Nutrition and Health
Series Editor: Adrianne Bendich

David S. Seres
Charles W. Van Way, III
Editors

Nutrition Support for the Critically Ill

Humana Press

Nutrition and Health

Adrianne Bendich, PhD, FASN, FACN, Series Editor

More information about this series at http://www.springer.com/series/7659

David S. Seres • Charles W. Van Way, III
Editors

Nutrition Support for the Critically Ill

Humana Press

Editors
David S. Seres, MD, ScM, PNS.
Director of Medical Nutrition
Associate Professor of Medicine in the Institute of Human Nutrition
Department of Medicine
Columbia University Medical Center
New York, NY, USA

Charles W. Van Way, III, MD, FACS, FCCM, FCCP, FASPEN
Emeritus Professor of Surgery
Truman Medical Center
Department of Surgery
University of Missouri, Kansas City,
School of Medicine
Kansas City, MO, USA

Nutrition and Health
ISBN 978-3-319-21830-4 ISBN 978-3-319-21831-1 (eBook)
DOI 10.1007/978-3-319-21831-1

Library of Congress Control Number: 2015952015

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Humana Press is a brand of Springer
Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Dedications

To our patients, our students and trainees,
and our colleagues. And to our wives, Kesiah E. Scully
and Gail E. Van Way, without whose love, support,
and encouragement this work, and all we do,
would not be possible.

Foreword

Nutritional support in the critically ill patient is like mother's milk, right? Indeed, there was a time, long ago and on a planet far away, when we felt we knew all the answers to feeding the critically ill. At the end of the 1970s, when I was undertaking my Fellowship in Critical Care Medicine, it was assumed that total parenteral nutrition (TPN) would ultimately take care of our sick patients' needs. To underscore the naivety of this concept, soon after my graduation as a neophyte intensivist at a major university medical center, I was appointed Chair of the Hospital TPN Committee. A classic case of the blind leading the blind!

Today, the world of nutritional support of the critically ill patient is not only far more complex but also more discouraging, because we now realize how little we know. As acute care physicians and surgeons, we continually search for evidence-based justification of our physiologically based theories. In the field of nutrition, however, we are likely to be overwhelmed by an increasing array of large randomized control trials (RCTs) that are often mutually contradictory, do not provide answers, and simply raise more questions. Moreover, the practitioner is likely to be completely overwhelmed by an extraordinary jungle of mnemonics that at last count included TICACOS, EDEN, OMEGA, REGANE, NUTRIREA 1, EPaNIC, SPN, SIGNET, REDOXS, among others.[1] And at the end of an extensive review of all the aforementioned RCTs in the *New England Journal of Medicine*, Casear and van den Bergh conclude, "These new insights limit the number of nutritional interventions that can be confidently recommended for daily critical care practice" [1].

Many are the questions that remain to be definitively answered regarding nutritional intervention in the critically ill. Should we attempt to assess nutritional status in preoperative patients undergoing major surgery (an opportunity that is obviously lacking in patients admitted to medical intensive care unit or after acute trauma)? Should we attempt to provide full feeding within the first 24 h of acute illness, trauma, or surgery? If yes, should we supplement enteral with parenteral nutrition? If no, is it

[1] **A Neophyte's Guide to Mnemonics in Nutritional RCTs:** TICACOS, The Tight Caloric Control Study; EDEN, Trophic vs. Full-Energy Enteral Nutrition in Mechanically Ventilated Patients with Acute Lung Injury; OMEGA, The Effect of Highly Purified Omega-3 Fatty Acids on Top of Modern Guideline-Adjusted Therapy after Myocardial Infarction; REGANE, The Gastric Residual Volume During Enteral Nutrition in ICU Patients; NUTRIREA 1, The Effect of Not Monitoring Residual Gastric Volume on the Risk of Ventilator-Associated Pneumonia In Adults Receiving Mechanical Ventilation and Early Enteral Feeding; EPaNIC, The Impact of Early Parenteral Nutrition Complementing Enteral Nutrition In Adult Critically Ill Patients; SPN, The Impact of Supplemental Parenteral Nutrition on Infection Rate, Duration of Mechanical Ventilation, and Rehabilitation in ICU Patients; EPN, Early Parenteral Nutrition; SIGNET, Scottish Intensive Care Glutamine or Selenium Evaluative Trial; REDOXS, Reducing Deaths Due to Oxidative Stress.

okay to allow hypocaloric enteral feedings for the first 5 days of acute illness or injury? Should we provide prokinetic agents or postpyloric feeding to avoid aspiration? Should we perform daily indirect calorimetry to assess caloric need during different phases of acute illness? How do we assess when the patient may be ready to transition from hypocaloric to full supplementation to reverse their accumulated nutritional deficit? Are there "magic bullets" that will enhance the success of nutritional support, such as glutamine, arginine, anti-inflammatory fatty acids, micronutrients, trace elements, fat-soluble vitamins or antioxidants such as selenium?

In *Nutrition Support for the Critically Ill*, David Seres and Charles Van Way and their colleagues provide a state-of-the-art resource to address the physiology, pharmacology, and evidence basis underlying these questions. This all-encompassing text addresses every conceivable aspect of nutritional support for the critically ill patient. Cogent chapters address the pathogenesis, impact, and assessment of malnutrition in the acutely ill patient; the vital role of gut endothelium and the microbiome in the immunologic response to stress and trauma; and the timing, indications, and access for enteral and/or parenteral nutrition in the critically ill. There are chapters that address nutritional support in specific situations, such as the patient admitted to a surgical intensive care unit following major trauma or surgery; the patient with severe sepsis; the patient who has developed single or multiple organ failure; or the patient with obesity. Even the ethical stone is turned, in a thoughtful consideration of whether nutritional support should be discontinued when aggressive life-prolonging interventions are futile. Practical considerations are not ignored either. There is emphasis on safe practice in enteral and parenteral nutrition; the economic impact of nutritional support; and the importance of a multidisciplinary approach to enhance patient management and outcome.

In a perfectly timed denouement, Drs. Seres and Van Way posit the many questions that remain to be fully answered by future research. Not surprisingly, these are questions that we have been asking for many years. Are there reliable markers of malnutrition and its impact on the systemic response to acute injury and sepsis? What are the important biologic interactions between the patient's nutritional status and their immunologic response to acute illness or injury? How will we settle the great areas of controversy that remain with regard to the timing and nature of nutritional support in the acute phase of illness, especially in the face of accelerated metabolism? When does the benefit of parenteral nutrition outweigh its potential computations?

Today, in-depth training in nutritional support appears to have been confined to a tiny cul de sac in the critical care curriculum of our students, residents, and fellows. We are focused on all the exciting aspects of acute care, such as invasive monitoring and inotropic agents, the latest cure for acute respiratory distress syndrome, or increasingly miniaturized mechanical circulatory support systems. Unfortunately, this is achieved to the detriment of our understanding of the physiology, pharmacology, and evidence basis for nutritional support. As long as a feeding tube is in place and enteral feeds are started, we're okay, right? If not, we'll get a nutritional consult—at our institution, Dr. Seres, of course!

I am convinced that this remarkable textbook will go a long way to restore the rightful place of nutritional support as an integral component of our daily management, right up there with our short-term focus on hemodynamics, antibacterial therapy, and organ system support. *Nutrition Support for the Critically Ill* re-emphasizes the inestimable role that appropriate nutrition plays in long-term outcome in the critically ill. It enhances our knowledge and understanding of the current concepts in this essential aspect of intensive care. As such, it should be required reading for every intensivist. There should be no excuse that "there's no way that I can digest such a big textbook" (so to speak). *Nutrition Support for the Critically Ill* has a modular approach that allows the reader to focus on individual

aspects of the theoretic, empiric, evidence-based, and practical considerations that should guide our approach today. As such, Drs. Seres and van Way and their collaborators should be lauded on their timely and much-needed contribution to the nutritional support—and overall care—of our critically ill patients. And I am honored to have been asked to be their flag-bearer!

Division of Critical Care, Department
of Anesthesiology, PH 527-B, CTICU
and SICU, College of Physicians & Surgeons
of Columbia University, 630 West 168th Street,
New York, NY 10032, USA

Robert N. Sladen, MBChB, FCCM
rs543@cumc.columbia.edu

Reference

1. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014;370:1227–36.

Preface

Nutrition is complex by its nature. Daily, we ingest hundreds of substances, comprising literally thousands of chemical entities. And yet, our bodies—plus our gut microflora, as we know now—sort these out and create homeostasis. But with all of our science and our history, we still have only a hazy idea of which nutrients are beneficial, which harmful, and how much of either should be in our diet. Worse, we change our collective minds from year to year. And that is just in normal people. Illness makes nutrition even more complex.

Patients with illnesses often use nutrients differently, or respond differently to particular nutrients. This is especially true of critically ill patients. In these most seriously ill patients, the homeostasis of so many metabolic systems goes into varying degrees of disarray. Too often, the gastrointestinal tract itself is dysfunctional. The so-called nutritional measurements such as calorie expenditure, protein utilization, and serum micronutrient and protein levels often fail to instruct us well on how we should approach nourishing our patients. The manifestations of malnourishment and the dysmetabolism of disease may be indistinguishable. It should be no surprise that the nutritional research that drives our recommendations for addressing the needs of this extraordinarily diverse patient population falls far short. All too often, we have little certainty concerning when, where, what, how much, and for how long we should feed our patients.

This book is based on evidence-based practice (EBP). But… there is significant misunderstanding about just what EBP is. When most residents of fellows are asked to describe the quality or quantity of evidence required for evidence-based practice, invariably the answer is that data from prospective, randomized studies is required. But EBP, in fact, requires no evidence whatsoever. The proper definition of EBP is practice based on *guidelines* in which the quality of the evidence has been graded. The lowest level of quality in any guideline is that which is driven solely by expert opinion, without data. But this may be all we have to support our approach to patients. As with any common terminology, meaning shifts, or is lost, as it is taken for granted.

But a sad truth about nutrition is that evidence is too often anecdotal, inadequate, or just not there. In this text, we have set out to provide the practitioner with the scientific underpinnings of these complex issues. We have tried to make the best of the evidence that we have. We have maintained as much transparency as possible when facts are weak or not present. Which is all too frequently true. We have tried to avoid the usual pitfall of opinion presented as fact. Our hope is that this approach will better prepare practitioners in the intensive care unit to evaluate not only their patients but also the advice they receive from guidelines and other professionals. Most of all, we hope to promote flexibility. No dogma lasts forever. Time-honored practices may become obsolete, or proven ineffective, or even found to be harmful as better evidence emerges and as the context of care surrounding these practices changes.

There are many textbooks and guides that will give specific guidelines for practice. We have tried to avoid this as a primary goal and suggest the reader become familiar with sources for evidence-based guidelines that are kept current. In this day and age of rapid access and constant updating, a textbook such as this is not an appropriate source for how to practice. Rather, it should be a guideline to how to *think* about the problems of nourishing our patients.

David S. Seres, MD, ScM, PNS
Charles W. Van Way III, MD, FACS, FCCM, FCCP, FASPEN

Series Editor Page

The great success of the "Nutrition and Health" book series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, interchapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Nutrition Support for the Critically Ill edited by David S. Seres, MD and Charles W. Van Way, III, MD is a welcome addition to the "Nutrition and Health" book series. The editors are experts in the care of seriously ill patients and have significant expertise in the development of nutritional strategies to aid in the stabilization of the energy and essential nutrient requirements of the acutely ill patient. They have invited the leaders in the field to develop the 16 relevant, practice-oriented chapters in this unique and clinically valuable volume. David S. Seres, MD, ScM, PNS, is Director of Medical Nutrition and Associate Professor of Medicine in the Institute of Human Nutrition, Columbia University Medical Center, New York, NY. Dr. Seres has 25 years' experience as a nutrition support specialist. He directs the nutrition support service, the medical school nutrition curriculum, and one of the few clinical nutrition fellowships for physicians in the USA. He was recipient of the 2014 Excellence in Nutrition Education Award from the American Society for Nutrition. Dr. Seres is also a clinical ethicist and a Columbia University/OpEd Project Public Voices Fellow. Dr. Seres is a member of the Medical Advisory Board for Consumer Reports. He was Chair of Physician Certification for the National Board of Nutrition Support Certification, and Chair of the Medical Practice Section for the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Dr. Seres' research includes

improving nutrition content in medical school curricula, the impact of feeding tube choice on patient outcomes and the indications for placing feeding tubes in patients placed in nursing homes, the risk of blood-stream infections in patients receiving parenteral nutrition, and metabolic derangements in acute illness. Charles W. Van Way, III, MD, FACS, F.C.C.M., F.C.C.P., FASPEN, is Director of Metabolic Support at Truman Medical Center, and Emeritus Professor of Surgery at the University of Missouri, Kansas City. He has nearly 50 years of clinical experience in nutrition support, dating back to his surgical residency at Vanderbilt University. Dr. Van Way is semi-retired and maintains his clinical practice in nutrition and critical care. He is the Director of the Shock Trauma Research Center of UMKC and continues research on nutrition support and on post-shock inflammation. Dr. Van Way served as the past President of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and as President of the A.S.P.E.N. Rhoades Research Foundation. He has been Editor in Chief of both the *Journal of Parenteral and Enteral Nutrition* and *Nutrition in Clinical Practice*. Dr. Van Way has more than 400 clinically related publications.

Nutrition Support for the Critically Ill fulfills an unmet need for health professionals including pediatric and adult medical specialists, residents and fellows, internists, pediatricians, nurses, dietitians, and general practitioners who treat patients who have often been seriously injured or at a critical juncture in disease progression. Several chapters address the specialized nutrition support that is needed to help the patient recover from critical illnesses that can affect multiple organ systems, can cause significant metabolic changes, and can adversely affect the ability to consume food orally. There are in-depth reviews of the hypermetabolic state that can result in severe catabolism of the body's reserves of protein, fat, and essential macro- and micronutrients. Malnutrition in critically ill patients is strongly associated with infection and impaired healing that is examined in the comprehensive chapter on immunity. A number of chapters provide recommendations for patients who are unable to consume food orally during critical illness and require specialized nutrition support provided as either enteral nutrition or intravenous, parenteral nutrition. Unique, relevant chapters include a critical discussion of ethical considerations of nutrition support for the critically ill patients and a separate chapter that reviews the economic impact of nutrition support. Thus, the volume contains comprehensive, relevant chapters for health professionals and advanced graduate, allied health and medical students interested in the care of the nutritional needs of the critically ill patient.

This volume provides data-driven advice concerning the balance between implementation of nutritional interventions and determining the value of such interventions for critically ill patients from infancy to adulthood. The book includes an introduction to the complexities involved in determining the cause of malnutrition in the critically ill patient and the metabolic consequences. The chapters are written by experts in their fields and include the most up-to-date scientific and clinical information. The volume provides chapters that can answer critical questions for health professionals as well as knowledgeable family members, educators, and others involved in the care of the critically ill patient.

Chapter 1, written by Dr. Seres, the volume's co-editor, provides an historic overview of the care of critically ill patients who are considered as malnourished. The numerous potential causes of malnutrition and the differences between malnutrition in the seriously ill patient with symptoms associated with inflammation compared to the malnourished individual who requires replenishment of calories/nutrients are reviewed in depth. There is also a discussion of newer definitions of malnutrition that reflect the patient's pathophysiology rather than concentrating on the presumed nutritional status. Chapter 2 reviews the importance of nutritional adequacy in the development of robust immune responses that are essential to prevent serious morbidity in the critically ill patient. The chapter, containing over 100 references and relevant tables and figures, reviews the importance of both the intestinal immune system and non-immunological aspects that prevent gut bacteria from becoming pathogenic. The chapter includes detailed descriptions of the immune cells, factors, and secretions and their mechanisms of action in the gut and systemically. There are insightful discussions of the effects of parenteral versus enteral nutrition on the intestinal lining, gut microbiome, as well as the gut immune system. The next chapter, Chap. 3, reviews the methodologies used for comprehensive patient

assessment in the intensive care unit (ICU) and the importance of multidisciplinary nutrition care to help ensure the proper route and timing for nutrition therapy that can promote a favorable patient outcome. The chapter includes an in-depth review of screening tools, including the Malnutrition Screening Tool, and the Malnutrition Universal Screening Tool for use in critical care because it includes a factor for acute illness. Both tables and figures add greatly to the understanding of the complexities involved in the rapid and accurate assessment of the ICU patient.

Chapters 4 and 5 examine the critical role of enteral nutrition (EN) for the critically ill patient. The chapters integrate clinical practice with the underlying science and summarize the evidence related to international recommendations for the timing of initiation, methods of delivery, and indications for enteral nutrition in the ICU. Chapter 4 recommends early enteral nutrition for patients who are likely to require ICU care for longer than 2 days and this should commence within the first 24 h of admission to an ICU. Early enteral nutrition has been shown to reduce mortality, reduce gut dysfunction, prevent ventilator-associated pneumonia, and shorten the duration of mechanical ventilation and ICU stay. Chapter 5 is coauthored by Donald F. Kirby, who is a co-editor of a volume entitled *Handbook of Clinical Nutrition and Stroke* which is also included in the "Nutrition and Health" book series. Chapter 5, containing over 100 references and relevant tables and figures, highlights the practice-oriented options for enteral access in critically ill patients and the complications that can be encountered. Options for enteral access that are reviewed include the blind placement of nasal and oral feeding tubes ending in the stomach or further into the small intestine; facilitated placement of nasal feeding tubes; gastrostomy or jejunostomy tubes. The latter are placed using endoscopic, radiologic, laparoscopic, or open surgical techniques. There are also discussions concerning the decision-making considerations involved in the determination of the placement of the feeding tube into the stomach or into the small intestine that is often based upon the expected length of EN, either for a short time (<4 weeks) or long term (≥4 weeks).

