produce HHM by secreting PTHrP are typically squamous carcinomas, adenocarcinoma of the breast or ovary, renal carcinoma, transitional cell carcinoma of the bladder, islet cell tumors of the pancreas, T cell lymphomas, and pheochromocytoma [107]. HHM typically develops in patients with a large tumor burden, so it is uncommon for HHM to be the presenting feature of a cancer. A high serum PTHrP level will confirm the diagnosis of HHM.

LOH occurs when a bony metastasis causes release of calcium through the elaboration of cytokines or other factors that activate bone resorption by osteoclasts. In LOH there is evidence of bone metastases by symptoms and/or imaging studies. Multiple myeloma, adenocarcinomas of the breast, and certain lymphomas may cause LOH.

PTH-independent hypercalcemia may occur in sarcoidosis, tuberculosis, and other granulomatous diseases, when granulomas release excessive calcitriol. Elevation of serum 25-hydroxyvitamin D indicates excessive vitamin D intake, while elevation of serum 1,25-dihydroxyvitamin D occurs in granulomatous diseases. Endocrine disorders that may occasionally lead to hypercalcemia include severe hyperthyroidism (which activates bone resorption) and Addison's disease (where volume depletion causes hypercalcemia). Immobilization stimulates bone resorption and can result in elevated serum calcium levels, particularly in bed-bound hospitalized patients. Thiazide diuretics may cause hypercalcemia due to enhanced retention of calcium by the kidney. In many cases this develops in individuals with underlying mild primary hyperparathyroidism [108].

Treatment of Hypercalcemia

A malignancy is often the cause of acute hypercalcemia. When the serum calcium level is significantly elevated, treatment should include intravenous hydration, along with measures to enhance renal calcium excretion and reduce bone resorption and/or intestinal calcium absorption, depending on which is the cause of calcium excess.

Saline Hydration

Most individuals with acute hypercalcemia have some degree of hypovolemia, which worsens their ability to excrete calcium. Thus, the first intervention should be fluid resuscitation with normal saline. The use of normal saline is important, as arrival of sodium at the distal nephron will enhance urinary calcium excretion. When the intravascular volume is repleted, a loop diuretic such as furosemide may be started to allow additional saline hydration and to enhance calcium excretion. A serum calcium·phosphate product above 70 indicates the patient is at risk for calciphylaxis, so reduction of the serum phosphate level with phosphate binders should be undertaken along with efforts to lower serum calcium.

Bisphosphonate Therapy

If the serum calcium does not return to an acceptable level with intravenous saline and diuresis, then pharmacologic therapy is required [109]. Most causes of severe hypercalcemia involve increased osteoclast-mediated bone resorption, so drugs that inhibit this process are helpful. The drug of choice is a bisphosphonate, such as pamidronate or zoledronic acid, both of which are given intravenously. Pamidronate 60–90 mg is given intravenously over a few hours and is generally well tolerated. Serum calcium levels will typically begin to decline within 24–48 h following the infusion, although the peak effect may take several days. The actions of pamidronate may last several weeks, but retreatment may be undertaken if renal function will allow. Zoledronic acid is given at 4 mg intravenously over at least 15 min [110]. It has a greater potency and a longer duration of action than pamidronate. A repeat dose may be provided after 7 days if renal function allows.

Other Treatments for Hypercalcemia

When a more rapid decline in serum calcium is desired, subcutaneous injections of calcitonin can be employed. Calcitonin is administered at a starting dosage of 4 U/kg every 12 h. Tachyphylaxis to the actions of calcitonin usually limits its effects to a few days. In severe or refractory hypercalcemia, hemodialysis against a low-calcium bath may be necessary.

Glucocorticoid therapy has an important role when hypercalcemia results from an increase in intestinal calcium absorption, as occurs in vitamin D intoxication or granulomatous diseases. Glucocorticoids inhibit the renal or granulomatous 1α-hydroxylase activity resulting in a decrease in production of calcitriol, and they also directly impair intestinal calcium transport. In hypercalcemia due to lymphoma, treatment with steroids may also indirectly reduce hypercalcemia due to their antineoplastic effect.

In malignancy-associated hypercalcemia, chemotherapy, surgery, or radiation therapy targeted at the tumor itself may also reduce the hypercalcemia.

Management of a patient with primary hyperparathyroidism is based upon the degree of hypercalcemia, the severity of symptoms or end-organ damage and the risk of future complications [111]. Guidelines for surgical intervention in patients with asymptomatic primary hyperparathyroidism were most recently updated at a National Institutes of Health workshop in 2008 [105].

In patients who are very hypercalcemic but cannot or will not have surgery, the calcimimetic agent cinacalcet has been used to control hypercalcemia. Calcimimetic agents such as cinacalcet activate the CaSR and thus diminish PTH production, ultimately leading to reduced serum calcium.

Hypocalcemia

Chronic, mild, or moderate hypocalcemia is often asymptomatic. However, when the serum calcium level falls below 7.5–8 mg/dL (in the setting of normal albumin), individuals may develop symptoms of neuromuscular irritability, including tremor, muscle spasms, and paresthesias.

The cause of hypocalcemia can usually be elucidated after a careful history. Dietary calcium and vitamin D intake, sun exposure, and alcohol intake should be evaluated. Head and neck surgery or irradiation can lead to hypoparathyroidism. Rare conditions, such as autoimmune disease and iron overload disorders should be considered. Other conditions, such as pancreatitis, rhabdomyolysis, tumor lysis syndrome, or transfusion therapy are possible causes for hypocalcemia.

On physical exam, Chvostek and Trousseau signs may be elicited. With more severe hypocalcemia, tetany or seizures may appear. Prolongation of the QTc interval may be evident on electrocardiogram, indicating the patient is at risk for cardiac arrhythmias.

Hypocalcemia is often caused by vitamin D deficiency or hypoparathyroidism. Injury or removal of the parathyroid glands during thyroidectomy can lead to hypoparathyroidism, which is manifested by hypocalcemia and a low serum PTH. Patients who have parathyroidectomy for primary hyperparathyroidism may have hypocalcemia due to deposition of large quantities of

calcium into the unmineralized matrix of the skeleton. This is known as "hungry bone syndrome."

Autoimmune destruction of the parathyroid glands may occur in certain conditions [112]. Infiltrative diseases, such as hemochromatosis, may impair parathyroid function, as can external-beam irradiation to the neck. Congenital absence of the parathyroid glands is seen in DiGeorge syndrome. Hypomagnesemia may cause hypoparathyroidism because magnesium is needed for both PTH release and PTH action. This is commonly seen in alcoholic patients who are frequently hypomagnesemic and malnourished.

Disorders of vitamin D supply, production, or activation may lead to hypocalcemia. In vitamin D deficiency, serum calcium concentrations are usually not severely affected, due to compensatory increases in PTH and its downstream effects to keep serum calcium normal.

Hypocalcemia can be seen in acute pancreatitis, when fatty acids released through the action of pancreatic enzymes complex with calcium. Hypocalcemia due to the formation of calcium phosphate complexes takes place in severe hyperphosphatemic states, such as renal failure, rhabdomyolysis, and tumor lysis syndrome. In these conditions, formation of calcium phosphate complexes results in a decrease in ionized calcium concentrations. Hypocalcemia may also be seen in patients given multiple red blood cell transfusions using cells to which calcium chelators have been added to prevent clotting.