Chapters 6 and 7 provide an historic perspective of the use of parenteral nutrition (PN) for patients who have gastrointestinal deficits that do not permit the use of either oral feeding or enteral nutrition and review the methods of delivering the PN and potential complications that are seen with this intervention. The development of PN solutions and balanced nutrients and advanced delivery methods have resulted in the ability to use PN in the ICU in patients who do not get sufficient nutrients from EN or cannot tolerate EN. Chapter 6 reviews the three large randomized studies of PN in critically ill patients. The three trials that included more than 6000 patients showed that early administration of supplemental PN did not have a clinical benefit. Unexpectedly, one of the studies showed net harm by early administration of supplemental PN. The comprehensive review of the data concerning the use of PN in critically ill patients points to delay in starting PN rather than the expected benefit from early administration of PN. Chapter 7 provides a detailed description of the flow of blood through the veins of the body as PN is delivered into the venous system. The benefits and risks of peripheral versus central venous catheter placement for provision of PN are also reviewed. The importance of the peripherally inserted central catheter (PICC) for delivery of PN directly into the vena cava near the heart's atrium is examined in detail. In addition to the types of access available, there is a comprehensive discussion of the composition of the PN and the potential for certain adverse metabolic effects with the institution of PN in the ICU patient. Additionally, patients on PN for a prolonged period are at risk for hepatic and renal failure, as well as bone disease and other adverse effects.

The next four chapters provide detailed insights into the management of specific population groups often seen in the ICU who require specialized nutritional care. Chapter 8, written by Dr. Van Way, the volume's co-editor, concentrates on the delivery of nutrients to the surgical patient in the ICU. We learn that surgical patients need intensive care because they have had a major acute event, usually either an injury or an operation. Major surgery is associated with the same acute response as seen with any type of severe physical stress and the chapter describes in detail the endocrine events, inflammatory response, and metabolic responses that affect the nutritional needs of the patient. Specific considerations of nutritional requirements for patients based upon the causes of the acute stress, including

severe burns, multiple injuries followed by surgery, stab wounds, military injuries, and others, are reviewed. The length of the hypermetabolic state, the prior intake of food, and the potential length of stay in the ICU are considered as well prior to determination of the route of nutritional support. There are detailed discussions of the nutritional needs of patients with abdominal surgeries, head injuries, and burn victims as well as the importance of specific nutrients including glutamine and other immuno-nutrients. Chapter 9 is coauthored by Dr. Seres, the volume's co-editor, and continues with the discussion of the nutritional requirements of ICU patients with serious local infections and/or sepsis. The chapter reviews the intestinal immune system and the risk of developing infection in the starved patient, and the sequence of events that may result in sepsis in patients receiving EN or PN. There is a discussion of the studies that have tested the value of immune-nutrition and other nutritional interventions in septic patients and those with severe infections. The chapter contains over 100 relevant references that point to the differences in findings between studies that have resulted in inconsistent guidelines and recommendations for the nutritional interventions for the patient with sepsis.

Organ failure can be the reason for admission to the ICU or may be a secondary consequence while in the ICU. Organs frequently affected include the lungs, liver, and kidney and/or multiple organ failure. Chapter 10, containing over 100 targeted references, examines the literature describing the results from clinical studies on the potential for specialized EN formulations to provide better outcomes for organ failure patients. Hyperglycemia and its negative effects on the immune system and metabolic activities are reviewed as hyperglycemia is a common, serious metabolic disturbance found in both diabetic and nondiabetic critically ill patients. Chapter 11 provides insights into the care of the obese patient in the ICU setting. As the percentage of obese individuals increases in the global population, there is a parallel increase in the number of obese patients admitted to the ICU. We learn that over 25 % of patients in the ICU are obese. Unfortunately, there are limited data available on nutrition therapy for obese hospitalized patients. The chapter reviews the limited scientific evidence for the metabolic care of hospitalized patients with obesity and provides practical suggestions and techniques for delivering, managing, and monitoring nutrition therapy. Detailed, practice-oriented guidelines for determining protein needs and nitrogen balance for the obese, critically ill patient are provided. The chapter includes 100 references, four tables, two case studies, and one figure that are most helpful in evaluating the effects of obesity on the nutritional well-being of the ICU patient.

Important considerations for the patient, family members, as well as the medical team are the ethical issues of nutritional support for the ICU patient especially when end-of-life decisions are being discussed. Chapter 12 provides sensitive discussions of methodologies that can be implemented proactively to help prepare all members of the ICU team if and when decisions need to be made regarding provision of nutrients and fluids to the patient. The chapter includes a detailed review of the four basic tenets of ethical decision making: autonomy, beneficence, non-maleficence, and distributive justice. Autonomy is the primary guide and refers to the right of any adult of sound mind to determine what will be done or not done to his or her body. Healthcare decisions must be made based on what is best for the patient after an educated conversation has taken place. Beneficence, or doing good for patients, is defined as acting in the best interests of the patient. The author indicates that fluid resuscitation, endotracheal intubation, and initiation of artificial nutrition and hydration (ANH), when the benefits outweigh the burdens, are examples of beneficence in action. Similarly, forgoing ANH where the burdens/risks outweigh the benefits is also an act of beneficence, since such action, objectively, is in the patient's best interest. Non-maleficence is defined as avoiding harm. In addition, the healthcare team is obligated to refrain from providing ineffective treatments. Under distributive justice, patients should all be treated equally, allowing for the differences in their clinical requirements. Patients should be treated fairly and justly. The importance of informed consent is stressed. The author reminds us that food and water are symbolic sources of life, nurturing, and caring. They have significant spiritual and ritual connotations, different from any other aspect of medical treatment. Thus, end-of-life decisions that include the provision of nutrients can be the most difficult. The numerous case studies, tables, figures, and over 100 references provide important guidance in the handling of ethical issues.

Chapter 13 is authored by Joseph Boullata, who is also the co-editor of the first and second editions of *Handbook of Drug-Nutrient Interactions* that is included in the "Nutrition and Health" book series. Chapter 13 addresses the safe practices for both EN and PN. Safe practices in EN and PN involve a broad interplay between the healthcare providers, departments, and administrative structures, interacting to assure that processes and procedures in place are carried out during the administration of nutrition support therapy. The chapter emphasizes the importance of identifying safety issues and reducing error rates in the ICU that are relevant to delivery of EN and PN. The chapter includes a detailed discussion as well as relevant tables and figures that provide guidance concerning the nutrition support therapy process. The process includes a number of critical patient-focused steps from the initial patient assessment, to a prescriber's order for a nutrition support regimen, the clinical pharmacist review of the orders, the preparation, labeling, and dispensing of the regimen, the administration of the nutrition support therapy to the patient, and finally subsequent monitoring of the patient with reassessment by the nutrition support service. This practice-oriented chapter reviews the documentation required at each step to assure that when errors are made, there is a mechanism to assess and correct processes going forward for the nutritionally supported patient in the ICU.

Another unique topic included in this comprehensive volume reviews the economic impact of nutritional support. Chapter 14 examines the evidence for the economic impact of providing nutrition to hospitalized patients so that clinicians can make a more informed decision when choosing the most appropriate intervention. The importance of using a multidisciplinary team approach for providing nutrition is discussed and suggestions for practice that can improve cost-effectiveness of providing nutrition support are included. The chapter includes a review of the literature concerning the costs associated with malnourished patients. There are also helpful appendices included in the chapter. The authors indicate that malnutrition in hospitalized patients is associated with both negative clinical and economic outcomes. Studies have demonstrated increased complications, increased length of hospital stay, increased readmissions, and increased risk of mortality. In addition, such patients require more healthcare resources compared to their counterparts without malnutrition. Provision of oral nutritional support and EN are both cost-effective in the critically ill patient in the ICU especially if EN can prevent the use of PN. The importance of the nutrition support team is emphasized.

The last two chapters examine areas where future research can be of value in providing novel nutritional modalities to the critically ill patient. Chapter 15 examines the role of the microbiome, the bacteria that inhabit the GI tract, as it relates to the provision of enteral and parenteral nutrition in the critically ill, including a discussion of current data, as well as areas for future study and intervention. The chapter includes data indicating that PN, which results in enteral deprivation, leads to a lack of microbiome diversity and poorer perioperative outcomes. Complications including anastomotic leak, wound infection, and bacteremia are more common in the PN-fed patients. Decreased microbial diversity is associated with poorer outcomes, particularly in the critically ill. PN secondarily depletes the nutrients needed by the gut bacteria, potentially leading to the loss of bacterial diversity. Future research may result in provision of beneficial intestinal bacteria to the PN patient. The last chapter on future research is authored by both volume editors. Areas for future research identified in this chapter include a determination of a clinically relevant and consistent definition of malnutrition including one for the critically ill patient with specific disease states such as cancer, obesity, pulmonary, kidney, gastrointestinal, and cardiovascular diseases. Research on the interactions between the immune system, the gut, and the microbiome and the impact of critical illness on the interactions with regard to nutritional needs is currently lacking, but the need for such data is great. Clinical studies to determine the best timing, mode of delivery, formulation contents and concentrations, drug-nutrient interactions, effects of aging, diabetes, and obesity are identified as major areas for focus.

The above description of the volume's 16 chapters attests to the depth of information provided by the 26 well-recognized and respected chapter authors. Each chapter includes complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. The volume includes 57 detailed tables and informative figures, several case studies, relevant

appendices, an extensive, detailed index, and more than 1250 up-to-date references that provide the reader with excellent sources of worthwhile information. Thus, the volume provides a broad base of knowledge concerning the pathology associated with critical illness and nutritionally relevant interventions that can enhance the potential for the patient's more healthful life.

In conclusion, *Nutrition Support for the Critically Ill* edited by David S. Seres, MD and Charles W. Van Way, III, MD provides health professionals in many areas of clinical research and intensive care unit practice with the most up-to-date, well-referenced volume on the importance of monitoring the nutritional status of the patient in the ICU regardless of cause from the day of admission through the remainder of their lifetime. Specific volume chapters carefully document the critical economic as well as clinical value of medical nutrition evaluation by a specialized ICU dietician/nutritionist as part of the nutrition support team, and review the treatment support and management of ICU patients who often have additional chronic diseases, such as diabetes and organ failures including the lung and/or liver. Each of these conditions is covered in depth in individual chapters. Unique chapters examine the nutritional requirements for the ICU patient who undergoes organ transplant, is obese, and who cannot consume food by mouth or through the enteral route. This volume will serve the reader as the benchmark in this complex area of interrelationships between acute, severe injuries due to accident or planned surgery, worsening of pre-existing conditions, and end stages of serious diseases such as cancer, and the determination of the appropriate nutritional intervention. Moreover, the critical importance of maintaining the microbiome within the gut even in the face of PN is discussed with the potential for future research in this important new area of clinical research. This comprehensive volume also includes a most sensitive and relevant chapter on the ethical considerations of nutritional support in the ICU including a discussion of end-of-life decision-making processes. The volume clearly delineates the complexities involved in the care of the nutritional needs of the critically ill patients so that medial students, nurses, dieticians, residents, fellows, as well as critical care specialists can better understand the interactions between malnutrition, increased risk of infection, inflammation, and stress responses. Unique chapters that examine the importance of safety and quality standards to improve patient outcomes following nutritional therapies are included. These chapters provide the health professional involved in the treatment of ICU patients with an enhanced understanding of the potential to stabilize the nutritional status of the critically ill patient. The editors are applauded for their efforts to develop the most authoritative resource in the field to date, and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, PhD, FACN, FASN
Series Editor

About the Series Editor

Dr. Adrianne Bendich, PhD, FASN, FACN has served as the "Nutrition and Health" Series Editor for 20 years and has provided leadership and guidance to more than 200 editors that have developed the 70+ well-respected and highly recommended volumes in the series.

In addition to **"Nutrition Support for the Critically Ill" edited by David S. Seres, MD and Charles W. Van Way, III, MD**, major new editions published in 2012–2016 include the following:

1. **Nutrition in Cystic Fibrosis: A Guide for Clinicians,** edited by Elizabeth H. Yen, MD and Amanda R. Leonard, MPH, RD, CDE, 2016.
2. **Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition,** edited by Adrianne Bendich, PhD and Richard J. Deckelbaum, MD**,** 2016.
3. **Glutamine in Clinical Nutrition,** edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015.
4. **Nutrition and Bone Health, Second Edition,** edited by Michael F. Holick and Jeri W. Nieves, 2015.
5. **Branched Chain Amino Acids in Clinical Nutrition, Volume 2,** edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015.
6. **Branched Chain Amino Acids in Clinical Nutrition, Volume 1,** edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015.
7. **Fructose, High Fructose Corn Syrup, Sucrose and Health,** edited by James M. Rippe, 2014.
8. **Handbook of Clinical Nutrition and Aging, Third Edition,** edited by Connie Watkins Bales, Julie L. Locher, and Edward Saltzman, 2014.

9. **Nutrition and Pediatric Pulmonary Disease,** edited by Dr. Youngran Chung and Dr. Robert Dumont, 2014.
10. **Integrative Weight Management,** edited by Dr. Gerald E. Mullin, Dr. Lawrence J. Cheskin, and Dr. Laura E. Matarese, 2014.
11. **Nutrition in Kidney Disease, Second Edition,** edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014.
12. **Handbook of Food Fortification and Health, volume I,** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013.
13. **Handbook of Food Fortification and Health, volume II,** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013.
14. **Diet Quality: An Evidence-Based Approach**, **volume I,** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013.
15. **Diet Quality: An Evidence-Based Approach**, **volume II,** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013.
16. **The Handbook of Clinical Nutrition and Stroke,** edited by Mandy L. Corrigan, MPH, RD, Arlene A. Escuro, MS, RD, and Donald F. Kirby, MD, FACP, FACN, FACG, 2013.
17. **Nutrition in Infancy**, **volume I,** edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013.
18. **Nutrition in Infancy**, **volume II,** edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013.
19. **Carotenoids and Human Health**, edited by Dr. Sherry A. Tanumihardjo, 2013.
20. **Bioactive Dietary Factors and Plant Extracts in Dermatology**, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013.
21. **Omega 6/3 Fatty Acids**, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson, and Dr. Sherma Zibadi, 2013.
22. **Nutrition in Pediatric Pulmonary Disease,** edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013.
23. **Magnesium and Health**, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012.
24. **Alcohol, Nutrition and Health Consequences**, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012.
25. **Nutritional Health, Strategies for Disease Prevention, Third Edition**, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012.
26. **Chocolate in Health and Nutrition**, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012.
27. **Iron Physiology and Pathophysiology in Humans**, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012.

Earlier books included **Vitamin D, Second Edition,** edited by Dr. Michael Holick; "**Dietary Components and Immune Function**" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; "**Bioactive Compounds and Cancer**" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "**Modern Dietary Fat Intakes in Disease Promotion**" edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "**Iron Deficiency and Overload**" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "**Nutrition Guide for Physician**s" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; "**Nutrition and Metabolism"** edited by Dr. Christos Mantzoros; and "**Fluid and Electrolytes in Pediatrics**" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include "**Handbook of Drug-Nutrient Interactions**" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "**Probiotics in Pediatric Medicine**" edited by Dr. Sonia Michail and Dr. Philip Sherman; "**Handbook of Nutrition and Pregnancy**" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; "**Nutrition and Rheumatic Disease**" edited by Dr. Laura Coleman; "**Nutrition and Kidney Disease**" edited by

Dr. Laura Byham-Gray, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; "**Nutrition and Health in Developing Countries**" edited by Dr. Richard Semba and Dr. Martin Bloem; "**Calcium in Human Health**" edited by Dr. Robert Heaney and Dr. Connie Weaver; and "**Nutrition and Bone Health**" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich is President of Consultants in Consumer Healthcare LLC and is the editor of ten books including "**Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition**" co-edited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the *Editorial Boards of the Journal of Nutrition in Gerontology and Geriatrics* and *Antioxidants* and has served as Associate Editor for *Nutrition* the International Journal, served on the Editorial Board of the *Journal of Women's Health and Gender-Based Medicine*, and served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. She is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

About the Volume Editors

David S. Seres, MD, ScM, PNS is Director of Medical Nutrition and Associate Professor of Medicine in the Institute of Human Nutrition, Columbia University Medical Center, New York, NY. Dr. Seres has 25 years' experience as a nutrition support specialist. He directs the nutrition support service, the medical school nutrition curriculum, and one of the few clinical nutrition fellowships for physicians in the USA. He was recipient of the 2014 Excellence in Nutrition Education Award from the American Society for Nutrition. Dr. Seres is also a clinical ethicist and a Columbia University/OpEd Project Public Voices Fellow.

Dr. Seres is currently a member of the Medical Advisory Board for Consumer Reports and has held numerous national leadership positions. He was Chair of Physician Certification for the National Board of Nutrition Support Certification, and Chair of the Medical Practice Section for the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). He is coauthor of multiple safety guidelines, chapters, editorials, and invited reviews, and appears frequently in the media advocating to consumers against dangerous foods, supplements, and nutritional practices.

Dr. Seres' research includes improving nutrition content in medical school curricula, the impact of feeding tube choice on patient outcomes and the indications for placing feeding tubes in patients placed in nursing homes, the risk of blood-stream infections in patients receiving parenteral nutrition, and metabolic derangements in acute illness.

Charles W. Van Way III, MD, FACS, FCCM, FCCP, FASPEN is Director of Metabolic Support at Truman Medical Center, and Emeritus Professor of Surgery at the University of Missouri, Kansas City. He has nearly 50 years of clinical experience in nutrition support, dating back to his surgical residency at Vanderbilt University. Although semi-retired, he maintains clinical practice in nutrition and critical care. He is the Director of the Shock Trauma Research Center of UMKC and continues research on nutrition support and on post-shock inflammation.

Dr. Van Way is a past President of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and has just finished 4 years as President of the A.S.P.E.N. Rhoades Research Foundation. He has been Editor in Chief of both the *Journal of Parenteral and Enteral Nutrition* and *Nutrition in Clinical Practice*. He has had many other leadership and editorial positions. He has more than 400 publications, most in peer-reviewed journals, including many editorials in regional and national publications.