Treatment of Hypocalcemia

In patients with symptoms of severe hypocalcemia (e.g., those with neuromuscular irritability), calcium (as calcium gluconate) should be administered by slow intravenous infusion to increase the serum calcium level until symptoms resolve. Bolus administration of intravenous calcium will have only a transient effect on serum calcium. An example of a calcium infusion is 10 ampules (total 100 mL) of 10 % calcium gluconate in 1 L of D_5W, infused at 50 cm^3/h. Serum calcium should be monitored frequently and the rate of infusion adjusted to maintain levels at the low end of the normal range. Simultaneously, any deficiency of magnesium and/or vitamin D should be corrected. Hypocalcemia may recur rapidly after discontinuation of the calcium infusion, so oral calcium should be administered prior to tapering the infusion. In patients with milder hypocalcemia, calcium infusion is not necessary and calcium can be administered orally as calcium carbonate or calcium citrate in doses starting at 1,000–1,500 mg of elemental calcium daily in divided doses with meals. If appropriate, vitamin D also should be provided.

In chronic hypoparathyroidism, treatment with calcitriol is necessary because renal production of calcitriol will not occur in the absence of PTH. Serum calcium should be kept at the lower end of the normal range, sufficient to relieve symptoms and reverse tetanic signs (e.g., Chvostek sign).

References

1. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27:553–91.
2. Honiden S, Inzucchi SE. Analytic review: glucose controversies in the ICU. J Intensive Care Med. 2011;26:135–50.
3. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. Circulation. 2008;117:1018–27.
4. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg. 1999;67:352–60.
5. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
6. NICE-SUGAR Study Investigators, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hébert PC, Heyland DK, Robinson BG. N Engl J Med. 2012 Sep 20;367(12):1108–18.
7. Kosiborod M, Inzucchi SE, Goyal A, Krumholz HM, Masoudi FA, Xiao L, Spertus JA. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA. 2009;301:1556–64.

8. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180:821–7.
9. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32:1119–31.
10. Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med. 2012;12:3251–76.
11. Surviving Sepsis Campaign. http://www.survivingsepsis.org/Guidelines/Pages/default.aspx. Accessed 3 Nov 2013.
12. Shetty S, Inzucchi SE, Goldberg PA, Cooper D, Siegel MD, Honiden S. Adapting to the new consensus guidelines for managing hyperglycemia during critical illness: the updated Yale insulin infusion protocol. Endocr Pract. 2012;18:363–70.
13. Finfer S, Wernerman J, Preiser JC, Cass T, Desaive T, Hovorka R, et al. Clinical review: consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013;17:229.
14. Avanzini F, Marelli G, Donzelli W, Busi G, Carbone S, Bellato L, et al. Transition from intravenous to subcutaneous insulin: effectiveness and safety of a standardized protocol and predictors of outcome in patients with acute coronary syndrome. Diabetes Care. 2011;34:1445–50.
15. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:16–38.
16. Maynard G, Wesorick DH, O'Malley C, Inzucchi SE, Society of Hospital Medicine Glycemic Control Task Force. Subcutaneous insulin order sets and protocols: effective design and implementation strategies. J Hosp Med. 2008;3:29–41.
17. Centers for Disease Control. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics/dkafirst/fig7.htm. Accessed 18 Aug.
18. Centers for Disease Control. National Diabetes Surveillance. System. http://www.cdc.gov/diabetes/statistics/mortalitydka/fRateDKAGenAgeAdjusted.htm. Accessed 18 Aug.
19. Kitabchi A, Umpierrez G, Miles J, Fisher J. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335–43.
20. Elisaf MS, Tsatsoulis AA, Katopodis KP, Siamopoulos KC. Acid-base and electrolyte disturbances in patients with diabetic ketoacidosis. Diabetes Res Clin Pract. 1996;34(1):23–7.
21. Yasuda K, Tanahashi H, Hayashi M, Yamakita N. Hyperglycemic crises in adult patients with diabetes: response to Kitabchi et al. Diabetes Care. 2009;32(12):e157; author reply e158.
22. Adrogué HJ, Wilson H, Boyd AE, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med. 1982;307(26):1603–10.
23. Kitabchi A, Nyenwe E. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin North Am. 2006;35(4):725–51, viii.
24. Ennis E, Kreisberg R. Diabetic ketoacidosis and the hyperglycemic hyperosmolar syndrome. In: LeRoith D, Taylor S, Olefsky J, editors. Diabetes mellitus. Philadelphia: Lippincott Williams & Williams; 2004. p. 627.
25. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, Ellis SE, O'Sullivan PS. Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. J Gen Intern Med. 1991;6(6):495–502.
26. Umpierrez G, Smiley D, Kitabchi A. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med. 2006;144(5):350–7.
27. Mauvais-Jarvis F, Sobngwi E, Porcher R, et al. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. Diabetes. 2004;53(3):645–53.
28. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. Endocr Rev. 2008;29(3):292–302.
29. Magee M, Bhatt B. Management of decompensated diabetes. Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Crit Care Clin. 2001;17(1):75–106.
30. Kitabchi A, Umpierrez G, Murphy M, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care. 2001;24(1):131–53.
31. Büyükaşik Y, Ileri N, Haznedaroğlu I, et al. Enhanced subclinical coagulation activation during diabetic ketoacidosis. Diabetes Care. 1998;21(5):868–70.
32. Stentz F, Umpierrez G, Cuervo R, Kitabchi A. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes. 2004;53(8):2079–86.
33. Joslin EP, Kahn CR, Weir GC. Joslins diabetes mellitus. 13th ed. Malvern: Lea & Febiger; 1994.
34. Umpierrez G, Freire A. Abdominal pain in patients with hyperglycemic crises. J Crit Care. 2002;17(1):63–7.
35. Umpierrez G, Kelly J, Navarrete J, Casals M, Kitabchi A. Hyperglycemic crises in urban blacks. Arch Intern Med. 1997;157(6):669–75.
36. Hillier T, Abbott R, Barrett E. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106(4):399–403.
37. Huang CC, Kuo SC, Chien TW, et al. Predicting the hyperglycemic crisis death (PHD) score: a new decision rule for emergency and critical care. Am J Emerg Med. 2013;31(5):830–4.

38. Slovis C, Mork V, Slovis R, Bain R. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. Am J Emerg Med. 1987;5(1):1–5.
39. Trence D, Hirsch I. Hyperglycemic crises in diabetes mellitus type 2. Endocrinol Metab Clin North Am. 2001;30(4):817–31.
40. Yadav D, Nair S, Norkus E, Pitchumoni C. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol. 2000;95(11):3123–8.
41. Nyenwe E, Loganathan R, Blum S, et al. Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. Endocr Pract. 2007;13(1):22–9.
42. Bratusch-Marrain P, DeFronzo R. Impairment of insulin-mediated glucose metabolism by hyperosmolality in man. Diabetes. 1983;32(11):1028–34.
43. Kitabchi A, Murphy M, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care. 2008;31(11):2081–5.
44. Umpierrez G, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med. 2004; 117(5):291–6.
45. Umpierrez G, Cuervo R, Karabell A, Latif K, Freire A, Kitabchi A. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care. 2004;27(8):1873–8.
46. Kitabchi A, Umpierrez G, Murphy M, Kreisberg R. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care. 2006;29(12): 2739–48.
47. Fisher J, Kitabchi A. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab. 1983;57(1):177–80.
48. Mitchell J, Wildenthal K, Johnson RJ. The effects of acid-base disturbances on cardiovascular and pulmonary function. Kidney Int. 1972;1(5):375–89.
49. Morris L, Murphy M, Kitabchi A. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med. 1986;105(6):836–40.
50. Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a Basal-bolus with a Basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care. 2013;36(8):2169–74.
51. Roberts M, Slover R, Chase H. Diabetic ketoacidosis with intracerebral complications. Pediatr Diabetes. 2001;2(3):109–14.
52. Sakharova OV, Inzucchi SE. Endocrine assessments during critical illness [review]. Crit Care Clin. 2007;23:467–90.
53. Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, et al. Reduced cortisol metabolism during critical illness. N Engl J Med. 2013;368:1477–88.
54. Annane D, Briegel J, Sprung CL. Corticosteroid insufficiency in acutely ill patients [letter]. N Engl J Med. 2003;348:2157–9.
55. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al.; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358:111–24.
56. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al.; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39:165–228.
57. Marik PE. Glucocorticoids in sepsis: dissecting facts from fiction. Crit Care. 2011;15:158.
58. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med. 2004;350:1629–38.
59. Steven KH. Adrenal cortical steroids. In: Drug facts and comparisons. 5th ed. St. Louis: Facts and Comparisons, Inc.; 1997. p. 122–128.
60. Havlik RJ, Cahow CE, Kinder BK. Advances in the diagnosis and treatment of pheochromocytoma. Arch Surg. 1988;123(5):626–30.
61. Steinsapir J, Carr AA, Prisant LM, Bransome ED. Metyrosine and pheochromocytoma. Arch Intern Med. 1997;157(8):901–6.
62. Gadelha M, Neto LV. Efficacy of medical treatment in Cushing's disease: a systematic review. Clin Endocrinol (Oxf). 2014;80:1–12.
63. Preda VA, Sen J, Karavitaki N, Grossman AB. Etomidate in the management of hypercortisolaemia in Cushing's syndrome: a review. Eur J Endocrinol. 2012;167:137–43 [Erratum]. Eur J Endocrinol. 2013;168(2):X1.
64. Schulte HM, Benker G, Reinwein D, Sippell WG, Allolio B. Infusion of low dose etomidate: correction of hypercortisolemia in patients with Cushing's syndrome and dose-response relationship in normal subjects. J Clin Endocrinol Metab. 1990;70(5): 1426–30.
65. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid. 2007;17(12):1211–23.
66. Williams RH, Melmed S. Williams textbook of endocrinology. 12th ed. Philadelphia: Elsevier/ Saunders; 2011. http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20090530966.
67. Roberts CG, Ladenson PW. Hypothyroidism. Lancet. 2004;363(9411):793–803.
68. Cooper DS. Clinical practice. Subclinical hypothyroidism. N Engl J Med. 2001;345(4):260–5.
69. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821):1142–54.

70. Product information: SYNTHROID(R) oral tablets lsotAL, North Chicago, IL, 2008. http://www.rxabbvie.com/pdf/synthroid.pdf.
71. Fliers E, Wiersinga WM. Myxedema coma. Rev Endocr Metab Disord. 2003;4(2):137–41.
72. Kohl BA, Schwartz S. How to manage perioperative endocrine insufficiency. Anesthesiol Clin. 2010; 28(1):139–55.
73. Schiff RL, Welsh GA. Perioperative evaluation and management of the patient with endocrine dysfunction. Med Clin North Am. 2003;87(1): 175–92.
74. Product information: levothyroxine sodium intravenous injection lsiiAP, LLC (per FDA), Schaumburg, IL, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202231s003lbl.pdf.
75. Weinberg AD, Brennan MD, Gorman CA, Marsh HM, O'Fallon WM. Outcome of anesthesia and surgery in hypothyroid patients. Arch Intern Med. 1983;143(5):893–7.
76. Ladenson PW, Levin AA, Ridgway EC, Daniels GH. Complications of surgery in hypothyroid patients. Am J Med. 1984;77(2):261–6.
77. Benfari G, de Vincentiis M. Postoperative airway obstruction: a complication of a previously undiagnosed hypothyroidism. Otolaryngol Head Neck Surg. 2005;132(2):343–4.
78. Drucker DJ, Burrow GN. Cardiovascular surgery in the hypothyroid patient. Arch Intern Med. 1985;145(9):1585–7.
79. Ashkar FS, Miller R, Gilson AJ. Thyroid function and serum thyroxine in thyroid storm. South Med J. 1972;65(3):372–4.
80. Mazzaferri EL, Skillman TG. Thyroid storm. A review of 22 episodes with special emphasis on the use of guanethidine. Arch Intern Med. 1969;124(6): 684–90.
81. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. 1993;22(2):263–77.
82. Larsen PR. Salicylate-induced increases in free triiodothyronine in human serum. Evidence of inhibition of triiodothyronine binding to thyroxine-binding globulin and thyroxine-binding prealbumin. J Clin Invest. 1972;51(5):1125–34.
83. Spell NO. Stopping and restarting medications in the perioperative period. Med Clin North Am. 2001;85(5):1117–28.
84. Langley RW, Burch HB. Perioperative management of the thyrotoxic patient. Endocrinol Metab Clin North Am. 2003;32(2):519–34.
85. Franzese CB, Fan CY, Stack BC. Surgical management of amiodarone-induced thyrotoxicosis. Otolaryngol Head Neck Surg. 2003;129(5):565–70.
86. Streetman DD, Khanderia U. Diagnosis and treatment of Graves disease. Ann Pharmacother. 2003;37(7–8):1100–9.
87. Adler SM, Wartofsky L. The nonthyroidal illness syndrome. Endocrinol Metab Clin North Am. 2007;36(3):657–72, vi.
88. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA. 1981;245(1):43–5.
89. Utiger RD. Altered thyroid function in nonthyroidal illness and surgery. To treat or not to treat? N Engl J Med. 1995;333(23):1562–3.
90. Chopra IJ. An assessment of daily production and significance of thyroidal secretion of 3, 3′, 5′-triiodothyronine (reverse T3) in man. J Clin Invest. 1976;58(1):32–40.
91. Chopra IJ, Williams DE, Orgiazzi J, Solomon DH. Opposite effects of dexamethasone on serum concentrations of 3,3′,5′-triiodothyronine (reverse T3) and 3,3′5-triiodothyronine (T3). J Clin Endocrinol Metab. 1975;41(5):911–20.
92. Chopra IJ. Clinical review 86: euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab. 1997;82(2):329–34.
93. Chopra IJ, Teco GN, Mead JF, Huang TS, Beredo A, Solomon DH. Relationship between serum free fatty acids and thyroid hormone binding inhibitor in nonthyroid illnesses. J Clin Endocrinol Metab. 1985; 60(5):980–4.
94. van der Poll T, Romijn JA, Wiersinga WM, Sauerwein HP. Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man. J Clin Endocrinol Metab. 1990;71(6):1567–72.
95. Stouthard JM, van der Poll T, Endert E, et al. Effects of acute and chronic interleukin-6 administration on thyroid hormone metabolism in humans. J Clin Endocrinol Metab. 1994;79(5):1342–6.
96. Corssmit EP, Heyligenberg R, Endert E, Sauerwein HP, Romijn JA. Acute effects of interferon-alpha administration on thyroid hormone metabolism in healthy men. J Clin Endocrinol Metab. 1995;80(11): 3140–4.
97. Nagaya T, Fujieda M, Otsuka G, Yang JP, Okamoto T, Seo H. A potential role of activated NF-kappa B in the pathogenesis of euthyroid sick syndrome. J Clin Invest. 2000;106(3):393–402.
98. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab. 1986;63(1):1–8.
99. Becker RA, Vaughan GM, Ziegler MG, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med. 1982;10(12):870–5.
100. Brown EM. Physiology and pathophysiology of the extracellular calcium-sensing receptor. Am J Med. 1999;106(2):238–53.
101. Marx SJ. Hyperparathyroid and hypoparathyroid disorders. N Engl J Med. 2000;343(25):1863–75.
102. Inzucchi SE. Management of hypercalcemia. Diagnostic workup, therapeutic options for hyperparathyroidism and other common causes. Postgrad Med. 2004;115(5):27–36.
103. Kebebew E, Hwang J, Reiff E, Duh QY, Clark OH. Predictors of single-gland vs multigland parathyroid disease in primary hyperparathyroidism: a simple and accurate scoring model. Arch Surg. 2006;141(8):777–82; discussion 782.

104. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658–71.
105. Bilezikian JP, Khan AA, Potts JT. Hyperthyroidism TIWotMoAP. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab. 2009;94(2):335–9.
106. Dunbar ME, Wysolmerski JJ. Parathyroid hormone-related protein: a developmental regulatory molecule necessary for mammary gland development. J Mammary Gland Biol Neoplasia. 1999;4(1):21–34.
107. Rankin W, Grill V, Martin TJ. Parathyroid hormone-related protein and hypercalcemia. Cancer. 1997; 80(8 Suppl):1564–71.
108. Wermers RA, Kearns AE, Jenkins GD, Melton LJ. Incidence and clinical spectrum of thiazide-associated hypercalcemia. Am J Med. 2007;120(10): 911.e919–915.
109. Ziegler R. Hypercalcemic crisis. J Am Soc Nephrol. 2001;12 Suppl 17:S3–9.
110. Novartis. Zometa package insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21223lbl.pdf
111. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med. 1999;341(17):1249–55.
112. Betterle C, Greggio NA, Volpato M. Clinical review 93: autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab. 1998;83(4):1049–55.

Geriatric Considerations

15

Ryan A. Lawless and Michael D. Pasquale

Introduction

The Current State

According to the Federal Interagency Forum on Aging document "Older Americans 2012: Key Indicators of Well-Being," the American population continues to get older [1]. In 2010, 40.4 million people in the USA were over the age of 65, comprising 13 % of the population. This is a 15 % increase since the year 2000. This number will rise to 72 million in 2030 and represent nearly 20 % of the total US population. Those age 85 and over comprised 5.5 million Americans in 2010 and are expected to rise to over 19 million by 2050. If a person lives to the age of 65, they can be expected to live another 19.2 years due to advances in medicine extending life expectancy. We are getting older but maybe not better: the prevalence of chronic health conditions has increased and the functionality of our elderly (>65 years) has declined with this increase in life expectancy. One quarter of the elderly population has difficulty with at least one activity of daily living (ADLs) and almost half report at least one functional limitation. These limitations in ADLs include bathing, dressing, getting in/out of a chair, walking, using a toilet, and the ability to feed oneself. Almost one fifth of those elderly in nursing care facilities require assistance with feeding [2]. In 2007–2008, elderly Americans met or exceeded federal dietary quality standards for only 3 of 12 nutritional components (whole fruit, total grain, and meat and beans) as determined by the Healthy Eating Index [1]. One out of 10 elderly living at home suffer from protein–energy malnutrition. This rises to 70 % of those hospitalized [3]. Improving nutritional support must be a part of any health care reform.

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Metabolic Requirements

Physiologic Changes of Aging

Aging decreases the human basal metabolic rate (BMR); however, physiologic aging does not progress at the same rate in each individual. From the ages of 30 to 70, the BMR decreases by 16 %. There is a concomitant body composition change toward increased fat and decreased protein content [4, 5]. Lean body mass changes dramatically on average, from 45 % of total body weight (TBW) for a 30 year old to 27 % for a 70 year old. There is a doubling of the total body fat,

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from 14 % of TBW at 30 years of age to 30 % of TBW at 70 years of age [6].

Appetite changes with age as well. Among the factors contributing to this change are changes in the senses of taste and smell. Both increase secondary to decreasing number of taste buds, peripheral olfactory atrophy, and decreasing saliva production. Sweet and salt quality change first due to loss of taste buds in those areas, leading to food tasting bitter with an unappetizing odor. Bitter and sour taste buds are lost later [3, 4, 7]. The physiologic regulation of appetite is a complex neural and hormonal network involving the autonomic nervous system, enteric nervous system, and hypothalamic–pituitary–adrenal axis in homeostatic balance. This balance is disrupted with chronic diseases, cancers, inflammatory processes, and polypharmacy resulting in an overall decrease in appetite [7].

Gastrointestinal tract changes affect geriatric nutrition. Age-related changes include esophageal dysmotility from a change in peristalsis, chronic atrophic gastritis, intestinal bacterial overgrowth, and chronic constipation. These factors in addition to laxative abuse, which occurs more commonly in the elderly population, impact the intake and absorption of nutrients [4, 5]. Dyspepsia, a frequent symptom among elderly patients, is most commonly related to peptic ulcer disease, gastroesophageal reflux, or gastric cancer [8]. Lactose intolerance develops in the elderly population as the quantity of lactase, an essential enzyme involved in dairy product digestion, decreases leading to stomach cramping and diarrhea. The result is malnutrition and vitamin/mineral deficiencies in the geriatric population [3]. When combined with age-related reductions in skin integrity, and immunocompetence, malnutrition increases the incidence of complications such as wound failure/infection and nosocomial infections. These complications in the critically ill geriatric patient lead to negative outcomes, even death [4, 5].

Changes in the renal system also influence nutritional requirements. Nephrosclerosis increases with age leading to a decline in renal function. Up to 40 % of available nephrons are sclerotic by age 85. Patients with diabetes, hypertension, dyslipidemia, and/or atherosclerosis exhibit even higher rates of sclerosis. As a result, the ability to regulate fluid balance and acid/base status deteriorates. This in turn predisposes the elderly to dehydration as the kidney is unable to respond to renal sodium and water losses. Decreased responsiveness to ADH, decreased renin–angiotensin system activity, and diminished thirst are likely causes [3, 8].

Vitamin Deficiencies

The risk for deficiencies in many vitamins and nutrients increases as we age. These deficiencies are caused in part by diminished appetite, the inability to masticate certain foods (e.g., fresh fruits and vegetables), and the increased incidence of lactose intolerance. This section will discuss the most common vitamin deficiencies in the aging population.

Vitamin D deficiency is one such deficiency. The cause is multifactorial, with decreased consumption of vitamin D-fortified dairy products secondary to an increased incidence of lactose intolerance. In institutionalized patients, limited exposure to direct sunlight disrupts the conversion of vitamin D to its active form. Lastly, as the kidney ages, the ability to convert vitamin D to the active form decreases in addition to the occurrence of nephrosclerosis. Therefore, to prevent deficiency, vitamin D should be supplemented (600 IU daily) in the diet and efforts should be directed at providing the elderly with more exposure to sunlight [6, 8].

The next most common vitamin deficiency is vitamin B12 or cobalamin. Vitamin B12 is obtained through the digestion of red meat. Deficiency is often related to food costs, dietary caloric restrictions, or difficulty with mastication due to poor dentition. Twenty percent of the geriatric population is deficient in vitamin B12 [8]. Gastric atrophy is a condition caused by decreased gastric acid secretion related to aging and/or the use of acid-reducing medications diminishing intrinsic factor production. Intrinsic factor is essential for the release of vitamin B12 from its carrier protein as well as absorption. Signs of vitamin B12 deficiency include anemia, neuropathy, and dementia [6, 8].