Contents

Contributors

Meredith Barrett, MD Department of Pediatric Surgery, Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Albert Barrocas, MD, FACS, FASPEN Atlanta Medical Center, Atlanta, GA, USA

Joseph I. Boullata, PharmD, RPh, BCNSP Pharmacology and Therapeutics, University of Pennsylvania, Philadelphia, PA, USA

Clinical Nutrition Support Services, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Rebecca A. Busch, MD Department of Surgery, University of Wisconsin-Madison, Madison, WI, USA

Michael P. Casaer, MD PhD Intensive Care Department and Burn Unit, University Hospitals Leuven, Leuven, Belgium

Burn Unit, University Hospitals Leuven, Leuven, Belgium

Robert DeChicco, MS Nutrition Support Team, Center for Human Nutrition, Cleveland Clinic, Cleveland, OH, USA

Roland N. Dickerson, PharmD, BCNSP Clinical Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA

Gordon S. Doig, PhD Intensive Care Research Unit, Northern Clinical School, Royal North Shore Hospital, University of Sydney, St. Leonards, Australia

Farshad Farnejad, MD, MPH Department of Surgery, University of Missouri - Kansas City and Truman Medical Cente, MO, USA

Tushar D. Gohel, MD Department of Gastroenterology, Cleveland Clinic, Cleveland, OH, USA

Jan Gunst, MD, PhD Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium

Philippa T. Heighes, Masters. of. Nursing (Education), B.A. (Nursing). Intensive Care Research Unit, Northern Clinical School, Royal North Shore Hospital, University of Sydney, St. Leonards, Australia

Donald F. Kirby, MD, FACP, FACN, FACG, AGAF, CNSC, CPNS Center for Human Nutrition, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

Kenneth A. Kudsk, MD Department of Surgery, University of Wisconsin-Madison, Madison, WI, USA

Stephanie N. Lueckel, MD Division of Trauma and Surgical Critical Care, Department of Surgery, Rhode Island, Hospital, Warren Alpert Medical School at Brown University, Providence, RI, USA

Kenneth A. Lynch Jr, MS, APRN-CNP Surgical Critical Care, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA

Ainsley Malone, MS, RD, LD, CNSC Pharmacy Department, Mt. Carmel West Hospital, Columbus, OH, USA

Dustin R. Neel, MD Surgical Intensive Care Unit, Department of Surgery, Truman Medical Center, Kansas City, MO, USA

Denise Baird Schwartz, RD, CNSC, FADA, FAND, FASPEN Food and Nutrition Services, Providence Saint Joseph Medical Center, Burbank, CA, USA

David S. Seres, MD, ScM, PNS Department of Medicine, Institute of Human Nutrition, Columbia University Medical Center, New York, NY, USA

Fiona Simpson, MND Intensive Care Research Unit, Northern Clinical School, Royal North Shore Hospital, University of Sydney, St. Leonards, Australia

Eoin Slattery, MD MRCPI Department of Preventive Medicine and Nutrition, Columbia University Medical Center-New York Presbyterian Hospital, New York, NY, USA

Ezra Steiger, MD Department of General Surgery, Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

Daniel H. Teitelbaum, MD Department of Surgery, University of Michigan, Ann Arbor, MI, USA

Charles W. Van Way III, MD, FACS, FCCM, FCCP, FASPEN Department of Surgery, Truman Medical Center, Kansas City School of Medicine, University of Missouri, Kansas City, MO, USA

Marion F. Winkler, PhD, RD, CNSC Department of Surgery, Nutrition Support Service, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA

Chapter 1
An Introduction to Malnutrition in the Intensive Care Unit

David S. Seres

Keywords Malnutrition • Starvation • Hypoalbuminemia • Albumin • Cachexia • Catabolism • Muscle wasting • Nutritional deficiency • Kwashiorkor • Marasmus • Protein-calorie malnutrition • Nutrition support

Key Points

- Malnutrition refers to two distinct syndromes: one due to imbalance between intake and physiological need, and the other resultant from systemic inflammatory disease.
- Distinguishing between disease-related and starvation-related malnutrition best selects patients appropriate for nutritional intervention.
- Careful screening and identification of patients with malnutrition identifies those patients with high risk for hospital complications, prolonged length of stay, and mortality.
- Malnutrition due to imbalance may be reversed by nutritional supplementation.
- Malnutrition due to systemic illness does not respond to nutritional supplementation.
- Deficiency is not solely a low level of a nutrient. It is a pathological syndrome resulting from inadequate intake or altered physiology that responds to supplementation.
- Contrary to common wisdom, neither disease-related malnutrition nor kwashiorkor is a protein-deficiency state, in that deficient protein intake does not cause them, nor does protein supplementation improve them.

Introduction

A full understanding of both the cause and treatment of malnutrition in critically ill patients is crucial, and is the key to understanding the complex role of nourishing them. Malnutrition is highly predictive of morbidity and mortality in the ICU [1], so are feeding difficulty [2] and feeding efficiency (percent

D.S. Seres, MD, ScM, PNS (✉)
Department of Medicine, Institute of Human Nutrition, Columbia University Medical Center, 650 W 168th Street, P&S 9-501, New York, NY 10032, USA
e-mail: dseres@columbia.edu

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_1,

of prescribed calories actually delivered) [3]. These associations, however, are all based on observational studies. Their causality is not proven. In fact, feeding difficulties and malnutrition (as traditionally defined in the ill) are to a large extent epiphenomena of disease, associated with disease severity, and often not reversed by supplementation or artificial nourishment. Stated in another manner, sicker patients eat less and are harder to feed. This also applies to traditional "nutritional" markers, such as albumin and transthyretin (aka prealbumin). Our current knowledge has led us to conclude that these nutritional markers have nothing at all to do with nourishment, which is explained further in the section on systemic inflammation below, and that we in fact have no direct measurement of adequacy of nourishment in the ill [4, 5].

This may sound fatalistic, especially at the start of a textbook about nourishment in the ICU. But the relationship between malnutrition and critical illness is complex. On the one hand, it is incontrovertible that starvation is fatal when allowed to occur over a period of time. On the other hand it is less clear how long and how severely starvation must persist to adversely affect clinical outcomes. What we call malnutrition in the acute and chronically ill is related both to inadequate nourishment and to the systemic effects of disease. It is the purpose of this chapter do discuss and define these relationships, and to provide a base on which subsequent chapters can be built.

Conceptualizing Malnutrition

Malnutrition is one of the more confusing of medical terms. It is a condition that that everyone feels they know when they see it, but few are able to define. Historically, it was commonly believed that malnutrition results when there is an alteration in level or function of any nutrient. But, after all, there is no (nonsurgically placed) substance in the body that isn't or wasn't a nutrient. Therefore, *all* disease could be construed to be malnutrition by this broad definition.

Recently, efforts have led to a significant improvement in understanding the etiology of malnutrition in the ill, and in the rigor with which we discuss it. Reviewing some of the historical definitions will help the clinician better understand malnutrition as it is currently described.

Since its first known use in 1862 [6], changes in the terminology and the defining characteristics for malnutrition have been proposed numerous times, and with fairly extreme variance. These definitions have changed in parallel to changes in our beliefs and our understanding of what it is we are observing. Until fairly recently, most have regarded the body more or less as a machine, which needs certain inputs (nutrients) in order to function well. But while nutrients are undeniably inputs of a sort, the body is not a machine, and disease is not a simple mechanical flaw. Knowledge about the interactions among body, nutrients, and disease are just beginning to be incorporated into nutritional science.

To be malnourished, a patient should have an imbalance between intake of macro- or micronutrients and the needs to maintain health. Undernourishment, whether in the presence or absence of illness, results in weight loss, muscle and fat loss, and/or vitamin deficiencies, and predisposes to morbidity and mortality dependent on what substance is deficient. Undernourishment, in the absence of disease, is a phenomenon entirely related to imbalance and can be treated by nourishment. Overnourishment results in obesity and/or vitamin toxicities. But obesity itself is a disease state associated with increases in inflammatory markers [7] and altered levels of a variety of nutrients [8]. Obesity may not be solely due to altered intake, and may or may not be simply a state of simple nutritional imbalance. Malnutrition, as we currently use the term, however, includes both the manifestations of imbalance, as in the starved, as well as the manifestations of systemic inflammation. This obvious conundrum will be explored in more detail below.

Historical Perspective

The history of treating malnutrition via tube or intravenously is fascinating. The practice is centuries old. In ancient Egypt, enemas of wine, milk, and grain were used to support health [9]. Intravenous mixtures of milk, blood, and alcohol all preceded modern parenteral nutrition [10]. Most authors credit Hiram Studley's 1936 paper [11] with the first demonstration of a quantitative relationship between weight loss and surgical outcome. He showed that the amount of weight lost before peptic ulcer surgery-predicted postoperative complications.

Definitions of malnutrition have been confused and variable, and the publication of a monograph in 1969 by the Wellcome Trust foundation attempted to provide some clarity [12]. This consensus paper set out clear criteria for diagnosing endemic malnutrition in children. These were widely adopted and shaped the way malnutrition was discussed in all patients for decades. Unfortunately, these definitions also added to our confusion about what we were observing.

The Wellcome Classification, as it has become known, defined the conditions of kwashiorkor and marasmus as opposite ends of a continuum of malnutrition in children. Kwashiorkor was thought due to protein deficiency and marasmus to calorie deficit. In the center, marasmic-kwashiorkor described the coexistent deficiency of both. The current term "protein-calorie malnutrition" is used in an attempt to explain what we see in our patients by fitting them into the same kind of thinking.

The Wellcome classification, however, was intended to define conditions seen in children in the tropics, where kwashiorkor and marasmus were prevalent. However, through the International Classification of Diseases, they have found their way into the hospital care of adults in the USA. This extension of the original classification has been wildly misleading. As will be discussed in Chap. 14 the diagnosis and treatment of malnutrition may significantly enhance payment to the hospital by Medicare. But the resulting use of the terms marasmus and kwashiorkor has led to embarrassing press accounts [13] and steep fines [14] to hospitals as regulators have skeptically questioned the high prevalence of a tropical childhood disease in adults hospitalized in America. Fortunately, the most significant redefinition of malnutrition in the ill to occur since the Wellcome consensus has been ongoing now for the past decade.

Kwashiorkor and Marasmus

Kwashiorkor is a syndrome characterized by a prodrome of kinky hair and irritability. Children then rapidly develop ascites, edema, and hypoalbuminemia, concurrent with the onset an acute illness (e.g., diarrheal illness, measles, malaria) that is not usually associated with such severe third space fluid losses. At the time that the Wellcome Classification was developed, it was believed that this syndrome was due to deficient protein intake in the diet. The children were eating, on average, a diet mostly reliant on corn. Many, but not all, were starved. It has become clear since that the manifestations of kwashiorkor do not require a poor protein intake, or starvation, and are most likely due to an exaggerated systemic inflammatory response. The onset of the edematous condition is more frequent in the rainy season, and it is theorized that kwashiorkor may be mediated by chronic ingestion of mold that contains pro-inflammatory substances such as aflatoxin. Hence the seasonality of onset [15]. The inflammatory response as a cause of malnutrition is reviewed later in this chapter.

Marasmus, on the other hand, is simple starvation, with definitions usually requiring that the child be less than 60 % of expected weight for age or weight for height, with no edema present. This cut-off, like so many definitions of malnutrition, was based on mortality rates associated with it [16].

Nutrition Support as a Specialized Therapy

As critical care developed as a field of specialized care in the 1960s, recognition that these patients often required specialized nutrition support resulted in the development of parenteral nutrition (PN) [17]. At the time, part of the impetus for this development was the observation that critically ill patients were "hypermetabolic" and were expending a huge number of calories based on indirect calorimetry. Then too, there was a feeling that if food was good, more food would surely be better. Hence, PN was originally called "hyperalimentation" (or "hyperal" for short), literally meaning over-feeding. For the next 30 or so years, nutrition experts were chasing after calorie burn with hyperalimentation while the critical care community learned to use calorimetry to drive improvements in care. With current critical care techniques, the manner in which we control ventilation, sedation, pain, temperature, and anxiety have all removed the excess calorie burn. To be sure, in such areas as trauma and burn care, an increase in calorie burn can still be demonstrated. But it is less, and for shorter periods, than previously thought.

Most critically ill patients are no longer hypermetabolic, as far as calories are concerned. They burn the same number of calories as a normal person spending most of the day in bed—less than half of what we once thought these patients need to be fed. Moreover, there is severe toxicity from overfeeding. When liver transplantation first became available, hepatic failure due to hyperalimentation-related steatohepatitis was a common indication. This is still an issue in pediatric care.

Critically ill patients, on the other hand, are "hypermetabolic" where protein is concerned, at least as reflected in urinary nitrogen excretion and muscle loss. But as will be discussed, there is essentially no proof that protein supplementation has a therapeutic benefit. This excludes, then, that this represents treatable nutrient deficiency.

There has long been a disconnection in how we think and speak about malnutrition. On the one hand, there are clear correlations between the alterations in nutrients seen in the ill and clinical outcomes. There is no question that the lower one's albumin, the more likely a poor outcome. However, time and again our attempts at supplementation and normalization of these altered nutrients have failed to benefit patients, and often cause frank harm. Our insistence in calling these alterations malnutrition leads to additional confusion.

Malnutrition and Deficiency vs. Epiphenomenon

What then should the definition of malnutrition be? To this author's thinking, it should be synonymous with the presence of deficiency. However, even with the newer definitions, it is not, and the term deficiency is also frequently misused. If one looks to Webster's, several definitions are found, all referring to the lack of something that is needed [18]. Thus, a nutritional deficiency occurs when there is a lack of something, due to altered intake, metabolism, digestion, etc., which leads to an undesirable health outcome, which itself should be reversible or preventable by supplementation. Unfortunately, when you read the scientific literature, the term has been used extremely lazily to describe any condition in which a nutrient level is low, whether or not a pathology results. This semantic error results in misunderstanding that leads to huge wastes in time and resources, and potential harm to patients, as we attempt to correct these phenomena, or less commonly properly study them.

For instance, vitamin D levels are on average quite low in the ICU, and the lower they are the worse patients do [19]. As a result of this observation, there have been numerous practitioners advocating D supplementation become standard of care. But supplementation has been shown recently to have no effect on mortality or other outcomes [20]. In truth, we really don't understand the significance of a low vitamin D level in a patient. It is likely an epiphenomenon of systemic inflammation, resulting from a decrement in vitamin D carrier proteins via the same mechanism that lowers albumin—capillary leak.

This important phenomenon is described below. It should be no surprise that lower levels of vitamin D are associated with worse outcomes, but not reflective of the state of vitamin D nourishment.

Similarly, muscle loss is severe and rapid in the ICU. Muscle is largely protein, so the process of muscle loss has been equated with protein deficiency in the ill. But this process proceeds unabated whether patients are fed or not, and feeding merely causes the addition of fat to the muscle while actual muscle mass continues to diminish [21].

On the other hand, a low vitamin B12 level, when associated with elevated methylmalonic acid and homocysteine levels, macrocytosis, and gait and cognitive dysfunction, does truly represent a deficiency. While this biochemical and clinical evaluation of certain micronutrients is possible, and it is possible to make assessments of calorie adequacy in the well population based on weight, there is no marker or test, no clinical or biochemical analysis, that accurately reflects adequacy of nourishment of calories and protein in sick patients [4, 5].

Systemic Inflammation vs. Starvation

As stated, much of the change in metabolism and physique that we observe in the sick patient is due to systemic inflammation. These changes may be acute or chronic, and may be indistinguishable from the impact of starvation (Table 1.1). For instance, both starvation and inflammation will cause muscle mass to decrease. The important difference is that the pathophysiology of each yield different syndromes. Simply stated, muscle mass loss from starvation is easily reversed by refeeding and exercise, while that due to systemic inflammation is perhaps slightly attenuated but not reversed or well prevented by any known nutritional approach.

The metabolic milieu of systemic inflammation is familiar to anyone caring for the critically ill. Sick patients have a number of responses to their illness. When severe, they have critical illness with hemodynamic instability and severe capillary leak. When indolent and chronic, they have disease-related wasting, such as seen for example in congestive heart failure, cancer, and HIV/AIDS wasting syndrome. The storm of increased cytokines has been described [22] and is the system likely mediating many of these manifestations. Carbohydrate metabolism is significantly altered [23]. Hyperglycemia, reflective of hepatic insulin resistance, and occurring despite probable increased glucose uptake and utilization by muscle, with suppression of glycogenesis and increased hepatic glucose release, all characterize the systemic inflammatory response.

Fat is far less available as a substrate in patients with systemic inflammation. Lipase function and mobilization of fat from tissues are altered, but free fatty acid levels are high [24]. Moreover, fat undergoes futile cycling. Futile cycling occurs when substrates are broken down and then reformed in a cycle. ATP is hydrolyzed and the cycle results in release of heat and net energy expenditure without physiological gain. Adrenergic hormones produced in excess may be responsible [25].

Table 1.1 Components of different types of malnutrition

Starvation	Disease-related malnutrition
Weight loss	Weight loss
Poor intake	Anorexia, gut dysfunction
Muscle loss	Muscle wasting
Subcutaneous fat loss	Slower subcutaneous fat loss
Muscle weakness	Muscle weakness
Normal albumin	Decreased albumin
Normal inflammatory mediator levels	Increased inflammatory mediator levels
	Edema

Muscle wasting and alterations in serum protein have long been considered markers for malnutrition, but have been well proven to have no relationship to nourishment in the ill [5]. Certainly the presence of age-related muscle loss predisposes to disability in the general population [26]. In the absence of illness, muscle wasting occurs due to bed rest [27], and this is attenuated by exercise in normal volunteers [28]. Catabolism, which the author uses to describe the clinical syndrome resulting from systemic inflammation, is characterized by an inexorable loss of muscle mass, nonresponsive to nourishment strategies [29].

Similarly, hypoalbuminemia is caused by edema, rather than the traditional teaching that edema is the result of hypoalbuminemia. The decrement in serum protein levels is a consequence of capillary leak resulting from systemic inflammation, rather than the converse. The notion that hypoalbuminemia is due to protein deficiency, and that it in turn causes edema by causing a hypo-oncotic state, ignores the physiological facts. Oncotic pressure exists when a semipermeable membrane is present such that a gradient may be created. In this normal state, oncotic pressure causes solvent to pass through the membrane toward the side of the membrane with higher concentration of solute. This cannot exist during capillary leak. Moreover, to the knowledge of the author, no one has directly measured the oncotic pressure of serum in hypoalbuminemic patients, or the oncotic gradient from serum to interstitium, to prove there is a hypo-oncotic state. One could easily surmise that the acute phase reactants, and other molecules secreted in the inflammatory state, could overcome the dilution of albumin and other molecules responsible for oncotic pressure in the normal state.