Vitamin K deficiency is not common in healthy adults; however, certain medications may lead to a deficiency such as anticoagulants, antibiotics, and sulfa drugs. Poor vitamin K intake may be related to fractures, osteoporosis, osteoarthritis, and atherosclerosis [9, 10]. Increasing intake of vitamin K is not recommended in those taking warfarin due to its counteracting the anticoagulant effect of the drug. This vitamin should be kept in mind when starting medications in the intensive care or general medical setting (e.g., warfarin) [6].

Nutritional Monitoring

A single standard assessment of nutritional status in the elderly population has not been agreed upon. Multiple screening tools assist in the identification of "at risk" individuals within the population. Identification of the "at risk" individual, as well as the malnourished patient, is important due to the impact nutrition has on outcomes in the intensive care and hospital setting. Malnourished patients have increased hospital length of stay, higher complication rate, and higher mortality rate overall. A discussion about risk factors, screening tools, and biochemical markers of malnutrition follows.

Risk Factors for Malnutrition

There are many risk factors related to malnutrition in the elderly population. These factors can be broken down into age related and age unrelated [2]. Age-unrelated risk factors include cancer, chronic and severe organ failure, gastrointestinal diseases, alcoholism, chronic infectious and/or inflammatory diseases, as well as all factors likely to cause one or more of the following: a reduction in food intake, an increase in energy requirements, and malabsorption.

Age-related risk factors include psychological, social, and environmental factors such as depression, grieving, financial hardship, and admission to long-term care facilities. Oral, dental, and swallowing disorders put the elderly at increased risk.

Dementia, other neurologic diseases and acute issues that result from trauma, such as pain, fractures, and surgery, increase the risk of malnutrition as well. These factors lead to decreased oral intake, loss of appetite, and decompensation of stable medical comorbidities, etc.

Screening Tools

Screening for malnutrition has several components. They include evaluating risk factors, appetite and caloric intake, comparison of weights, and calculation of body mass index (BMI). These may contribute to the diagnosis of malnutrition, but most will not be obtainable in the obtunded patient. Valuable information can be obtained from nursing home and rehabilitation hospital records if these patients are being transferred from those facilities.

The Mini Nutritional Assessment (MNA) is one standard screening tool for the elderly recommended in an evidence-based guideline from France [2]. The assessment addresses various areas including appetite, meals, weight loss, and calf and mid-arm circumference. A short form exists containing six items called the MNA-SF.

Albumin

Serum albumin concentration can help assess visceral protein stores in the nonacute care setting. Albumin is a plasma protein that maintains plasma oncotic pressure and is a carrier protein for multiple elements and medications. Testing serum levels is routinely available and the normal range is between 3.5 and 5 g/dl. The half-life of serum albumin is approximately 20–21 days. Therefore, albumin levels are not useful in the short term. Serum albumin is a reliable marker in the absence of liver disease, renal disease, prolonged bed rest, infection/sepsis, and cancer. However, many of these conditions are present in the hospitalized elderly [11, 12].

Measurement of C-reactive protein may help in interpreting albumin levels in the presence of an inflammatory process. An elevated C-reactive

protein indicates an active inflammatory response, which calls into question the serum albumin level in the assessment of nutritional status. Serum albumin may distinguish between two forms of malnutrition: that due to a deficiency in food intake (albumin may be normal) and that due to inflammation and a catabolic state (a rapid fall in albumin) [2].

Transferrin

Transferrin is an iron-binding plasma glycoprotein that binds iron for transport to bone. Levels are affected by total body iron storage [12]. Normal serum levels are from 200 to 400 mg/dl [12]. Body tissue iron stores increase with aging, which leads to a decrease in transferrin levels in healthy individuals. If elderly patients are malnourished with decreased protein and low iron stores, they may express a falsely normal transferrin level. In younger patients, the 8–10 day half-life makes transferrin a good choice to assess the nutritional status, but should not be used in the geriatric population due to the changes with aging [5].

Prealbumin

Prealbumin is a protein made in the liver and functions as a carrier, binding thyroxine, and retinol binding protein. Normal serum levels are between 18 and 40 mg/dl [6, 12]. Its short half-life of 2 days makes it a promising marker of protein storage and short-term nutritional status.

Total Lymphocyte Count

The total lymphocyte count (TLC) is a marker of immunocompetence. Normal TLC is greater than 1,500 cells per cubic millimeter [6]. Depression of this count may be associated with malnutrition, but can be altered by a host of other factors. These factors include hypoalbuminemia, infection, chronic comorbid conditions, and malignancy. For this reason, the TLC is not an adequate indicator of nutritional status and should not used in the geriatric population [13].

Diagnosis of Malnutrition

The April 2007 clinical practice guideline on "Nutritional support strategy for protein-energy malnutrition in the elderly" established diagnostic criteria for malnutrition. The diagnosis of malnutrition is based on one of more of the following criteria: weight loss $\geq$5 % in 1 month or $\geq$10 % in 6 months, BMI < 21 (BMI > 21 does not exclude the diagnosis), serum albumin concentration <35 g/l, and MNA score <17. Severe malnutrition may be diagnosed by one or more of the following: weight loss $\geq$10 % in 1 month or 15 % in 6 months, BMI < 18, and serum albumin <30 g/l. Severe malnutrition requires rapid nutritional management.

Nutritional Requirements

Carbohydrates

Carbohydrates comprise half of the calories consumed in the Western diet. The human body can store approximately 1,200 calories in the liver and muscle in the form of glycogen. During stress and starvation, these stores are immediately available. If the stressor is not removed, these stores are depleted within 3 days. The storage process begins between 8 and 16 h postprandially. Glycogenolysis occurs as insulin levels decrease, mobilizing glucose from hepatic stores. Alanine is essential for this process in muscle and is used for gluconeogenesis since muscle cannot mobilize glucose from glycogen due to its lack of glucose-6-phosphatase [7]. Age-related changes in the ability to metabolize glucose lead to chronically elevated blood glucose levels and advanced glycosylation end products. These end products promote fibrosis, decrease connective tissue flexibility, and change the extracellular matrices of the heart, kidney, skin, and central nervous system. Many of the common comorbid conditions in the geriatric population stem from these advance glycosylation end products: neuropathy, nephropathy, cardiomyopathy, atherosclerosis, etc. [7] Based on these facts it is recommended that elderly individuals consume more complex carbohydrates and less simple sugars [6].

Proteins

The protein requirement in the average adult is 0.8 g of protein per kilogram body weight daily. Large amounts of protein can be stored in the human body but only 50 % can be utilized without serious consequences [7]. The body may require up to 1.5 g/kg/day in the stressed state to support wound healing, immune function, etc. Patients who are bedbound or institutionalized require more than average protein to maintain nitrogen balance. One may incorrectly draw the conclusion that since lean muscle mass decreases in the elderly population, protein requirements would follow suit. This is not the case. The amount of nitrogen retained by the body decreases with decreased caloric intake and additional protein must be provided in order to maintain positive nitrogen balance. The average elderly person requires 1.0 g/kg/day of protein. Promotion of skeletal muscle protein metabolism requires a larger amount of essential amino acids [6, 14]. By day 4 of their hospitalization, only 25 % of undernourished patients achieve protein and energy requirements [15]. Protein intake is essential and should not be overlooked or under-recognized.