Finally, as with our history of overfeeding calories based on measuring calorie burn, it is conceivable, but unproven, that our prescription of supplementary protein to the ill, based on urinary urea nitrogen excretion, may in fact result in hyperalimentation of protein and may be deleterious. This possibility is mentioned in the hope that when protein need is finally appropriately studied, the reader will have an open mind to the sea change this will represent if our protein prescription methods prove wrong. There are plentiful observations that show a strong correlation between whether nitrogen balance is achieved and how well the patient does during critical illness. There are no high-quality prospective randomized trials, however, that prove a causal relationship between intervening to achieve nitrogen balance and clinical outcomes. Moreover, one can easily imagine that if more nitrogen is excreted when one is sicker, and it is harder to feed sicker people, that there are two good reasons, unrelated to a nitrogen balance-based intervention, that a greater nitrogen deficit predisposes to poor outcomes.

New Definitions

As stated previously, one might assume incorrectly, since the term malnutrition includes “nutrition,” that malnutrition refers solely to pathological phenomena due to and/or responsive to alterations in nourishment. While some aspects of illness-related malnutrition do result from imbalance between intake and need, such as that seen with starvation or vitamin deficiency, much of the malnutrition observed in the acutely and chronically ill is epiphenomenon of disease. Conceptually then, malnutrition can be divided into two main categories: imbalance-related, and disease process related [30]. In common terms, the former is malnourishment and the latter is catabolism or cachexia. Where confusion occurs is the number of manifestations that are common to both (see Table 1.1).

New definitions for malnutrition have been recently published by national organizations [30]. These guidelines recommend that the presence of two or more of poor intake, weight loss, muscle mass loss, subcutaneous fat loss, edema, and/or decreased muscle strength is diagnostic of malnutrition (Table 1.2). As stated throughout this chapter, the terminology used for malnutrition is confusing. These new definitions claim to acknowledge the impact of systemic inflammation as distinct from those of starvation, and yet generalize the definition of malnutrition as meaning poor nourishment. Unfortunately, even these newest definitions continue to conflate the manifestations of systemic inflammation with the manifestations of altered nourishment. Despite removing such measurements as serum protein levels from the definition, citing the strength of evidence that they are unrelated to

Table 1.2 New definition of malnutrition [30]

Two or more of the following:
Poor/inadequate intake
Weight loss
Muscle mass loss
Subcutaneous fat loss
Edema
Decreased muscle strength

calorie or protein intake, manifestations of inflammation such as edema, muscle strength, and muscle mass loss (whether or not in the presence of adequate nourishment) are still included. In other words and for the sake of argument, a patient with severe septic shock, who has been receiving full feeding via parenteral nutrition, who is edematous and has lost a large amount of muscle, is still diagnosed with malnutrition.

While these definitions continue to provide potential confusion, there is a benefit to the continued inclusion in the definition of the manifestations of inflammation. Because these are all indicative of severity of illness, they are predictive of the complexity of care. As discussed in Chap. 14 hospital reimbursement is adjusted for comorbidities that increase the complexity of care. Therefore, carefully screening for malnutrition, even as currently defined, results in increased payment for caring for sicker patients, which is as it should be. Moreover, and potentially even more valuable to patients, diagnosis of malnutrition identifies the patients at highest risk for complications. Methods for assessing patients are reviewed in detail in Chap. 3. Patients identified by the screening and assessment protocols already well described can be designated for more intensive monitoring and preventive multidisciplinary care by experienced and specialized clinical teams. Multidisciplinary care should be the standard of care for all complex patients. Fewer preventable complications, a decrease in cost of care, and improved reimbursement via better identification all should justify the expense of such teams.

Conclusion

Malnutrition, while familiar to any medical practitioner, remains a complex syndrome to describe and understand. It is comprised of phenomena due to altered nutrient balance, such as in starvation or vitamin toxicity. It is also comprised of epiphenomena of illness, such as muscle wasting and hypoproteinemia. Part of the complexity in understanding malnutrition lies in the terminology we use to describe it, and part lies in the fact that many components are common to both imbalance-related malnutrition and disease-related malnutrition. It is clear that these are two distinct syndromes that often coexist. The components due to altered nourishment may simply be treated with nourishment when systemic disease is absent. The components that are epiphenomena of disease are unresponsive to nourishment-based interventions and may hamper response to nourishment that is targeted at starvation when starvation and systemic illness coexist.

References

1. Fontes D, Generoso Sde V, Toulson Davisson correia MI. Subjective global assessment: a reliable nutritional assessment tool to predict outcomes in critically ill patients. Clin Nutr. 2014;33(2):291–5.
2. Reintam Blaser 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.

3. Tsai JR, Chang WT, Sheu CC, Wu YJ, Sheu YH, Liu PL, et al. Inadequate energy delivery during early critical illness correlates with increased risk of mortality in patients who survive at least seven days: a retrospective study. Clin Nutr. 2011;30(2):209–14.
4. Seres DS. Surrogate nutrition markers, malnutrition, and adequacy of nutrition support. Nutr Clin Pract. 2005;20(3):308–13.
5. Koretz RL. Death, morbidity and economics are the only end points for trials. Proc Nutr Soc. 2005;64(3):277–84.
6. Merriam-Webster On-line Dictionary. http://www.merriam-webster.com/dictionary/malnutrition.
7. Murray ET, Hardy R, Hughes A, Wills A, Sattar N, Deanfield J, et al. Overweight across the life course and adipokines, inflammatory and endothelial markers at age 60–64 years: Evidence from the 1946 birth cohort. Int J Obes (Lond). 2015;39(6):1010–8.
8. Lima KV, Lima RP, Goncalves MC, Faintuch J, Morais LC, Asciutti LS, et al. High frequency of serum chromium deficiency and association of chromium with triglyceride and cholesterol concentrations in patients awaiting bariatric surgery. Obes Surg. 2014;24(5):771–6.
9. Harkness L. The history of enteral nutrition therapy: from raw eggs and nasal tubes to purified amino acids and early postoperative jejunal delivery. J Am Diet Assoc. 2002;102(3):399–404.
10. Levenson SM, Hopkins BS, Waldron M, Canham JE, Seifter E. Early history of parenteral nutrition. Fed Proc. 1984;43(5):1391–406.
11. Studley HO. Percentage of weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer. JAMA. 1936;106(6):458–60.
12. Classification of infantile malnutrition. Lancet. 1970;2(7667):302–3.
13. Williams LDS. Prime Hospital Abruptly Stops Billing Medicare for Rare Ailment. 2012. http://ww2.kqed.org/news/2012/12/20/prime-hospital-abruptly-stops-billing-medicare-for-rare-ailment.
14. Virbitsky S. University Hospitals Case Medical Center Incorrectly Billed Medicare Inpatient Claims With Kwashiorkor. 2014. https://oig.hhs.gov/oas/reports/region3/31300031.pdf.
15. Seres DS, Resurreccion LB. Kwashiorkor: dysmetabolism versus malnutrition. Nutr Clin Pract. 2003;18(4):297–301.
16. Waterlow JC. Classification and definition of protein-calorie malnutrition. Br Med J. 1972;3(5826):566–9.
17. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery. 1968;64(1):134–42.
18. Merriam-Webster On-line Dictionary. http://www.merriam-webster.com/dictionary/deficiency. Accessed 23 Mar 2015.
19. Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, Diaz-Fuentes G. Vitamin D deficiency is associated with mortality in the medical intensive care unit. Crit Care. 2011;15(6):R292.
20. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA. 2014;312(15):1520–30.
21. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Güiza FG, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med. 2013;41(10):2298–309.
22. Galley HF, Webster NR. The immuno-inflammatory cascade. Br J Anaesth. 1996;77(1):11–6.
23. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. Am J Med. 1995;98(1):75–84.
24. Andersen SK, Gjedsted J, Christiansen C, Tonnesen E. The roles of insulin and hyperglycemia in sepsis pathogenesis. J Leukoc Biol. 2004;75(3):413–21.
25. Wolfe RR, Herndon DN, Jahoor F, Miyoshi H, Wolfe M. Effect of severe burn injury on substrate cycling by glucose and fatty acids. N Engl J Med. 1987;317(7):403–8.
26. Janssen I. Influence of sarcopenia on the development of physical disability: the cardiovascular health study. J Am Geriatr Soc. 2006;54(1):56–62.
27. Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. Am J Physiol. 1996;270(4 Pt 1):E627–33.
28. Salanova M, Gelfi C, Moriggi M, Vasso M, Viganò A, Minafra L, et al. Disuse deterioration of human skeletal muscle challenged by resistive exercise superimposed with vibration: evidence from structural and proteomic analysis. FASEB J. 2014;28(11):4748–63.
29. Casaer MP. Muscle weakness and nutrition therapy in ICU. Curr Opin Clin Nutr Metab Care. 2015;18(2):162–8.
30. 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.

Chapter 2
The Immunological Role of Nutrition in the Gut

Rebecca A. Busch and Kenneth A. Kudsk

Keywords Parenteral nutrition • Enteral nutrition • Innate immunity • Acquired immunity • Gastrointestinal-associated lymphoid tissue • Mucosa-associated lymphoid tissue • Immunoglobulin A • Mucosal immunity • Cytokines • Adhesion molecules

Key Points

- Nutrition support is necessary for recovery from serious injury and illness.
- Route and type of nutrition support have immunological consequences.
- All branches of the immune system are affected by route and type of nutrition.
- Symbiosis typically exists between humans and gastrointestinal tract bacteria; however, physical stresses can result in dysbiosis.
- The body has an array of immunological defenses against mucosal pathogens including non-immunologic defenses, the innate immune system, and the adaptive immune system.
- Nutrition plays a role in local and systemic inflammatory responses.
- Enteral feeding is the preferred method of nutrition support whenever possible.

Introduction

Specialized nutrition support is recognized as a key factor in recovery from critical illness, particularly when injuries preclude resumption of adequate oral intake for a prolonged period of time. Serious injury and illness affect multiple organ systems within the body, resulting in a substantial metabolic changes necessary to combat the initial insult and inflammatory responses, support healing and recovery, and defend against further injury. This dynamic response results in an overall hypermetabolic state that results in severe catabolism unless countered with appropriate nutrition support [1–4]. Without nourishment, stores of body protein, fat, and essential macronutrients and micronutrients are depleted, resulting in complications including inability to maintain immunity. Malnutrition in

R.A. Busch, MD • K.A. Kudsk, MD (✉)
Department of Surgery, University of Wisconsin-Madison, 600 Highland Avenue, G5/341, Madison, WI 53792-7375, USA
e-mail: kudsk@surgery.wisc.edu

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_2,

critically ill patients is strongly associated with infection and impaired healing [5, 6]. Many patients remain unable to resume adequate oral intake during critical illness and require specialized nutrition support provided as either enteral nutrition (EN) or intravenous, parenteral nutrition (PN). This chapter provides strong immunological, theoretical, and clinical evidence to support the advantages of enteral over parenteral feeding.

The sentinel experiments spurring investigation of nutrition and gut immunity began in the late 1970s in the laboratory of Dr. George Sheldon. These studies examined the effects of malnutrition on susceptibility to infection using hemoglobin and *Escherichia coli* in an animal model of intraperitoneal sepsis. Peterson et al. demonstrated that well-nourished animals survived the septic challenge approximately 70 % of the time [7]. Only 10 % of animals administered a nutrient-poor oral diet for 2 weeks, with a resultant 20 % weight loss, survived the septic challenge. Refeeding malnourished animals with chow prior to the septic challenge returned the survival rate back to about 70 %. Most animals died if fed parenterally either with or without fat. It remained unclear, however, whether some deficiency in the parenteral formula itself or the route of feeding caused the high mortality. A subsequent series of studies examined that question and confirmed that malnourished rats refed with oral ingestion of the PN solution experienced improved survival after the septic challenge, while those refed PN intravenously sustained significantly higher mortality [8]. Subsequent experiments concluded that parenteral feeding neither improved survival after bacterial challenge in malnourished rats nor maintained high survival in well-nourished animals, while feeding the identical solution enterally significantly improved survival [8, 9]. These studies confirmed that route of nutrition with decreased enteral stimulation altered an animal's response to intraperitoneal sepsis.

Within a few years, clinical studies examined the effect of route of nutrition in trauma patients. Early clinical studies randomized trauma patients to experimental groups who were either unfed or received either PN or EN via jejunostomy tube [10–12]. Interestingly, unfed and PN-fed patients sustained significant increases in pneumonia and intra-abdominal abscesses compared with patients fed enterally (Fig. 2.1). In combination with the aforementioned murine studies, these results highlighted the importance and clinical applicability of enteral feeding in resistance to infection. It remained to be determined whether the improvement was metabolic and/or immunologic in nature.

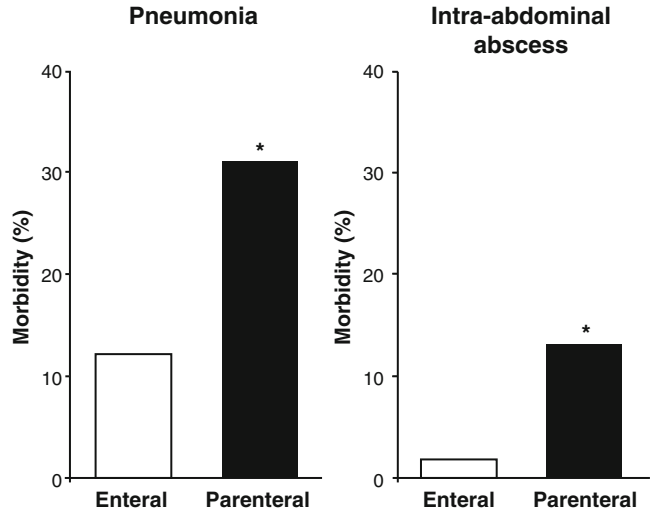


Fig. 2.1 Frequency of infectious complications in critically injured patients fed enteral nutrition or parenteral nutrition. *$p<0.05$ vs. enteral nutrition. From Kang W, Kudsk K. Journal of Parenteral and Enteral Nutrition (31/3). Copyright © 2007 by the American Society for Parenteral and Enteral Nutrition. Reprinted with Permission of SAGE Publications

Human and Bacterial Relationships in the Gut

The body is in constant contact with potential pathogens covering all epithelial surfaces. The most intense exposure occurs in the gastrointestinal tract. The human gut contains an estimated 500–1000 species of bacteria, and total numbers of bacteria exceed the total number of human cells 150-fold [13–15]. The mucosa of the gastrointestinal tract serves a gatekeeper function between the lumen and the systemic circulation. While the mucosa allows absorption of nutrients and other molecules, it also defends against bacterial pathogen invasion. Direct contact between pathogen and the epithelial surface represents the most basic form of exposure [4]. However, not all bacteria are pathogenic, especially under normal homeostatic conditions [16]. In the intestine, humans and bacteria coevolved and developed a symbiotic relationship whereby the intestine provides nutrients to the bacteria, while the bacteria aid in digestion of food, nutrient absorption, and vitamin production [17]. Despite this huge and constant bacterial challenge, the gastrointestinal barrier is rarely overwhelmed by microbial pathogens, implying effective defenses against pathogen invasion. These defenses include non-immunological protective mechanisms, innate immune defenses, and adaptive mucosal immune defense systems that provide increasingly specific bactericidal and bacteriostatic locoregional and systemic deterrents against invasion.

However, when the human body responds to stress or injury with changes in metabolism, hormone secretion, and systemic perfusion among other factors, the gastrointestinal tract environment also acts in response to the stress. The work of Alverdy et al. introduced the concept of quorum sensing to the nutritional and surgical literature in the 1990s [18, 19]. Quorum sensing represents a process whereby bacteria respond to hormone-like molecules called auto-inducers to regulate specific target genes within the bacteria. In a non-hostile environment, bacterial virulence genes remain downregulated while the imposition of stressors leads to upregulation of these genes [17, 20]. The type of stressors vary and include many forms of standard intensive care unit therapy such as antibiotics, administration of vasoactive drugs, blockade of gastric acid production, opiate administration reducing gut motility, PN, and gut starvation due to lack of enteral feeding. For instance, quorum sensing can activate virulence genes which increase a flagellar response by the bacteria, rendering them more adhesive to the mucosa and more virulent to the host [21–24]. Activation of virulence genes by bacteria can be replicated in vitro by inducing stress conditions. Interestingly, incubation of the pro-virulent bacteria with FC fragments from immunoglobulin A (IgA) inhibits the virulent phenotype [19]. This latter observation suggests that virulent bacteria can be contained and controlled by effective defenses.

Aside from the constant exposure to a huge bacterial load, interest in the gastrointestinal tract and its immune system stem from the previously popular theory of bacterial translocation [25]. Defined as the passage of viable bacteria from the gastrointestinal tract to extraintestinal sites such as mesenteric lymph nodes (MLN), liver, spleen, kidney, and bloodstream, bacterial translocation provided a potential explanation for intra-abdominal infectious complications, i.e., abscesses, developing in an otherwise sterile environment. Traditionally, there are three ways bacteria are thought to enter the systemic circulation from the gut: intestinal overgrowth, increased mucosal permeability, and deficiencies in the host immune defenses [1]. It was postulated that during stress, translocation of indigenous bacteria from the gastrointestinal tract explained the pathogenesis of opportunistic infections. While bacterial translocation recently fell out of favor, this hypothesis stimulated a significant amount of research in the area, greatly enhancing our understanding of the gastrointestinal immune system.

Intestinal Antibacterial Barriers

Non-immunological Gastrointestinal Protective Mechanisms

Non-immunological protective mechanisms provide a significant first line of defense against potential pathogens. These mechanisms include mechanical barriers, secretions, dynamic peristalsis, and commensal microbial flora. Frequently this defense has been referred to as the "weep and sweep" defense as the focus of its action is to first bathe the pathogens in a milieu of secretions and then wash them through the system while proficiently extracting nutrients and preventing bacterial adherence to the mucosa of the gastrointestinal tract.

Mucosal cells themselves provide a critical defense against attachment to and invasion of the gastrointestinal mucosa by bacteria. This barrier is mainly formed by the epithelial cells of the intestine. Stem cells within the intestine generate four main types of epithelial cells: (1) absorptive enterocytes, (2) mucus-secreting goblet cells, (3) hormone-secreting enteroendocrine cells, and (4) immune effector Paneth cells, which are discussed later. All of these cell types play a part in protecting the host from bacterial invasion (Fig. 2.2).