Lipids

Fats comprise up to 40 % of the calories that make up the average Western diet. A fair amount of these calories (10 %) are in excess amounting to at least 600 unnecessary kilocalories each day. The greatest amount of energy storage in the body is in the form of fat. Free fatty acids are released during starvation. However, the mobilization of fat does not occur as readily in the elderly population, leading to mobilization of protein stores, protein breakdown, and sarcopenia [6, 14]. Although fat is a requirement in every diet, it should not exceed 30 % of total caloric intake. If fats are being administered via total parenteral nutrition, triglyceride levels should be monitored and infusion should be reduced if levels become elevated.

Vitamins and Minerals

Certain vitamins and minerals have been shown to improve outcomes in critically ill surgical patients receiving nutritional support. They include vitamin E, vitamin C, zinc, copper, and selenium. The addition of selenium to the nutrition source being given has been shown to reduce mortality in patients with sepsis and septic shock [16, 17].

Calcium

Total body calcium content is affected by multiple factors. Osteoporosis is aggravated by age-related hormonal changes leading to decreased total body calcium, particularly in women. Total bone mass decreases with age and inadequate intake of calcium leads to hip, lower vertebral, femoral, and cervical spine fractures. Due to gender specific hormonal changes, dieting, childbearing, breastfeeding, and life longevity, women are more affected than men. Calcium requirements increase with age. Therefore, the recommended intake is 800–1,200 mg per day. Supplementation is necessary if levels cannot be maintained with diet [4, 8].

Fluids

The recommended fluid intake is 30 mL of fluid per kilogram of body weight. Cellular dehydration and hypovolemia are the two main factors involved in thirst regulation. Thirst sensitivity decreases with age, increasing the risk of dehydration. Thus, dehydration is a major concern in the geriatric population. In the presence of vomiting or diarrhea, fluid requirements increase and should be based on clinical findings, such as skin turgor, urine output, laboratory values, etc. [6].

Glutamine

Glutamine is a conditionally essential amino acid used by intestinal epithelium for maintenance of function.

During catabolic states of injury and critical illness, increased glutamine is necessary. Enterocytes, lymphocytes, and macrophages utilize glutamine to maintain intracellular levels of ATP. In critical illness, the gut is susceptible to loss of mucosal integrity secondary to decreased blood flow and disuse. This increases the risk of bacterial translocation which can lead to sepsis and death. Hospital mortality in burn and mixed ICU patients has been shown to decrease with the addition of glutamine (0.3–0.5 g/kg/day) to enteral formulas [18, 19].

Indications for Nutritional Support

A malnutrition screen should be performed on every patient that is admitted to the hospital, as there is an increased complication rate, mortality rate, and length of stay in malnourished patients. The maintenance of immunological integrity, preservation of lean body mass, and aversion of metabolic complications are the goals of early aggressive nutritional support [16, 18].

Patients with loss of appetite, depression, decreased metabolism with aging, and decreased colonic motility lose the desire to eat. Patients with oral/esophageal obstructions, dysphagia, psychomotor diseases (Parkinson's disease, Huntington's disease, multiple sclerosis, dementia), polytrauma, poor dentition, and xerostomia have difficulty consuming nutrients orally. Even though patients may eat, their caloric intake may be inadequate. Infections (e.g., urinary tract), polypharmacy, and electrolyte imbalances contribute to this risk [6, 16, 19].

Patients deemed to be "at risk" by initial screening should then have their nutritional status assessed. The traditional nutritional assessments include anthropometry, as well as laboratory values such as albumin, prealbumin, transferrin, and TLC. These values are valid in "normal" patients outside the intensive care setting, but can also be useful within the critical care arena.

Anthropometric data obtained should include height (cm), weight (kg), body mass index (kg/cm^2), and skinfold measurements to determine fat and protein stores. The accuracy of these measurements has been questioned due to a great deal of variability between testers and even when repeated by the same tester. These measurements should be obtained by a trained technician or physician with validity testing performed often. The measurements obtained are more useful in the outpatient setting assessing long-term nutritional status in serial fashion [6].

Specific laboratory values are discussed within the nutritional monitoring section of this chapter. The values are more applicable for nutritional monitoring rather than determination of nutritional status. Most of the substances are acute phase reactants affected by a patients' metabolic state. Once a patient is identified as being malnourished, interventions should be made in the form of enteral nutrition, parenteral nutrition, or supplementation [16].

Enteral Nutrition

"If the gut works, use it." This simple dogmatic statement has been backed by many studies throughout the literature. Using the patients' intestinal tract as the primary means of nutritional administration is preferred for multiple reasons. A decreased rate of infectious comorbidities including pneumonia, central venous catheter infection, and abdominal abscess in trauma has been shown with enteral nutrition versus parenteral nutrition. Decreases in length of stay and cost have also been shown. Other benefits include the preservation of intestinal mucosal integrity [16]. Feeding the enterocytes promotes the release of endogenous hormones, intestinal blood flow, and secretory IgA immunocytes. By not feeding the gut, these three factors decrease, leading to increasing gut permeability, breakdown of the mucosal defense system and the theoretical risk of bacterial translocation, systemic infection, and multiorgan system failure [16]. Means of delivering enteral nutrition include nasogastric and nasojejunal tubes or gastrostomy and jejunostomy tubes.

When should enteral nutrition be initiated? The general answer to this is the earlier the better. However, the practical answer has to do with the

patient's nutritional status, timing of presentation to the hospital, and the procedure to be performed. If the patient is determined to be protein malnourished prior to elective surgery, nutritional support should begin 10 days preoperatively [20]. In the case of emergent/unplanned admissions, extensive preoperative planning is not possible. The answer then becomes the point at which the patient is hemodynamically stable and fully resuscitated. This may be within a time frame between 24 and 48 h from admission. If the patient is hemodynamically unstable or under resuscitated, or being started on vasopressor agents, feedings should not be started, and should be held due to the risk of ischemic bowel. In patients requiring vasopressors to maintain adequate perfusion, feedings may be started once the vasopressor requirement has been stable. This requires close monitoring for intolerance as evidenced by high gastric residuals, abdominal pain/distention, regurgitation of tube feeds if administered through a postpyloric feeding tube [16].

In the past, the presence of bowel sounds was used as criteria for the initiation of enteral nutrition. The absence of bowel sounds has not been shown to be associated with intolerance to enteral nutrition. Therefore, bowel sounds should not be used as criteria for initiation. During the infusion of tube feedings, gastric residuals are often checked as an indicator of tolerance. The literature has shown the range of aspirates in the literature is quite wide, with 200 and 500 cm^3 being elevated [3, 16]. Unless the patient is showing other signs of intolerance (pain, distention, absent flatus), tube feedings should not be held and interventions to promote gastric emptying and decrease aspiration risk should be initiated in response to residuals in this range. These include administration of a prokinetic agent, elevation of the head of the bed, and possibly inserting a small bowel feeding tube. Gastric residuals >500 cm^3 should prompt cessation of enteric feeding with the intent of re-initiating in the near future after the aforementioned interventions are performed [16].

Complications of enteral nutrition arise from the formulation, infection, or route of delivery. Formulation complications include diarrhea, vomiting, constipation, aspiration, hyperglycemia, and electrolyte imbalance. Patients may have diarrhea secondary to an infectious etiology while on tube feedings. Therefore, if a patient develops loose stools, an investigation into the cause is prudent. Diarrhea may be caused by hyperosmolar substances/formulation, recent broad spectrum antibiotic usage, and Clostridium difficile colitis, to name a few. Workup should include physical exam, fecal white blood cell count, stool quantification, and a basic metabolic profile [16].

Aspiration is a serious complication and the most common cause of death after percutaneous gastrostomy tube insertion [3]. Patients who develop chronic cough with enteral access may have subclinical aspiration. Changing the nasogastric tube to a nasoenteric tube may decrease the incidence of aspiration.

The mechanics of the route of delivery can also lead to complications. The feeding tube may get clogged with inspissated tube feedings. This occurs in 18–45 % of tubes placed. Attempts are made at flushing the tube or dissolving the tube feeds with warm water, cola, pancreatic enzyme, or meat tenderizer [21]. With percutaneous endoscopically or surgically placed tubes, mechanical obstructions can occur. The bowel may volvulize around the tube or the balloon may cause a lead point of obstruction at the pylorus or within the small bowel lumen by migration [21, 22]. Also, patients may inadvertently pull the tube out. Re-insertion should only be attempted if the tube has been present long enough for a tract to form between the lumen of the bowel and the exit site (approximately 2 weeks). Re-insertion should then occur in a timely fashion as the gastrocutaneous tract may be lost if enough time passes. If dislodgement occurs shortly after placement, the tract has not had enough time to form. Leakage of gastric or small bowel contents is then likely to occur, which is a surgical emergency.

Parenteral Nutrition

Parenteral nutrition dates back to the work of Dudrick and Rhoads in the late 1960s. Research showed that infusion of hypertonic solution with nitrogen and nutrients could sustain nitrogen

balance and stimulate growth and development [23, 24]. In patients who are unable to tolerate oral or enteral feedings, parenteral nutrition should be considered. The ideal time for the initiation of parenteral nutrition in the specific subset of patients that require it continues to be debated. The initiation of parenteral nutrition preoperatively in a patient with protein malnutrition and continuation postoperatively is beneficial in elective general surgery. However, in patients who are well nourished preoperatively or prior to admission to the intensive care unit who cannot receive enteral nutrition, parenteral nutrition should be initiated only after 7 days without enteral nutrition [16, 20]. Patients with a nonfunctional gastrointestinal tract should be started on parenteral nutrition as well [6].

Restoration of nitrogen balance and creation of an anabolic state are the goals of parenteral nutrition. Energy requirements are calculated by the equations that are beyond the scope of this chapter. Permissive underfeeding or hypocaloric alimentation is beneficial in the critical care setting. It is recommended that 80 % of calculated energy expenditure be used as a goal for this. Benefits include avoidance of insulin resistance, decreased infectious morbidity, less time requiring mechanical ventilation, and decreased length of stay. Much literature has been written about tight glucose control. Maintenance of a blood glucose between 110 and 150 mg/dL has been shown to decrease rates of sepsis, ICU length of stay, and in-hospital mortality [16].

The administration of parenteral nutrition containing hypertonic solutions must be done through a central venous catheter. The complication rate of insertion of a central venous catheter is between 5 and 19 %. Pneumothorax is one of the more frequent complications with a range of 1–1.5 % and is also considered a "never event." The incidence of pneumothorax increases with multiple passes of the access needle, insertion of larger catheters, and emergent placement. Venous thrombosis, toxicity, and venous perforation can result from malpositioning of the catheter. Potential vascular injuries include arterial puncture and hematoma, hemothorax, cannulation of the artery leading to stroke or neurologic deficits with infusion, pseudoaneurysms, and arteriovenous fistulas. Cardiac arrhythmias may result from insertion of the guidewire. A small number of the arrhythmias become symptomatic while most subside with removal of the guidewire. However, complete heart block and sudden death can occur. Infection is a major complication that can lead to a catheter-associated bloodstream infection/sepsis with a mortality rate of 18 %. Thrombosis increases the rate of infectious complications as well. Measures have been taken to prevent catheter-associated bloodstream infections. These include strict hand hygiene, surgical preparation with chlorhexidine, full sterile precautions during insertion, and catheter removal when it is no longer required. The central venous thrombosis rate related to indwelling central venous catheters ranges between 33 and 59 %. However, only a small percentage is symptomatic. Over time, mechanical forces on the catheter can lead to fracture and embolization of the catheter, which is a rare complication. This can also occur during removal of the catheter making it imperative to inspect the catheter integrity upon removal. Other catheter removal complications include air embolism and hemorrhage [25].

Nutrition in Palliative Care and the Terminally Ill

Nutrition can still be used in palliative care. This should only occur when the goals of nutrition in palliative care are consistent with palliative care principles. Therefore, the use of nutrition must palliate symptoms and improve the quality of life. Nutrition may be indicated for the malnourished or those who may become malnourished during the remaining course of their disease.

Psychosocial Aspects

Loss of appetite can be quite distressing to patients and loved ones. Meals are often social events. Anorexia and cachexia near the end of life can be subject to many fears and misconceptions. Care can be refocused through education and

reassurance. Eating will not reverse terminal illness. The body will only take what it needs in cases of terminal illness. The illness alters the body's needs and the ability to metabolize food. This manifests by decreased intake. This is simply a part of the natural process of terminal illness and does not shorten life.

Anorexia

Reversible causes should be looked for in cases of reduced intake. These include xerostomia, nausea, constipation, electrolyte disturbances, and psychological issues such as depression. Altering the temperature or presentation of the food can compensate for altered taste sensation. Using different types of food that are lower in urea and spicing or marinating foods may also help. Commercial supplements may in reality contribute to appetite suppression. The best appetite stimulant is the patients preferred foods themselves, when feasible. Pharmacologic appetite stimulants do not affect prognosis but may improve quality of life [22]. Megestrol acetate and dexamethasone are among the stimulants used.

Giving permission to the patient to eat less may be the most important and effective intervention providers can offer. Intake can be improved by reducing the stigma of loss of appetite and altering the way in which food is available and meals are offered. Smaller, more frequent meals, having food available at all times whenever the patient is hungry and having patients take part in meal planning are some interventions that may help [26].

Cachexia

Wasting of protein and energy stores is an effect of disease called cachexia (Table 15.1 [27]). Hyper-caloric feedings do not help in these cases. Protein and energy deficiency that is not part of a disease process is called starvation [27]. In cachexia related to terminal illness, the process is mediated by cytokines, such as tumor necrosis factor, IL-1 and IL-6 [28–30]. This is most widely studied in cancer patients. Appetite is suppressed early and hunger pains generally are not part of the clinical picture. Functionality or survival is not improved by re-feeding. This may not be true of certain subsets of AIDS patients [31].

Table 15.1 Differences between starvation and cachexia of terminal illness

	Starvation	Cachexia of terminal illness
Appetite	Suppressed late	Suppressed early
BMI	Not predictive of mortality	Predictive of mortality
Albumin	Low late	Low early
Cholesterol	May be normal	Low
Total lymphocyte count	Low, responds to re-feeding	Low, no response to re-feeding
Cytokines	N/A	Elevated
Response to re-feeding	Reversible	Resistant

Ethical Decision Making Regarding Artificial Nutrition

Controversy surrounds the use of artificial nutrition. Very few of the terminal illnesses most commonly encountered in the geriatric population show favorable response to artificial feeding. No improvement in outcomes is seen in patients with dementia and most patients with advanced cancer [27]. Patients with head and neck or esophageal cancer may show improvement in outcomes [32]. The National Institute for Health and Clinical Excellence in Britain recommended the following in their clinical guidelines with regards to patients with dementia [33]:

- Encourage people with dementia to eat and drink by mouth for as long as possible.
- Do not generally use tube feeding in severe dementia if dysphagia or disinclination to eat is a manifestation of disease severity.
- Consider nutritional support, including tube feeding, if dysphagia is thought to be transient.
- Apply ethical and legal principles to decisions to withhold or withdraw nutritional support.