Absorptive enterocytes are the most abundant cell type of the small intestine, and maintenance of their integrity is key to preventing bacterial invasion [26]. A significant amount of their barrier function derives from the maintenance of junctional complexes between enterocytes and other cells types [27, 28]. These junctions consist of zonula occludens, zonula adherens, and macula adherens, all of which specialize in cell-cell adhesion. Together these complexes, mainly composed of claudins, occludens, and ZO-1, allow passage of water and specific ions but provide a mechanical barrier to macromolecules. This barrier prevents passage of luminal contents between epithelial cells, and forces macromolecules to selectively enter the cells in order to pass through the tissue. Substances that either pass through the junctional complexes or are absorbed by enterocytes reach the systemic circulation via fenestrated capillaries in the lamina propria (LP) or the lymphatic lacteals. Enterocytes survive approximately 3–5 days, rendering their turnover relatively rapid, to provide another form of defense should a barrier breakdown or cellular invasion by pathogens occur.

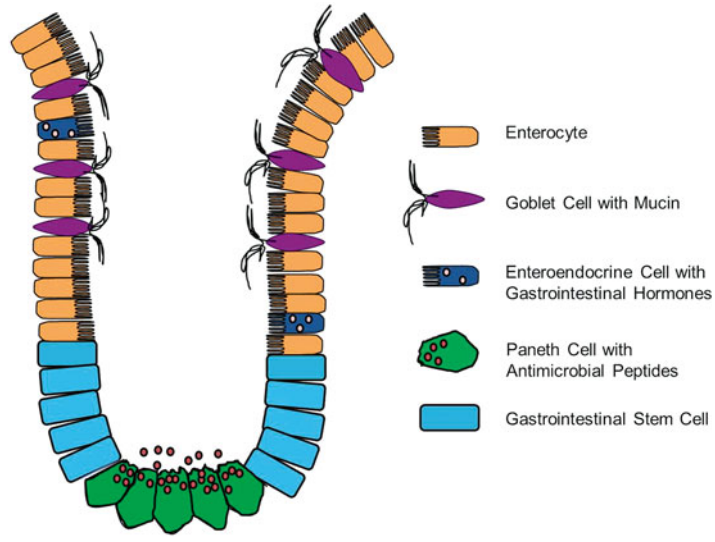


Fig. 2.2 Schematic overview of intestinal crypt of Lieberkuhn containing four types of epithelial cells and gastrointestinal progenitor cells in their relative locations. Image created with Microsoft PowerPoint

Goblet cells represent another specialized form of epithelial cell found throughout the gastrointestinal tract [29–32]. The life span of goblet cells is only slightly longer than that of enterocytes, lasting 5–6 days, with the relatively rapid cell turnover providing the potential for rapid recovery after insult. Goblet cells synthesize and secrete mucins which form a physical barrier over the epithelium, protecting against dehydration, mechanical damage, and luminal contents. Mucins consist of a family of high molecular weight glycoproteins that accumulate at the apical end of goblet cells prior to release into the gastrointestinal lumen, which possess the ability to bind pathogens and form gels, allowing for both a physical and chemical layer of defense.

Functionally, the mucus creates a viscoelastic layer allowing the smooth passage of food during peristalsis with little mechanical injury to the gut mucosa. From an immunological standpoint, mucins are anionically charged allowing localization and concentration of cationic Paneth cell antimicrobial peptides and secretory IgA (sIgA) at the epithelial cell surface to limit bacterial interaction with the underlying epithelium [30]. The colon contains two distinct layers of mucus, while the layers appear to be indistinguishable in the small intestine [33]. The mucous layer functions as a dynamic protective barrier. Studies demonstrating altered goblet cell responses in germ-free animals and enhanced mucus secretion with infection support active changes in mucin production during inflammatory states [34]. The mucus layer of the gastrointestinal epithelium represents the front line of innate host defense. Mucins also provide a nutrient source for endogenous bacteria. Certain commensal bacteria metabolize the mucin glycoprotein sugar structures, encouraging nonpathogenic bacteria to grow in close proximity to the host and physically limit colonization of that micro-niche by opportunistic pathogens. Mucin-2 (MUC2) is the most abundant mucin in the intestine [32]. Animal knockout experiments demonstrate that loss of MUC2 produces severe spontaneous colitis that can be lethal upon bacterial challenge [35].

The third type of intestinal cell is the enteroendocrine cell, a specialized endocrine cell located most commonly in the proximal gastrointestinal tract within the stomach, duodenum, and pancreas. This cell population secretes hormones in response to peptide or hormone stimuli that act as local or systemic messengers, or activate the enteric nervous system. The enteroendocrine cells release gastrin, cholecystokinin, and vasoactive intestinal peptide as well as other hormones that respectively stimulate secretion of gastric acid, pancreatic digestive enzymes, and secretion of water and electrolytes. These secretions present a caustic environment for many bacteria due to their respective acidic and basic natures and the sheer volume of secretions (over 7 L a day). Further, these secretions assist in digestion and promote gastric and intestinal motility combining to flush and move products through the gastrointestinal tract, preventing stasis and overgrowth. These cells also exhibit relatively rapid turnover with a life span of 3–5 days.

An essential component of the non-immunological defenses of the gastrointestinal tract is the commensal bacterial flora. These bacteria reside in symbiosis with the host within the gastrointestinal tract with the capability of modulating the host response while providing colonization resistance against pathogens. In the healthy gastrointestinal tract, anaerobic bacteria including Firmicutes and Bacteroidetes phyla predominate [36–39]. Their presence hinders proliferation of pathogenic bacteria by direct competition for nutrients and space along the mucosa. Interestingly, stresses that alter the microbiome, affect the composition of the bacterial flora, but not necessarily the total number of bacteria present, signifying the shift as pathogenic, not necessarily overgrowth [40, 41]. Novel research suggests a specific maintenance of mucosal health by commensal bacteria. For example, within the Bacteroidetes phylum, Bacteroidales ferment fiber to short-chain fatty acids and release polysaccharides shown to enhance colonic health and exert immunomodulatory functions important in mucosal homeostasis.

Immunological Gastrointestinal Protective Mechanisms

The Innate Immune System

The fourth cell line produced from intestinal stem cells consists of Paneth cells, which serve as the primary effectors of the gastrointestinal innate immune system. While enterocytes, goblet cells, and enteroendocrine cells provide physical defensive mechanisms against pathogen invasion, Paneth cells produce bactericidal, antimicrobial products important to innate immunity [42, 43]. The innate immune system is a teleologically ancient branch of the immune system that is conserved across a broad range of species, signifying its fundamental importance in host defense against pathogens. The innate immune system works in concert with non-immunological barriers to exert locoregional control against pathogen invasion.

Unlike the other three epithelial cell lines which migrate out of the crypts of Lieberkuhn and onto the intestinal villi before sloughing off and replacement within 3–5 days, Paneth cells migrate to the base of the crypts of Lieberkuhn surviving 30 days or longer [42]. They produce, store, and release cationic antimicrobial proteins and peptides ($sPLA_2$, α-defensins, lysozymes, RegIII-ϒ, and other glycoproteins) [37, 39, 43–45]. Some of these antimicrobial peptides/proteins are stored in acidophilic intracellular granules located at the cell's apical surface while others are cytosolic. The intracellular granule membrane fuses with the apical surface membrane of the Paneth cell prior to release of the antimicrobial peptides into the mucous layer coating the epithelium. Once released, the cationic antimicrobial peptides remain concentrated within the anionic mucous layer and exert their bactericidal properties through bacterial cell membrane binding and direct opsonization.

Antimicrobial peptide binding to bacteria is nonspecific, i.e., the antimicrobial peptide is not generated specifically for one type of bacteria. Instead, many of the antimicrobial peptides are constitutively produced, while other are induced during times of stress such as infection and inflammation. Antimicrobial peptides exhibit more than mere bactericidal properties. Current research demonstrates increased interplay between these constitutive antimicrobial peptides, the composition of the host microbiome, and direct and indirect effects on an array of immune-modulatory properties [43, 46]. Paneth cells themselves also directly affect pathogens as they phagocytize bacteria and protozoa and either directly, or indirectly regulate intestinal flora through their antimicrobial peptides [47].

While the non-immunological barriers and innate immunity function to prevent the vast majority of bacterial invasion of the gastrointestinal tract, circulating innate immune cells such as neutrophils and macrophage cell lines form a secondary innate antimicrobial arsenal, should the mucosal barrier be breached by pathogens. However, the mucosal immune system developed a more sophisticated method to prevent bacterial invasion through adaptive (acquired) immunity.

The Adaptive (Acquired) Immune System

Beyond the physical and chemical barriers described above, the body possesses a more advanced network of mucosal immunologic protection through the adaptive immune system, otherwise referred to simply as the mucosal immune system. This system functions to prevent invasion of the gastrointestinal mucosa by *specific* pathogens. The mucosal immune system resides primarily within the LP of the gastrointestinal tract and compromises 60–70 % of the total immunity of the body, including that which resides in the upper and lower respiratory tracts, urogenital tract, mammary gland, and salivary glands [48]. In toto these constitute the mucosa-associated lymphoid tissue (MALT), which protects the body's 400 m^2 of epithelial surface exposed to bacteria. While methods for broadly excluding pathogens have been discussed, one must appreciate that the host requires a system to access and sample antigens from the bacteria at these mucosal surfaces in order to induce a specific immune response directed against specific pathogens.

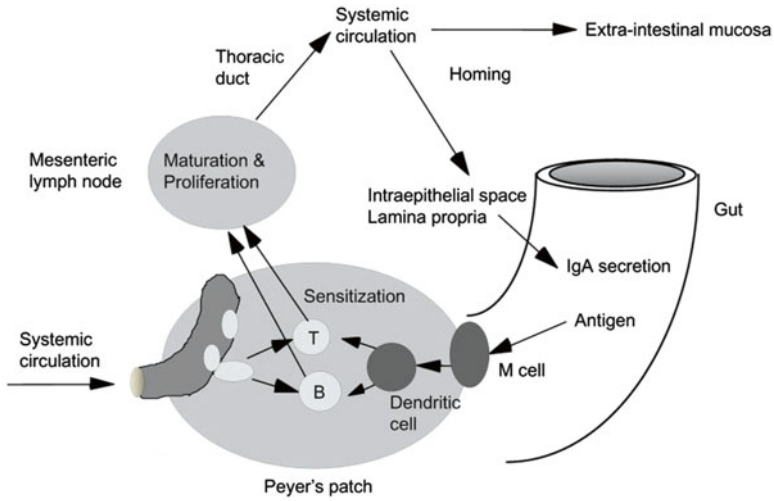


Fig. 2.3 Gut associated lymphoid tissue (GALT) and systemic mucosal immunity. GALT is a center of systemic mucosal immunity. Naïve lymphocytes are sensitized at Peyer's patches, migrate to mesenteric lymph nodes, enter the systemic circulation via the thoracic duct, and home to mucosal sites. Reprinted from Surgical Clinics of North America, 91/4, Fukatsu K, Kudsk KA, Nutrition and gut immunity, 755–70, vii, Copyright 2011, with permission from Elsevier

Mechanistically, the mucosal immune system is composed of inductive and effector sites. While overlap does exist, for the purposes of this review we consider them to be distinct, with Peyer's patches (PP) representing the main inductive site and the LP representing the effector site [49]. We focus on the structure and function of the gastrointestinal-associated lymphoid tissue (GALT) as a representation of the greater MALT established across all mucosal surfaces via the common mucosal immune hypothesis (Fig. 2.3).

While direct proof of the common mucosal immune hypothesis is still limited, experimental and clinical studies highlight interdependency between intestinal and extraintestinal mucosal sites. The common mucosal immune hypothesis postulates that cells sensitized within one local mucosal site can be distributed to distant mucosal sites providing antigen specific immunity across mucosal sites distant form the site of inoculation [50]. The most well-studied example in favor of the common mucosal immune hypothesis demonstrates that cells sensitized to antigens within the PP of the small intestine are subsequently distributed to submucosal locations in both intestinal and extra intestinal sites such as the upper and lower respiratory tracts and the mammary gland of lactating females [51]. A supporting study found that cells from the GALT of immunized animals populated secretory tissues of non-immunized recipients with IgA-secreting cells. Additional research demonstrated that these sIgA antibodies produced in different glands display comparable molecular properties suggesting common clonal origins.

Human vaccination studies also support this hypothesis as humans react with a sIgA immune response in mucosal secretions after oral but not parenteral immunization [52]. To further validate that this hypothesis was applicable in humans, Czerkinsky et al. showed that following antigen ingestion, peripheral blood contains antigen specific precursors of IgA plasma cells prior to the appearance of sIgA antibodies in external secretions, providing more evidence of communication between mucosal sites [53]. The major site of exposure and induction of the immune response though, consistently appears to be the GALT.

The GALT consists of an intricately layered system with discretely organized lymphoid structures, namely PP and isolated lymphoid follicles, which are surrounded by mucosal epithelium and the LP. These lymphoid structures, including PP, are composed of specialized follicle-associated epithelium

(FAE), which is uniquely structured for antigen and microorganism sampling and processing and subsequent activation of the mucosal immune system [54, 55]. Under normal circumstances, approximately 80 % of circulating lymphocytes are destined for the mucosal immune system in humans and mice [56]. These lymphocytes can be identified by expression of two integrins on the lymphocyte surfaces: L-selectin and α4β7. Naïve T and B cells expressing both integrins (but L-selectin to a greater degree) adhere to a mucosal addressin adhesion molecule-1 (MAdCAM-1), a molecule constitutively expressed on the high endothelial venules of the PP in the small intestine [57]. MAdCAM-1 at this site is *modified* with a specific carbohydrate which is especially attractive to L-selectin [58]. After attachment of the naïve T and B cells to MAdCAM-1, the chemokines CCL-19 and CCL-21 for T cells and CXCL-13 for B cells stimulate diapedesis and entry of these cells into the PP [59]. This process is discussed in more detail later. Once the naïve lymphocytes enter the PP, they interact with and become sensitized to gastrointestinal antigens that have been absorbed from the intestinal lumen and processed within the PP by a fixed population of dendritic cells [60]. After this time, $\alpha_4\beta_7$ becomes the predominant integrin expressed on the sensitized T and B cells.

The FAE is subdivided into two layers: one for antigen exposure and the other for antigen processing. Antigen exposure occurs through unique microfold cells, or M cells of the FAE [61]. M cells are specialized cells located at the luminal outskirts of the FAE which readily encounter luminal antigens, including microorganisms. They play a key role in regulating access of antigens and microorganisms to the GALT. Specifically, M cells lack the thick mucin glycocalyx associated with absorptive enterocytes, which allows easier luminal access of gastrointestinal sampling [62]. Once in contact, M cells endocytose luminal antigens and transport them across the epithelium to underlying dendritic cells. Dendritic cells are antigen presenting cells which can process the antigen for presentation to the naïve lymphocytes where an immune response to the foreign antigen can be initiated through lymphocyte sensitization.

Dendritic cells may also directly sample luminal antigens and microorganisms; however, they are located beneath the FAE of the PP. Current theory suggests that dendritic cells gain access to luminal contents by extending dendrite projections between epithelial cells, disrupting their tight junctions, to directly internalize bacteria before retreating back to the submucosal layer. Once dendritic cells are isolated from the intestinal lumen and tight junctions have resealed, the dendritic cell then presents the antigen to naïve T cells. While there is evidence for this dynamic movement of dendritic cells in vitro, in vivo research is currently lacking and some authors have countered that internalization of antigen by dendritic cells only occurs following M cell-mediated transepithelial transport, questioning the role of direct luminal sampling by dendritic cells.

Following sensitization, lymphocytes migrate through the MLNs and into the thoracic duct to enter the systemic circulation. From the systemic circulation, these lymphocytes "home," or find their way back to the LP of the MALT, including the GALT, and interact with MAdCAM-1 [63]. This form of MAdCAM-1 differs slightly from that expressed on the high endothelial venules in that it lacks the specific carbohydrate molecule. That carbohydrate molecule expressed on the *modified* MAdCAM-1 in the PP is no longer present and *unmodified* MAdCAM-1 exhibits less affinity for L-selectin and greater affinity for integrin $\alpha_4\beta_7$ which is the predominant integrin expressed on sensitized lymphocytes. Hence, unsensitized cells are preferentially excluded from peripheral sites and preferentially attracted to PP. The LP is the major effector component of the GALT as the cells become antigen mature and are primed for antibacterial action here [64]. Once there, B lymphocytes mature into plasma cells capable of producing IgA for specific bacterial antigens which is the true effector arm of the adaptive immune system. Typically the number of B cells possessing cytoplasmic IgA consistent with B cell maturation to plasma cells is demonstrated by an increase from 2 % in PP to 50 % in MLNs, 75 % in the thoracic duct lymphatics, and approaching 100 % in the LP [65].

IgA is the most common immunoglobulin in the mammalian intestine. It is a dimeric protein produced by plasma cells located in the LP under cytokine regulation. Following production, dimeric IgA complexes with the protein, polymeric immunoglobulin receptor (pIgR), expressed on the basolateral surface

of enterocytes. This complex allows transportation of IgA across the mucosal epithelium to the intestinal lumen. pIgR represents the sole mechanism for IgA to move from the LP, through the epithelium, and onto the mucosal surfaces. Upon release of the pIgR–IgA complex into the goblet cell mucus of the intestinal lumen, a portion of pIgR remains attached to the IgA [66]. Known as the secretory component, it distinguishes sIgA originating within the MALT from IgA found within serum or tissue.

Once transported into the lumen, sIgA recognizes both specific and nonspecific antigens expressed on luminal bacteria. Following antigen recognition, sIgA binds to the antigen and prevents mucosal invasion by blocking pathogen adherence to the mucosal wall and promoting clearance from the intestinal tract [67]. Approximately 95 % of human pathogenic microorganisms can target host cells by evading innate defenses to invade mucosal tissue; the main protective defense against this invasion is through production of pathogen-specific local sIgA, which can only be achieved with activation of the mucosal immune system. Interestingly, the basolateral surface of the FAE expresses no pIgR receptors; this suggests that these epithelia are only part of the inductive arm of the immune system since they cannot secrete IgA [68, 69]. Also notable is that few goblet and Paneth cells are present in the FAE crypts and production of membrane-associated digestive hydrolases is significantly reduced over the FAE [70], again reinforcing their role as immune system inductors to provide efficient access to antigen sampling.