Quality of life and the dying process may actually worsen with feeding. By-products of the malnourished state, mainly ketones, can produce a euphoric feeling and reduce hunger pains. Tube feed aspiration can lead to pneumonia. Patients with feeding tubes can require use of restraints and the complications that result from their use [30].

In 2008, the Cochrane Collaborative review did not find enough good quality trials to make any recommendations with regards to the use of medically assisted nutrition in palliative care patients [34]. As a result, decisions regarding artificial nutrition must be undertaken with careful consideration of the clinical situation, the underlying disease, the patient's wishes, and artificial nutrition's possible benefits or burdens.

Conclusions

The risk of malnutrition rises dramatically in the hospitalized elderly. There are many factors related to age and are listed in the table in this section. Nutritional deficiencies need to be addressed and requirements maintained. Assessment must be a routine part of the care if the hospitalized elderly. The tables in this section will function as a quick reference for practitioners taking key points from the chapter and placing them at your fingertips.

References

1. The Federal Interagency Forum on Aging-Related Statistics. Older Americans 2012: key indicators of well-being. http://www.agingstats.gov/agingstatsdotnet/main_site/default.aspx. Accessed 20 Sept 2013.
2. Haute Autorité de Santé, Clinical Practice Guideline. Nutritional support strategy for protein-energy malnutrition in the elderly; April 2007. http://www.has-sante.fr/portail/upload/docs/application/pdf/malnutrition_elderly_guidelines.pdf.
3. Dorner B, Pasthauer ME, Friedrich EK, Robinson GE. Enteral nutrition for older adults in nursing facilities. Nutr Clin Pract. 2011;26(3):261–72.
4. Thompson M. Briefs: geriatric nutrition. J Natl Med Assoc. 1980;72(8):795–803.
5. Cutungo CL. The "graying" of trauma care: addressing traumatic injury in older adults. Am J Nurs. 2011; 111(11):40–8.
6. Johnston RE, Chernoff R. Geriatrics. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice. 2nd ed. Philadelphia: Saunders; 2003. p. 377–83.
7. D'Olimpio JT. Physiology of nutrition and aging. In: Walsh DT, Caraceni AT, Fainsinger R, Foley KM, Glare P, Goh C, Lloyd-Williams M, Nunez Olarte J, Radbruch L, editors. Palliative medicine. 1st ed. Philadelphia: Saunders; 2009 [Chapter 104].
8. King M, Emery E. Nutrition management of the geriatric patient. Support Line. 2007;29(5):21–8.
9. Booth SL. Vitamin K status in the elderly. Curr Opin Clin Nutr Metab Care. 2007;10(1):20–3.
10. Erkkila AT, Booth SL, Hu FB, Jacques PF, Lichtenstein AH. Phylloquinone intake and risk of cardiovascular diseases in men. Nutr Metab Cardiovasc Dis. 2007; 17(1):58–62.
11. Kagansky N, Berner Y, Koren-Morag N, Perelman L, Knobler H, Levy S. Poor nutritional habits are predictors of poor outcomes in very old hospitalized patients. Am J Clin Nutr. 2005;82:784–91.
12. Martindale RG, Cresci GA, Leibach FH. Nutrition and metabolism. In: O'Leary JP, Capote LR, editors. Physiologic basis of surgery. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 133–68.
13. Kuzuya M, Kanda S, Koike T, Suzuki Y, Iguchi A. Lack of correlation between total lymphocyte count and nutritional status in the elderly. Clin Nutr. 2005;24(3):427–32.
14. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia: protein, amino acid metabolism and therapy. Curr Opin Clin Nutr Metab Care. 2009;12(1):86–90.
15. Leistra E, Willeboordse F, van Bokhorst MAE, Visser M, Haans-van der Oord A, Weijs PJM, Oostenbrink A, Evers AM, Kruizenga HM. Predictors for achieving protein requirements in undernourished hospital patients. Clin Nutr. 2011;30(4):484–9.
16. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Crescit G. ASPEN Board of Directors, American College of critical care medicine guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. J Parenter Enteral Nutr. 2009;33(3):277–316.
17. Read J, Clarke S. Clinical nutrition. In: Walsh DT, Caraceni AT, Fainsinger R, Foley KM, Glare P, Goh C, Lloyd-Williams M, Nunez Olarte J, Radbruch L, editors. Palliative medicine. 1st ed. Philadelphia: Saunders; 2009 [Chapter 107].
18. Jacobs DG, Jacobs DO, Kudsk KA, Moore FA, Oswanski MF, Poole GV, Sacks GS, Scherer LR, Sinclair KE. Practice management guidelines for nutritional support of the trauma patient. J Trauma. 2004;57:660–79.
19. Mueller C, Cimpher C, Ellen DM. ASPEN Board of Directors. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. J Parenter Enteral Nutr. 2011;35(1):16–24.

20. Silk D, Green CJ. Perioperative nutrition: parenteral versus enteral. Curr Opin Clin Nutr Metab Care. 1998;1(1):21–7.
21. Grant MJ, Martin S. Delivery of enteral nutrition. In: Verger JT, Schears G, Lord LM, editors. AACN Clin Issues Adv Pract Acute Crit Care. 2000; 11(4):507–16.
22. Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Ramierez-Perez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. J Clin Nurs. 2001;10:482–90.
23. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Can intravenous feeding as the sole nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. Ann Surg. 1969;169(6): 974–84.
24. Dudrick SJ, Wilmire DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery. 1968; 64(1):134–42.
25. Kusminsky RE. Complications of central venous catheterization. J Am Coll Surg. 2007;204(4): 681–96.
26. Dy M. Enteral and parenteral nutrition in terminally ill cancer patients: a review of the literature. Am J Hosp Palliat Med. 2006;23(5):369–77.
27. Thomas D. Distinguishing Starvation from Cachexia. Clin Geriatr Med. 2002;18:883–91.
28. Alexander H. Prevalence and pathophysiology of cancer cachexia. In: Portenoy RK, Bruera E, editors. Topics in palliative care. New York: Oxford University Press; 1998. p. 91–129.
29. Inui A. Cancer anorexia–cachexia syndrome: are neuropeptides the key? Cancer Res. 1999;59(18): 4493–501.
30. Dunlop RJ, Campbell CW. Cytokines and advanced cancer. J Pain Symptom Manage. 2000;20(3): 214–32.
31. Nemechek PM, Polsky B, et al. Treatment guidelines for HIV-associated wasting. Mayo Clin Proc. 2000; 75(4):386–94.
32. Ganzini L. Artificial nutrition and hydration at the end of life: ethics and evidence. Palliat Support Care. 2006;4:135–43.
33. National Institute for Health and Care Excellence. Clinical Guideline 42: Dementia. http://www.nice.org.uk/guidance.nice.org.uk/CG42.
34. Good P, Cavenagh J, Mather M, Ravenscroft P. Medically assisted nutrition for palliative care in adult patients. Cochrane Database Syst Rev. 2008;4: CD006274.

Index

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