Primed T cells within the GALT produce cytokines that influence the production of IgA in a variety of ways. In general, the systemic anti-inflammatory Th2 type cytokines interleukin (IL)-4, -5, -6, -10, and -13 stimulate IgA production, while the systemic pro-inflammatory Th1 type cytokines IL-2, interferon ϒ (IFN-ϒ), and tumor necrosis factor α (TNF-α) *typically* inhibit IgA production in the small intestine; however, Th1 type cytokines increase pIgR expression [4, 71–73]. Th2 type cytokines stimulate IgA production both directly and indirectly. For example, IL-4 plays a critical role in the stimulation and maintenance of MAdCAM-1 expression in PP, which as discussed, allows cell entry into the GALT. These two molecules, IL-4 and MAdCAM-1, also stand intimately linked since their production requires signaling of lymphotoxin β (LTβ) through interaction with LTβ receptor (LTβR) expressed on the surface of activated T cells. This LTβ: LTβR interaction activates intracellular nuclear factor-κB (NFκB); yet another signaling pathway necessary for mucosal immune system development and IgA production. Further, IL-4 and IL-6 increase IgA production by stimulating maturation of plasma cells within the LP. IL-4 also increases expression of pIgR, as does IL-10 which simultaneously actively inhibits Th1 type cytokine IFN-ϒ. Conversely, IL-2 and IFN-ϒ actively inhibit production of IgA as well as IL-10. Non-T-cell derived cytokines also play a role in IgA production as epithelial cytokine transforming growth factor β (TGF-β) promotes class-switch recombination and the resultant antigen-specific IgA^+ B cells and IL-5 enables terminal differentiation of sIgA+ B cells. These categories of anti- or pro-inflammatory are not absolute, however, as IFN-ϒ and TNF-α increase pIgR as mentioned previously. In fact, several cytokines exhibit properties of both classes and actual events likely relate to complex cellular crosstalk and cytokine concentration gradients.

In its normal state, the gastrointestinal tract favors the production of Th2 type cytokines, thus promoting IgA production. Th2 type cytokines IL-4 and IL-10 also suppress the expression of intracellular adhesion molecule-1 (ICAM-1), a molecule expressed on both the vascular endothelium in general and on the high endothelial venules within the GALT. ICAM-1 plays an important role in attracting and sequestering neutrophils traversing the vessels within the LP to exert an increased inflammatory response (discussed in detail later). In contrast, IFN-ϒ stimulates ICAM-1 expression. This phenomenon imparts important effects on PMN priming and augmented inflammatory responses during PN.

Chemokines serve as chemotactic cytokines that control lymphatic migration of immune cells. Specifically within the GALT, chemokines stimulate diapedesis of immune cells into tissue through a concentration gradient and increase integrin cellular adhesion molecule binding avidity to induce changes in lymphocyte polarity (Table 2.1). Chemokines stimulate chemotaxis and diapedesis once

Table 2.1 Common immunologic chemokines, their function, and their tissue site of expression[a]

Tissue	Chemokine	Function
Peyer's Patches (PP)	CXCL-13	Regulates B-cell entry into PP
	CCL-19	Regulates T-cell entry into PP
	CCL-21	Regulates T-cell entry into PP
	CCL-25	Mucosal immune memory/ homing
Small intestine	CCL-20	Dendritic cell chemoattractant
	CCL-25	Recruits antibody-secreting cells
Lung	CCL-28	Recruits antibody-secreting cells

[a] From Hermsen JL, Gomez FE, Maeshima Y, Sano Y, Kang W, Kudsk K, Journal of Parenteral and Enteral Nutrition (32/9). Copyright © 2008 by the American Society for Parenteral and Enteral Nutrition. Adapted with permission of SAGE Publications

Table 2.2 Common stresses to the gastrointestinal immune system frequently seen with intensive care for critically ill and injured patients

Stresses to gastrointestinal immune system
Antibiotics
Vasoactive drugs
Acid blockade
Opioids (exogenous and endogenous)
Acidosis
Gut starvation/parenteral nutrition
Hypotension/hypoperfusion
Hypoalbuminemia/capillary leak

lymphocytes bind to MAdCAM-1. As mentioned, CCL-19 and CCL-21 stimulate T cell entry into PP, while CXCL-13 stimulates B cell entry. Also important for lymphocyte migration is CCL-25, which is responsible for mucosal immune memory and homing under normal homeostatic conditions. Chemokines can have direct antimicrobial properties (CCL-28) as well as play a significant role in routing the coordinated adaptive immune response [74]. For example, CCL-20 acts within the small intestine to bring dendritic cells (antigen presenting cells) to the lymph nodes for antigen processing while CCL-25 and CCL-28 act as plasma cell recruiters for antibody production. In areas of the MALT, such as the lung, different chemokines also play an active role. For example, within the lung CCL-28, in particular, recruits antibody-secreting cells, such as plasma cells for immune-specific respiratory defense.

Nutrition and Immunity

So how does nutrition affect the immune system other than providing a fuel for protein and immunoglobulin production? Clinically and experimentally, both malnutrition and route of nutrition—particularly lack of enteral stimulation by nutrients—negatively influence the mucosal immune system and its barrier function [12, 75–77]. In addition to these nutritional factors, the host's stress response

also can negatively impact the host susceptibility to pathogenic invasion and subsequent infection as critical illness disrupts the host/bacteria balance (Table 2.2). Hypotension with hypo-perfusion, acidosis, endogenous and exogenous opioids, antibiotic pressure, and a host of other physiologic and medical therapies including lack of enteral stimulation all negatively alter this balance [18]. The remainder of this chapter focuses on the mechanisms through with lack of enteral stimulation during PN adversely affects the mucosal immune system.

Institution of PN spread worldwide in the 1960s since it provided a practical means of providing nutrition to patients unable to be fed adequate nutrition via the gut due to feeding intolerance or medical contraindication to gastrointestinal feeding (intestinal obstruction, high-output fistulas, ileus, etc.) [78]. PN clinically allows gut rest while preventing progressive starvation. PN saved countless lives that would otherwise be lost due to complications of starvation and progressive, unrelenting starvation-related malnutrition. However, prospective clinical trials comparing route and type of nutrition demonstrate convincing differences in clinical outcome between EN and PN nutrition support when patients are capable of being fed enterally, with increased infection rates, particularly pneumonia, in patients receiving PN rather than EN [75, 79].

Experimentally, PN allows the study of the effect of route and type of enteral stimulation without development of the confounding variable of progressive starvation, which is ultimately fatal in mice within just a few days. PN also allows the dissection of the intricacies of the mucosal barrier and of the host/bacterial interactions many of which depend on the presence or absence of enteral nutrients and gut stimulation. It also allows investigation of whether PN feeding itself affects these relationships or whether simply the lack of enteral stimulation by nutrients induces these changes. Not surprisingly, changes occur within all components of the barrier—non-immunologic, innate immunity, and adaptive immunity—and across many organ systems including the gastrointestinal tract, the lung, and the upper respiratory tract [26, 80] (Table 2.3). In addition, the response to stress and injury can be markedly affected in these organs resulting in augmented inflammation [81, 82].

Effect of Lack of Enteral Nutrition on Non-immunologic Barriers

Multiple changes within the non-immunologic barrier occur as result of PN and lack of enteral stimulation. On the most basic level, gut morphology and cell counts demonstrate generalized mucosal atrophy with PN [83]. Experiments in piglets identified decreases in wet weight, villus height, and

Table 2.3 Effects on various components of mucosal immune system in the setting of parenteral nutrition compared to enteral nutrition

Effect of PN	
Microbiome size	No Δ
Firmicutes	↓
Bacteroidetes	↓
Proteobacteria	↓
Goblet cell number	No Δ
MUC-2	↓
Paneth cell number	No Δ
$sPLA_2$	↓
Lysozyme	↓
GALT size	↓

(continued)

Table 2.3 (continued)

Effect of PN	
Peyer's patches cellularity	↓
T:B cells	No Δ
CD4+:CD8+	No Δ
LTβR	↓
MAdCAM-1	↓
MLN cellularity	No Δ
MAdCAM-1	No Δ
Lamina Propria cellularity	↓
CD4+ cells	↓
pIgR	↓
sIgA	↓
Lung	
T cells	↓
B cells	↓
pIgR	↓
sIgA	↓
Cytokines	
IL-4	↓
IL-5	No Δ
IL-6	No Δ
IL-10	↓
IFN-ϒ	No Δ
Chemokines	
CXCL13 (Peyer's patches)	↓
CCL21 (Peyer's patches)	↓
CCL20 (small intestine)	↓
CCL25 (small intestine)	↓
CCL28 (small intestine)	↓
CCL28 (lung)	↓
Functional	
Survival after viral challenge	↓
Survival after bacterial challenge	↓
Inflammatory markers	
MPO	↓
ICAM-1	↓
P-selectin (gut)	↓
E-selectin (lung)	↓

Δ means change

villus area of small intestinal segments in PN-fed animals as well as diminished total protein and DNA content from those samples [84]. Further significant reductions in number intraepithelial lymphocytes occurred with PN, even when cell counts are corrected for villus size differences between PN and EN-fed animals. Interestingly, no differences in crypt depth or the number of goblet cells per villus has been noted.

PN also affects the intestinal mucous layer [85]. While the numbers of goblet cells per villus remain stable with PN, the amount of mucin, specifically MUC2, produced and secreted by goblet cells decreases significantly with PN. Consequently the mucus layer becomes significantly thinner in PN-fed animals compared to EN-fed animals, reducing the physical separation between the gastrointestinal epithelium and bacterial load of the gut lumen.

In addition to the increased proximity between gastrointestinal mucosa and luminal bacteria, Teitelbaum et al. also showed significant alterations in epithelial barrier function with PN [86]. Accordingly, substantial decreases develop in expression and number of tight junction molecules including occluden, multiple claudins, ZO-1, JAM-1, and E-cadherin. They also observed occluden internalization or endocytosis with PN, a phenomenon also seen during clinical disease processes associated with loss of epithelial barrier function such as inflammatory bowel disease [87–89]. While evidence points to increases in intestinal permeability to bacteria as a result of decreased epithelial barrier function, increases in bacterial translocation are not seen.

Clinical studies confirm the intestinal morphological and functional changes associated with PN in humans as well [90]. In a study of healthy volunteers exclusively fed PN, Buchman et al. found decreases in total mucosal thickness related to villus height and not crypt depth, consistent with findings in animal models. Further villus cell counts are decreased with PN while crypt cell counts remain stable. PN is also associated with increased intestinal permeability in humans. These PN-induced morphologic and functional changes progress back toward normal with reinitiating EN.

In addition to altering gastrointestinal morphology, PN results in changes in the gastrointestinal microbiome [40, 41] (Fig. 2.4). At the phylum level, PN decreases total Firmicutes but increases total Bacteroidetes and Proteobacteria when compared to EN feeding. Interestingly, total bacterial load does not change, but rather changes occur in microbiome composition. The concept of quorum sensing therefore becomes increasingly important in determining which bacteria will survive to compete for limited nutrients. These population shifts in the gastrointestinal microbiome further reinforce the microbiome as a dynamic entity that responds to changes in diet and health.

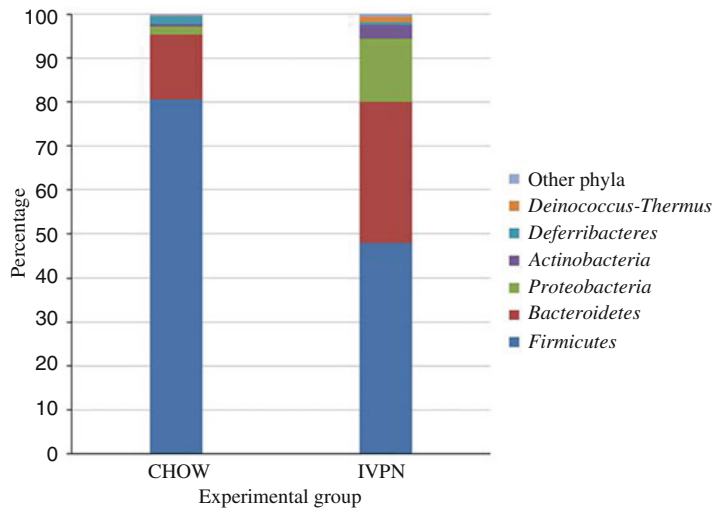


Fig. 2.4 Pyrosequencing analysis of ileal wash samples with enteral nutrition (chow) or parenteral nutrition (IVPN). From Heneghan AF, Pierre JF, Tandee K, Shanmuganayagam D, Wang X, Reed JD, et al., Journal of Parenteral and Enteral Nutrition. Copyright © 2013 by the American Society for Parenteral and Enteral Nutrition. Reprinted by Permission of SAGE Publications

Effect of Lack of Enteral Nutrition on Immunologic Barriers

Innate Immunity

The effects of route and type of nutrition on innate immunity have just recently been explored experimentally. As mentioned, Paneth cells are the primary effectors of the gastrointestinal innate immune system and produce, store, and release a variety of antimicrobial peptides. The study of immunologic effects with decreased enteral stimulation began with examination of these Paneth cell products.

Paneth cell peptide, $sPLA_2$, is the first of these peptides to undergo testing in a nutrition model [45]. In this study, PN, representing decreased enteral stimulation, and EN served as independent variables for the gastrointestinal production of $sPLA_2$ in mice, the dependent immunological variable. Mice experienced significant declines in $sPLA_2$ activity in small intestinal washings following PN compared to EN. However, tissue levels of $sPLA_2$ in both the jejunum and ileum remained unchanged by route of feeding implicating a decrease in $sPLA_2$ production, secretion, or both with PN. Specific study of the bactericidal capability of intestinal $sPLA_2$ obtained after PN established a lower bactericidal activity in the specimens than those obtained from EN-fed mice despite equivalent sPLA2 peptide concentrations.

Given altered $sPLA_2$ expression and effectiveness with PN, subsequent work examined other Paneth cell antimicrobial peptides as well as examination of the functional effects of PN on innate immunity. In quantitative studies of Paneth cell antimicrobial products, PN caused significant decreases in expression of $sPLA_2$, lysozyme, RegIII-ϒ, and cryptidin-4 (the most abundant murine α-defensin) compared to EN [40]. In addition the bactericidal activity against *Pseudomonas aeruginosa* (*P. aeruginosa*) was significantly lower in culture media obtained from intestinal segments of PN-fed animals compared to EN feeding. However, this work required cholinergic stimulation of the specimens for antimicrobial peptide release, demonstrating that autonomic stimulation plays a role in the release of the antimicrobial products from the Paneth cells. In further tests designed to test intestinal segment barrier function against mucosal invasion, PN increased susceptibility of isolated intestinal segments to bacterial enteroinvasion by a pathogenic strain of *Escherichia coli* [40, 91].

Adaptive Immunity

Alterations to the adaptive immune system occur during PN with lack of EN stimulation. Changes occur in both the inductive and effector branches of the adaptive immune system.

Inductive Site Changes with PN and Lack of Enteral Stimulation

The size of PP decreases during PN due to decreases in cellularity [92]. Microscopically, this finding relates to reductions in total numbers of T and B cells within the PP; however, the T to B cell ratio remains stable at 1:2. The ratio of CD4:CD8 positive T cells remains unchanged at 4:1 with PN as well. Experimentally, naïve T and B lymphocytes reductions in PP relates to changes in cell entry into the PP with decreased distribution to distal sites including the LP and lungs. Lymphocyte attachment to PP vascular endothelium depends upon adhesion between MAdCAM-1 and lymphocyte L-selectin and α4β7. During PN, expression of the constitutively expressed MAdCAM-1 drops significantly with decreases observed within 8 h of initiating PN and reaching a statistically significant decrease by 24 h [93]. Levels remain low as long as PN continues. MAdCAM-1 levels also decrease with 12 h of fasting demonstrating that the effect relates to decreased enteral stimulation and not to a component of PN [94].

Administration of an antibody to chow fed mice that blocks MAdCAM-1 reproduces the same decrease in PP lymphocyte cellularity, and provides convincing evidence of the role of MAdCAM-1 in cell entry [95]. These changes in lymphocyte mass appear uniquely linked to route of nutrition, particularly as lymphocyte mass in PN treated animals returns to normal with 3 days of oral nutrition while MAdCAM-1 levels return to normal within 24 h. Interestingly, decreases in MAdCAM-1 expression occur only in the PP: MAdCAM-1 levels in the remaining small intestine and the MLNs remain unaffected with PN.

A reduction in LTβR expression initiates this decrease in MAdCAM-1 levels. Experimentally, lack of enteral stimulation during PN significantly reduces expression of LTβR on naïve T cells resulting in lower levels of NFκB, IL-4 and MAdCAM-1 [96]. Investigators established direct relationships between these variables experimentally by stimulating LTβR with a specific monoclonal antibody during PN resulting in PP lymphocyte cell counts and small intestinal sIgA levels returning to normal. Administration of a specific monoclonal antibody which blocked activity of LTβR during chow feeding resulted in reduction of NFκB, IL-4, and MAdCAM-1 to PN levels [97].

Once T and B cells attach to MAdCAM-1, diapedesis depends on CCL-19 and CCL-21 for migration of T cells and CXCL-13 for B cells. With PN, PP CCL-21 protein significantly increases while CXCL-13 protein significantly decreases [98]. The increase in CCL-21 protein in the setting of decreased T lymphocytes in PP is unexpected, and authors suggested that this increase may be temporally late or a delayed attempt by PP to compensate for its decreased lymphocyte mass associated with PN. Interestingly, PP chemokine CCL-21 can be pro-inflammatory in nature, which may play a role in this observation.

Decreased T and B lymphocyte mass in PP may suppress the adaptive immune system, but alternations in antigen sampling also occurs resulting in lack of appropriate immune signaling. PN decreases M-cell mediated antigen uptake in rabbits despite no differences in M-cell structure by electron microscopy to explain this decrease [61]. It remains unclear if the changes relate to a defect in the M-cells or alterations in the availability or accessibility of luminal antigen for uptake during PN. PN induced significant decreases in small intestinal CCL-20, a chemokine, which normally attracts dendritic cells to the lymph nodes for antigen processing, further suggesting that alterations in antigen presentation plays a role in deficient immune responses seen with PN [98].

While there appear to be profound effects on lymphocyte populations in PP with PN, relatively few changes occur in MLNs during PN. Size of the MLNs and number of T and B lymphocytes within these structures appear unaffected by PN. However, rat studies examining bacterial translocation to the MLNs did demonstrate a significantly increased bacterial presence during PN particularly following injury [5, 99, 100]. This finding has not been established to be clinically relevant to the development of infectious complications.

Effector Site Changes with PN and Lack of Enteral Stimulation

PN and lack of enteral stimulation substantially alter the effector side of the adaptive immunity. Since T and B cell reductions occur in PP with PN, there are resulting decreases in distribution of activated lymphocytes to the MALT. The LP serves as the main effector site of the adaptive immune system. PN decreases the absolute number of T and B cell lymphocytes within the LP while changing the ratio of CD4:CD8 positive cells from 2:1 to 1:1 due to a drop in $CD4^+$ cells [92]. $CD4^+$ lymphocytes preferentially produce Th2 type cytokines which drive production of pIgR and sIgA as discussed previously, and the lowered levels of $CD4^+$ lymphocytes with PN result in lower levels of IL-4, IL-10, pIgR, and sIgA during PN [101]. These cytokines are typically anti-inflammatory under normal conditions, hence their decrease favors an inflammatory state. Chemokines CCL-25 and CCL-28, which are plasma cell recruiters within the small intestine, also decrease with PN. This result is consistent with

decreased B cell populations and decreased IgA production in the small intestine of PN fed animals. Experimentally this sIgA drop occurs gradually over 3 days after initiating PN, consistent with the earlier decline in expression of PP MAdCAM-1 and the related decreases in PP and LP lymphocytes. Lack of enteral stimulation reduces levels of pIgR protein, resulting in effects on the transport mechanisms of IgA secretion [102].

Okamoto et al. observed that experimental reductions in T cell populations with PN-fed mice also occur in PN-fed humans [103, 104]. In an examination of terminal ileum specimens from 62 patients undergoing right colectomy for colon cancer, they found that T cell numbers in both the intraepithelial space and LP and the number of IgA-producing cells in the LP were significantly reduced in 15 non-randomized patients receiving PN exclusively in the preoperative 4–50 days compared to patients receiving some enteral nutrition. This occurred despite no differences in baseline nutritional variables including body mass index, serum proteins, and serum albumin. They found no differences in total numbers of mature and immature dendritic cells in the LP; however, the number of mature dendritic cells was reduced in the PN group. Postoperative infection rates in PN patients were triple that of EN-fed patients but there were no significant differences in noninfectious complication rates between the two groups. These findings confirm that PN is associated with GALT cell loss in humans as it is in mice and supports the notion of associations between infectious morbidity, mucosal immune status, and route of nutrition.

Simultaneous decreases in lung T and B cell populations occur with PN in mice, resulting in 15 % fewer T cells and 50 % fewer B cells compared with EN-fed mice [105]. Decreases in pulmonary lymphocyte mass may be the result of a diminished pool of activated T and B cells released from the GALT; however, pulmonary chemokine reduction with PN also plays a role [98, 105]. CCL-28 within the lung is a strong attractant for mucosal antibody producing cells (B cells), and it is significantly reduced in PN-fed mice. Together, decreased lymphocyte mass and altered signaling provide at least a partial explanation for IgA production dependent impairments in respiratory immunity as there are fewer cells physically available for immunoglobulin production [106].

PN also affects protein expression in other MALT tissues but in varied manners. For instance, PN decreases pIgR expression in the small intestine but increases its expression in the lung [107]. Interestingly, despite the differential expression of IgA transporters in these tissues, sIgA secretion remains decreased with PN in both the small intestine and lung [108] (Fig. 2.5). PN also increases chemoattractant adhesion molecules such as P selectin in the small intestine and E selectin in the lung, which will come into play when we discuss inflammatory aberrations associated with PN [109].

Functional Effects of PN-Induced Changes in Adaptive Immunity

While the cellular and chemical properties altered as a result of PN in lieu of EN are interesting, the core clinical concern rests in whether these changes affect immunologic function. To this end, specific experiments address this very question.

Clinically, viral and bacterial pulmonary infections account for over 50,000 deaths annually in the USA [110]. Nosocomial pneumonia is the most common infection in intensive care unit patients, and its incidence in critically ill and injured patients is affected by route and type of nutrition [111, 112]. Clinically, EN reduces septic morbidity, especially from pneumonia, in severely injured trauma patients by 60–70 %, an observation confirmed in both individual randomized trials and published meta-analysis [112–114]. Further, lack of EN is linked to deterioration of intestinal and respiratory mucosal immune defenses which has experimentally been investigated in murine models.

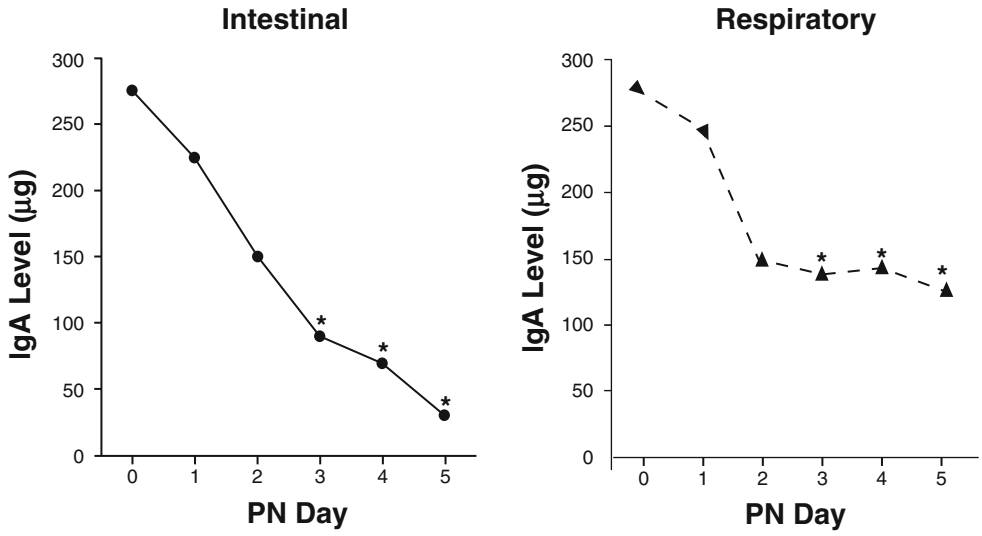


Fig. 2.5 The kinetics of IgA levels in the intestine and respiratory tract after parenteral nutrition (*PN*) with lack of enteral feeding. PN significantly decreased intestinal and respiratory IgA levels by day 3; *p <0.05 vs. day 0. From Kang W, Kudsk K, Journal of Parenteral and Enteral Nutrition (31/3). Copyright © 2007 by the American Society for Parenteral and Enteral Nutrition. Reprinted with Permission of SAGE Publications

The initial experiment examining respiratory tract immunity during PN studied IgA-mediated viral immunity in a murine model with four established diets [115]. Mice underwent intranasal inoculation with a mouse-specific H1N1 influenza virus to establish immunity. Three weeks later, mice were randomized to receive experimental diets of chow, a complex enteral diet delivered by gastric tube, intragastrically delivered PN, or standard IV delivered PN. Following 5 days of experimental diet, the mice were challenged with intranasal virus prior to sacrifice 40 h later to examine viral shedding within the upper respiratory tract. Results demonstrated a significant relationship between upper respiratory viral immunity and route of nutrition. Animals feed via the gastrointestinal tract (chow, complex enteral diet, or intragastric PN) demonstrated no virus present in the upper airways, whereas 50 % of animals fed IV–PN continued to shed live virus. Follow-up work demonstrated no relationship between serum influenza-specific IgG titers and the degree of viral shedding, but loss of respiratory immunity stemmed from a decrease in sIgA levels, related to a reduction in IgA-producing antibody-forming cells in nasal secretions of PN-fed animals [116, 117]. Further, refeeding PN animals with EN for 5 days restored nasal immunity with prompt elimination of the virus. These studies established that EN maintains established IgA-mediated antiviral respiratory immunity otherwise lost with PN [118].

While viruses are increasingly recognized as pathogens in critically ill patients, most pneumonias are bacterial rather than viral in origin, affecting the lower rather than the upper respiratory tract. Subsequent experiments examined the effects of route and type of nutrition on established IgA-mediated respiratory immunity against *P. aeruginosa* in a model of bacterial pneumonia [119]. Twelve days after intranasal immunization with *P. aeruginosa*, mice were again randomized to four experimental diets. After 5 days of experimental feeding, mice received a nearly lethal (LD90-lethal for 90 % of animals) intratracheal dose of *P. aeruginosa*. Non-immune chow-fed mice served as controls. IV-PN completely destroyed established antibacterial immunity resulting in mortality rates comparable to unimmunized mice. The immunity of animals fed chow or a complex liquid diet maintained normal immunity and a high survival rate. Intragastric PN partially maintained the immune response.

In summary, both route and type of nutrition influence the integrity of established respiratory mucosal immunity. Memory, however, remains intact despite susceptibility to infection with PN, as reinstitution of EN restores viral immunity. Further, these shifts in immunity correlate with gastrointestinal and respiratory sIgA levels: decreased immune protection occurs with decreased sIgA production. These findings are consistent with clinical results [120–122].

Nutrition, Local and Systemic Inflammation

Route and type of nutrition affect the body's inflammatory response to stress, sometimes by down-regulating the natural inflammatory response and at other times upregulating it. Both responses may clinically advantageous or detrimental. The mechanisms of these effects are being investigated and defined through both experimental and clinical studies.

Route of Nutrition and Local Organ Inflammation

The ability to mount a mucosal sIgA response appears to be a conditioned response to injury—presumably an acute response to control bacterial adherence and reduce infection. The first observation of this response occurred in a clinical trial of 12 severely injured trauma patients where sIgA levels were quantified in bronchoalveolar lavage (BAL) specimens obtained during the first 24–48 h after injury [123]. Compared to control BAL specimens obtained from healthy patients undergoing elective surgery, severely injured intubated patients significantly increased the amount of epithelial lining fluid (ELF) and the sIgA concentration in the ELF denoting significant increases in airway sIgA in response to injury. Subsequent work confirmed a similar response in mice following injury [123]. Analysis of cytokine levels in the alveolar fluid and serum of the mice and humans showed very similar responses.

This airway sIgA increase following injury represented a previously unrecognized mucosal acquired immune respiratory response present clinically in humans that presumably delineated a protective response. Since it was reproducible in mice, subsequent experiments characterized the effects of route of nutrition on this post-injury respiratory sIgA response. BAL sIgA levels significantly increase following injury after EN but not PN [124]. The normal response to injury appears to be cytokine driven since TNF-α blockade (and for the most part IL-1β blockade) eliminates the airway sIgA response to injury in mice [125]. The mechanism associated with this PN-induced immune depression may be due to alterations in pIgR since both TNF-α and IL-1β stimulate pIgR production [108]. Clinical implications of impaired lung sIgA responses with PN remain unknown, but the alterations by diet may be involved in the increased incidence of pneumonia with PN feeding.

Similar events occur within the gastrointestinal tract [82]. Consistent with airway response, intestinal IgA levels increase shortly after surgical injury. PN completely eliminates this response while enteral feeding preserves it. Similarly, pIgR expression in the small intestine increases following injury in EN-fed animals but does not increase following injury in those fed PN. Interestingly the local cytokine response of the gastrointestinal tract differed from that of the lung. Neither TNF-α nor IL-1β locally increased in the small intestine with injury, and blockade of TNF-α or IL-1β with monoclonal antibodies failed to prevent the rise in gastrointestinal sIgA following injury, contrary to the effects seen in the lung. Curiously, only IL-6 increased in the small intestine following injury. However, a cytokine cocktail of TNF-α, IL-1β, and IL-6, but not just two of them alone, generated the same increase in intestinal sIgA that occurred with injury. These findings suggest that while the lung and gastrointestinal tract do share many overlapping features in the response of mucosal immunity to injury, their underlying stimulatory mechanisms appear under different mechanisms of control.

Route of Nutrition and Systemic Inflammation

Route of nutrition plays a significant role in activation of systemic inflammatory responses. For example, PN alters expression of multiple endothelial cellular adhesion molecules in multiple organs when compared to EN. IL-4 and IL-10 normally inhibit expression of ICAM-1 expression on vascular endothelium, while IFN-ϒ promotes ICAM-1 expression. As PN lowers LP levels of IL-4 and IL-10 with no change in IFN-ϒ, the cytokine changes shift the endothelial milieu toward greater ICAM-1 expression [101, 126]. ICAM-1 is the ligand counterpart of β2 integrins (CD11a/CD18 and CD11b/CD18) on polymorphonuclear neutrophils (PMNs), the major cellular component of the nonspecific immune response in host resistance to infection. Tissue activation of PMNs is closely regulated through specific mechanisms for adhesion, stimulation, and migration through endothelial cells in acute inflammation. While aimed at fighting infection, this acute inflammation contributes to tissue injury through the release of reactive oxygen species. Derangement of PMN-endothelium interaction and PMN accumulation can increase susceptibility to bacterial infection and PMN mediated tissue injury. Experimentally, increased intestinal ICAM-1 expression with PN results in greater intestinal myeloperoxidase (MPO) activity, indicating PMN accumulation [127]. ICAM-1 also increases in both the lung and kidney tissue during PN although MPO remains normal in these tissues as well as the liver. Both ICAM-1 and MPO levels return to normal in intestinal tissue soon after reinstitution of EN.

In vitro, sIgA reduces PMN chemotaxis and blunts the release of proinflammatory cytokines. As described above, PN clinically and experimentally reduces IgA responses to injury, providing a cogent explanation for increased infections in PN fed patients. Lack of IgA-driven inhibition of PMNs may also contribute to increased systemic inflammation following PN with injury. The harmful and destructive results of an unregulated inflammatory response are best exemplified in cases of multiple organ dysfunction syndrome (MODS) which frequently complicate the clinical course of critically ill and injured patients and have been shown to increase in incidence in PN-fed patients [128].

MODS encompasses an uncontrolled systemic inflammatory response, which is frequently associated with injury, infection, increased metabolism, and hypoperfusion resulting in ischemia with reperfusion (I/R) injury. The gut is particularly vulnerable to hypoperfusion following injury because of disproportionate splanchnic vasoconstriction in response to stress. Further, studies show unrecognized flow-dependent oxygen consumption in the gastrointestinal tract may produce ongoing mesenteric ischemia in patients thought to be adequately resuscitated by standard measures [129]. While initial studies blamed uncontrollable infection for MODS, definitive foci of infection have not been identified in many patients and the concept of the systemic inflammatory response syndrome has become a popular explanation for delayed organ injury following initial stress. Experiments by Moore et al. strongly support the "two-hit" hypothesis whereby sequential sublethal events are responsible for MODS as opposed to a single event [130]. This model is characterized by an initial localized event which serves as a priming mechanism for an augmented inflammatory response triggered by a second event.

In support of this concept, Moore et al. studied intestinal I/R as a "first hit" priming event for PMNs in a rodent model [131]. They showed that the gut serves as a priming bed for circulating PMNs in response to superior mesenteric artery (SMA) occlusion followed by resuscitation. By measuring superoxide generation by PMNs following I/R in the SMA (mesenteric inflow) and portal vein (mesenteric outflow), they confirmed that PMN priming occurs in the reperfused gut preceding systemic priming. This result implicated the gut as a priming bed for circulating PMNs following I/R. They subsequently studied effects of sequential insults involving SMA I/R followed by low dose endotoxin to evaluate systemic effects, particularly lung injury as it is frequently involved in MODS [131]. The dose of endotoxin used independently produced no systemic effects. Using MPO activity to determine pulmonary PMN sequestration and ^{125}I albumin to evaluate pulmonary capillary leak, they found that gut I/R alone did not promote PMN sequestration to the lung or cause pulmonary

capillary leak; however, gut I/R followed by low dose endotoxin increased both pulmonary sequestration and pulmonary capillary leak. Further, the sequential insult resulted in a 40 % rodent mortality with no mortality with I/R or endotoxin alone. Of note, low dose endotoxin did independently increase pulmonary PMN sequestration but without significant effects on pulmonary capillary leak or animal mortality unless combined with gut I/R. These results support their hypothesis that a first insult primes leukocytes, likely through gut I/R secondary to hypoperfusion, and a second insult activates the "primed" leukocytes to an augmented inflammatory response which injures the vascular endothelium of multiple organs resulting in MODS [132–134].

Preliminary work with nutritional models showed that PN increased PMN accumulation in the small intestine. This finding prompted investigation of intestinal expression of endothelial adhesion molecules in the gut vasculature and their role in PMN priming. Experiments established that expression of ICAM-1 (an adhesion molecule primarily responsible for PMN adherence to the endothelium) increased in the gut vasculature during PN resulting in accumulation of PMNs in the intestinal vasculature. These changes were isolated to the gut with no changes occurring within the lung ICAM-1 or other tissues [146]. ICAM-1 expression is normally suppressed in the intestine by endogenous levels of IL-4 and IL-10, two IgA-stimulating Th2 cytokines, but promoted by IFN-ϒ. Usually a balance exists between these cytokines but this balance appears to be disrupted with PN which suppresses IL-4 and IL-10 levels in the gut but leave IFN-ϒ levels unchanged. Therefore we attributed the ICAM-1 increase to lower IL-4 and IL-10 levels in the LP and an unbalance between the Th2 cytokines and the IFN-ϒ levels. Fukatsu et al. examined whether these PN-induced changes in ICAM-1 and PMN levels themselves constituted a "first hit" that would lead to augmented inflammation throughout the body in a manner similar to the Moore studies with hemorrhagic shock, i.e., did the small intestinal PMN accumulation "prime" the PMNs [135]. In a series of experiments employing a 15 min occlusion of the SMA to produce gut I/R injury raised mortality after PN but not EN. Studies examining CD11b and CD18 expression confirmed that the leukocyte/gut endothelial interaction with PN had primed the PMNs to the subsequent gut I/R injury [152]. While CD11b, a marker of neutrophil activation, was similar in PN and EN fed animals *prior* to ischemic insult, increased CD11b levels after the ischemic event occurred only in the PN group confirming and augmented inflammation response in the PMNs.. This was particularly evident within the lungs of PN mice where expression of CD18, the final component of β-integrins and another marker of myeloid cell activation, markedly increased in lung tissue after gut I/R. There was no evidence of augmented inflammation in EN fed mice. Simultaneously, gut I/R increased vascular permeability within the lungs and livers of the PN animals.

Taken in toto with findings from Moore et al., these results implicate PN as a cause of an augmented inflammatory response to subsequent injury by priming of PMNs within the splanchnic vasculature. A variety of insults to the gastrointestinal tract, however, appear capable of causing increased expression of leukocyte chemoattractant adhesion molecules, potentiating greater leukocyte adhesion to vascular endothelium, and augmenting priming of PMNs to subsequent insults (Fig. 2.6).

Decreased Enteral Stimulation Versus PN

A final issue warranting discussion remains the primary etiology of these nutritional effects, i.e., is it gut starvation due to the lack of enteral stimulation or is it the PN feeding itself. Experimentally, animals cannot be starved for these experiments since most changes in mucosal immunity progress over the first 3 days of PN and 3 days of starvation is uniformly fatal. If the experiments were terminated at 48 to 60 h for study, one could not separate the effects of gut starvation from effects of severe malnutrition that develops this rapidly. The use of PN allows the ability to study effects of lack of enteral nutrition and "gut starvation" on mucosal immunity without the confounding variable of severe

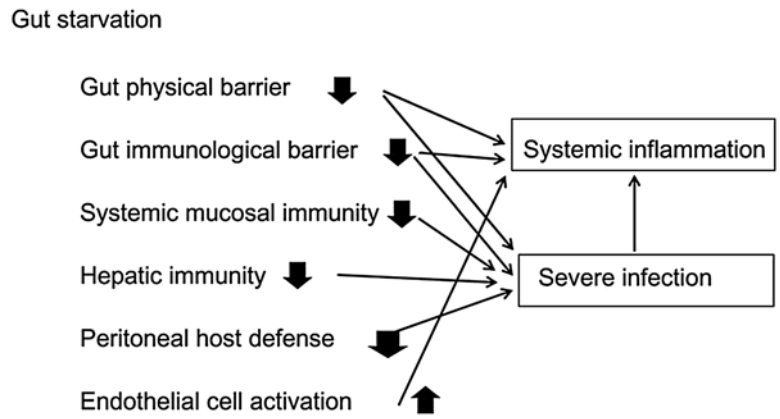


Fig. 2.6 Influences of decreased enteral stimulation on host immunity and inflammation. Gut starvation impairs various host defense systems, while causing inappropriate activation of endothelial cells. Reprinted from Surgical Clinics of North America, 91/4, Fukatsu K, Kudsk KA, Nutrition and gut immunity, 755–70, vii, Copyright 2011, with permission from Elsevier

malnutrition but the quandary of PN vs. lack of enteral stimulation still remains. Another stream of research investigating interaction between the enteric nervous system (ENS) and mucosal immunity convinces us that it is the lack of enteral feeding which is responsible for gastrointestinal immune variations rather than PN itself.

The ENS contains as many neurons as the spinal cord, which infiltrates the gastrointestinal tract with 2 m of nerve for every cubic centimeter of GI tissue. The ENS affects GI motility, absorption, and secretion through various mechanisms including the release of neuropeptides. One of these neuropeptides is gastrin-releasing peptide (GRP), a peptide released soon after enteral stimulation which stimulates the release of subsequent neuropeptides such as gastrin and cholecystokinin. An analogue of GRP, bombesin (BBS), contains the same functional peptide segment as GRP and elicits the same response experimentally. Experimentally, the addition of BBS during PN administration reverses most of the immune aberrations that occur during PN alone, including: normalization of T and B cell populations within the GALT and lungs; increases in levels of certain Th2 type cytokines; augmentation of MUC2 production; restoration of small intestinal and respiratory IgA levels; and reestablishment of respiratory antibacterial and antiviral immunity lost during PN feeding [136–141]. These observations lead to the conclusion that the lack of enteral stimulation—and loss of GI responses that it generates—ultimately explain the defects in mucosal immunity which occurs during parenteral feeding.

Conclusion

Specialized nutrition support may be indicated during critical illness and injury. While various forms of specialized nutrition support can meet the protein and energy requirements for physical recovery, the route of nutrition delivery significantly influences the body's ability to maintain host defenses. EN affects gastrointestinal host defenses, mucosal immunity, and intestinal inflammatory responses in ways that are not possible with PN. These different immunological responses may help explain the resulting fewer infections and control of inflammation with EN. This review highlights the importance of immunology and the immunologic effect of gastrointestinal delivery of nutrients when feasible.

Acknowledgements The material is supported in part by Award Number I01BX001672 from the Biomedical Laboratory Research and Development Service of the VA Office of Research and Development. The contents of this body of work do not represent the views of the Veterans Affairs or the US Government. This work is also supported by the NIH Surgical Oncology Research Training Program: T32CA090217-13.

References

1. Deitch EA. Nutrition and the gut mucosal barrier. Curr Opin Gen Surg. 1993:85–91.
2. Long CL, Schaffel N, Geiger JW, Schiller WR, Blakemore WS. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. JPEN J Parenter Enteral Nutr. 1979;3(6):452–6.
3. Cerra FB, Siegel JH, Coleman B, Border JR, McMenamy RR. Septic autocannibalism. A failure of exogenous nutritional support. Ann Surg. 1980;192(4):570–80.
4. Hanna M, Kudsk K. Nutritional and pharmacological enhancement of gut-associated lymphoid tissue. Can J Gastroenterol. 2000;14(Suppl D):145D–51.
5. Deitch EA, Ma WJ, Ma L, Berg RD, Specian RD. Protein malnutrition predisposes to inflammatory-induced gut-origin septic states. Ann Surg. 1990;211(5):560–7. discussion 7-8.
6. Calder PC. Feeding the immune system. Proc Nutr Soc. 2013;72(3):299–309.
7. Petersen SR, Kudsk KA, Carpenter G, Sheldon GE. Malnutrition and immunocompetence: increased mortality following an infectious challenge during hyperalimentation. J Trauma. 1981;21(7):528–33.
8. Kudsk KA, Carpenter G, Petersen S, Sheldon GF. Effect of enteral and parenteral feeding in malnourished rats with E. coli-hemoglobin adjuvant peritonitis. J Surg Res. 1981;31(2):105–10.
9. Kudsk KA, Stone JM, Carpenter G, Sheldon GF. Enteral and parenteral feeding influences mortality after hemoglobin-E. coli peritonitis in normal rats. J Trauma. 1983;23(7):605–9.
10. Moore F, Moore E, Jones T, McCroskey B, Peterson V. TEN versus TPN following major abdominal trauma – reduced septic morbidity. J Trauma. 1989;29(7):916–22. discussion 22-3.
11. Moore E, Jones T. Benefits of immediate jejunostomy feeding after major abdominal trauma – a prospective, randomized study. J Trauma. 1986;26(10):874–81.
12. 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 11-3.
13. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. Science. 2001;291(5505):881–4.
14. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635–8.
15. Curtis MM, Sperandio V. A complex relationship: the interaction among symbiotic microbes, invading pathogens, and their mammalian host. Mucosal Immunol. 2011;4(2):133–8.
16. Corthésy B. Role of secretory IgA in infection and maintenance of homeostasis. Autoimmun Rev. 2013;12(6): 661–5.
17. 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.
18. Alverdy J. The effect of nutrition on gastrointestinal barrier function. Semin Respir Infect. 1994;9(4):248–55.
19. Laughlin RS, Musch MW, Hollbrook CJ, Rocha FM, Chang EB, Alverdy JC. The key role of Pseudomonas aeruginosa PA-I lectin on experimental gut-derived sepsis. Ann Surg. 2000;232(1):133–42.
20. Alverdy J, Stern E. Effect of immunonutrition on virulence strategies in bacteria. Nutrition. 1998;14(7-8):580–4.
21. Ramos HC, Rumbo M, Sirard JC. Bacterial flagellins: mediators of pathogenicity and host immune responses in mucosa. Trends Microbiol. 2004;12(11):509–17.
22. Wu LR, Zaborina O, Zaborin A, Chang EB, Musch M, Holbrook C, et al. Surgical injury and metabolic stress enhance the virulence of the human opportunistic pathogen Pseudomonas aeruginosa. Surg Infect (Larchmt). 2005;6(2):185–95.
23. Wu L, Holbrook C, Zaborina O, Ploplys E, Rocha F, Pelham D, et al. Pseudomonas aeruginosa expresses a lethal virulence determinant, the PA-I lectin/adhesin, in the intestinal tract of a stressed host: the role of epithelia cell contact and molecules of the Quorum Sensing Signaling System. Ann Surg. 2003;238(5):754–64.
24. Kohler JE, Zaborina O, Wu L, Wang Y, Bethel C, Chen Y, et al. Components of intestinal epithelial hypoxia activate the virulence circuitry of Pseudomonas. Am J Physiol Gastrointest Liver Physiol. 2005;288(5):G1048–54.
25. Deitch EA. Bacterial translocation of the gut flora. J Trauma. 1990;30(12 Suppl):S184–9.
26. Fukatsu K, Kudsk KA. Nutrition and gut immunity. Surg Clin North Am. 2011;91(4):755–70. vii.

27. Lu Z, Ding L, Lu Q, Chen YH. Claudins in intestines: distribution and functional significance in health and diseases. Tissue Barriers. 2013;1(3), e24978.
28. Ivanov AI. Structure and regulation of intestinal epithelial tight junctions: current concepts and unanswered questions. Adv Exp Med Biol. 2012;763:132–48.
29. Deplancke B, Gaskins HR. Microbial modulation of innate defense: goblet cells and the intestinal mucus layer. Am J Clin Nutr. 2001;73(6):1131S–41.
30. Dharmani P, Srivastava V, Kissoon-Singh V, Chadee K. Role of intestinal mucins in innate host defense mechanisms against pathogens. J Innate Immun. 2009;1(2):123–35.
31. Johansson ME, Hansson GC. Mucus and the goblet cell. Dig Dis. 2013;31(3–4):305–9.
32. Kim YS, Ho SB. Intestinal goblet cells and mucins in health and disease: recent insights and progress. Curr Gastroenterol Rep. 2010;12(5):319–30.
33. Johansson ME, Ambort D, Pelaseyed T, Schutte A, Gustafsson JK, Ermund A, et al. Composition and functional role of the mucus layers in the intestine. Cell Mol Life Sci. 2011;68(22):3635–41.
34. Petersson J, Schreiber O, Hansson GC, Gendler SJ, Velcich A, Lundberg JO, et al. Importance and regulation of the colonic mucus barrier in a mouse model of colitis. Am J Physiol Gastrointest Liver Physiol. 2011;300(2): G327–33.
35. Van der Sluis M, De Koning BA, De Bruijn AC, Velcich A, Meijerink JP, Van Goudoever JB, et al. Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. Gastroenterology. 2006;131(1):117–29.
36. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5(7):e177.
37. Salzman NH, Underwood MA, Bevins CL. Paneth cells, defensins, and the commensal microbiota: a hypothesis on intimate interplay at the intestinal mucosa. Semin Immunol. 2007;19(2):70–83.
38. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science. 2012;336(6086):1268–73.
39. Masuda K, Sakai N, Nakamura K, Yoshioka S, Ayabe T. Bactericidal activity of mouse α-defensin cryptdin-4 predominantly affects noncommensal bacteria. J Innate Immun. 2011;3(3):315–26.
40. Heneghan AF, Pierre JF, Tandee K, Shanmuganayagam D, Wang X, Reed JD, et al. Parenteral nutrition decreases paneth cell function and intestinal bactericidal activity while increasing susceptibility to bacterial enteroinvasion. JPEN J Parenter Enteral Nutr. 2014;38(7):817–24.
41. Demehri FR, Barrett M, Ralls MW, Miyasaka EA, Feng Y, Teitelbaum DH. Intestinal epithelial cell apoptosis and loss of barrier function in the setting of altered microbiota with enteral nutrient deprivation. Front Cell Infect Microbiol. 2013;3:105.
42. Bevins CL, Salzman NH. Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. Nat Rev Microbiol. 2011;9(5):356–68.
43. Dommett R, Zilbauer M, George JT, Bajaj-Elliott M. Innate immune defence in the human gastrointestinal tract. Mol Immunol. 2005;42(8):903–12.
44. Ogawa H, Fukushima K, Naito H, Funayama Y, Unno M, Takahashi K, et al. Increased expression of HIP/PAP and regenerating gene III in human inflammatory bowel disease and a murine bacterial reconstitution model. Inflamm Bowel Dis. 2003;9(3):162–70.
45. Pierre JF, Heneghan AF, Tsao FH, Sano Y, Jonker MA, Omata J, et al. Route and type of nutrition and surgical stress influence secretory phospholipase A2 secretion of the murine small intestine. JPEN J Parenter Enteral Nutr. 2011;35(6):748–56.
46. Cash HL, Whitham CV, Behrendt CL, Hooper LV. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. Science. 2006;313(5790):1126–30.
47. Vaishnava S, Behrendt CL, Ismail AS, Eckmann L, Hooper LV. Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. Proc Natl Acad Sci U S A. 2008;105(52): 20858–63.
48. McGhee JR, Mestecky J, Dertzbaugh MT, Eldridge JH, Hirasawa M, Kiyono H. The mucosal immune system: from fundamental concepts to vaccine development. Vaccine. 1992;10(2):75–88.
49. Brandtzaeg P, Pabst R. Let's go mucosal: communication on slippery ground. Trends Immunol. 2004;25(11): 570–7.
50. Czerkinsky C, Prince SJ, Michalek SM, Jackson S, Russell MW, Moldoveanu Z, et al. IgA antibody-producing cells in peripheral blood after antigen ingestion: evidence for a common mucosal immune system in humans. Proc Natl Acad Sci U S A. 1987;84(8):2449–53.
51. Czerkinsky C, Svennerholm AM, Quiding M, Jonsson R, Holmgren J. Antibody-producing cells in peripheral blood and salivary glands after oral cholera vaccination of humans. Infect Immun. 1991;59(3):996–1001.
52. Czerkinsky C, Svennerholm AM, Holmgren J. Induction and assessment of immunity at enteromucosal surfaces in humans: implications for vaccine development. Clin Infect Dis. 1993;16 Suppl 2:S106–16.

53. Czerkinsky C, Prince SJ, Michalek SM, Jackson S, Moldoveanu Z, Russell MW, et al. Oral immunization with bacterial antigen induces IgA-secreting cells in peripheral blood in humans. Adv Exp Med Biol. 1987;216B: 1709–19.
54. Husband AJ, Gowans JL. The origin and antigen-dependent distribution of IgA-containing cells in the intestine. J Exp Med. 1978;148(5):1146–60.
55. Craig SW, Cebra JJ. Peyer's patches: an enriched source of precursors for IgA-producing immunocytes in the rabbit. J Exp Med. 1971;134(1):188–200.
56. Bargatze RF, Jutila MA, Butcher EC. Distinct roles of L-selectin and integrins alpha 4 beta 7 and LFA-1 in lymphocyte homing to Peyer's patch-HEV in situ: the multistep model confirmed and refined. Immunity. 1995;3(1):99–108.
57. Berlin C, Berg EL, Briskin MJ, Andrew DP, Kilshaw PJ, Holzmann B, et al. Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. Cell. 1993;74(1):185–95.
58. Sikorski EE, Hallmann R, Berg EL, Butcher EC. The Peyer's patch high endothelial receptor for lymphocytes, the mucosal vascular addressin, is induced on a murine endothelial cell line by tumor necrosis factor-alpha and IL-1. J Immunol. 1993;151(10):5239–50.
59. Campbell JJ, Hedrick J, Zlotnik A, Siani MA, Thompson DA, Butcher EC. Chemokines and the arrest of lymphocytes rolling under flow conditions. Science. 1998;279(5349):381–4.
60. Guy-Grand D, Griscelli C, Vassalli P. The gut-associated lymphoid system: nature and properties of the large dividing cells. Eur J Immunol. 1974;4(6):435–43.
61. Man AL, Prieto-Garcia ME, Nicoletti C. Improving M cell mediated transport across mucosal barriers: do certain bacteria hold the keys? Immunology. 2004;113(1):15–22.
62. Didierlaurent A, Sirard JC, Kraehenbuhl JP, Neutra MR. How the gut senses its content. Cell Microbiol. 2002;4(2):61–72.
63. Mestecky J, Lamm ME, Strober W, Bienenstock J, McGhee JR, Mayer L. Mucosal immunology. 3rd ed. Philadelphia, PA: Elsevier; 2005.
64. Brandtzaeg P, Kiyono H, Pabst R, Russell MW. Terminology: nomenclature of mucosa-associated lymphoid tissue. Mucosal Immunol. 2008;1(1):31–7.
65. Parrott DM. The gut as a lymphoid organ. Clin Gastroenterol. 1976;5(2):211–28.
66. Mostov KE, Friedlander M, Blobel G. The receptor for transepithelial transport of IgA and IgM contains multiple immunoglobulin-like domains. Nature. 1984;308(5954):37–43.
67. Morowitz MJ, Babrowski T, Carlisle EM, Olivas A, Romanowski KS, Seal JB, et al. The human microbiome and surgical disease. Ann Surg. 2011;253(6):1094–101.
68. Pappo J, Owen RL. Absence of secretory component expression by epithelial cells overlying rabbit gut-associated lymphoid tissue. Gastroenterology. 1988;95(5):1173–7.
69. Gehrke I, Pabst R. The epithelium overlying rabbit bronchus-associated lymphoid tissue does not express the secretory component of immunoglobulin A. Cell Tissue Res. 1990;259(2):397–9.
70. Giannasca PJ, Giannasca KT, Falk P, Gordon JI, Neutra MR. Regional differences in glycoconjugates of intestinal M cells in mice: potential targets for mucosal vaccines. Am J Physiol. 1994;267(6 Pt 1):G1108–21.
71. Lebman DA, Coffman RL. The effects of IL-4 and IL-5 on the IgA response by murine Peyer's patch B cell subpopulations. J Immunol. 1988;141(6):2050–6.
72. Coffman RL, Savelkoul HF, Lebman DA. Cytokine regulation of immunoglobulin isotype switching and expression. Semin Immunol. 1989;1(1):55–63.
73. Roux ME, McWilliams M, Phillips-Quagliata JM, Lamm ME. Differentiation pathway of Peyer's patch precursors of IgA plasma cells in the secretory immune system. Cell Immunol. 1981;61(1):141–53.
74. Hieshima K, Ohtani H, Shibano M, Izawa D, Nakayama T, Kawasaki Y, et al. CCL28 has dual roles in mucosal immunity as a chemokine with broad-spectrum antimicrobial activity. J Immunol. 2003;170(3):1452–61.
75. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg. 1992;216(2):172–83.
76. 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):1–7.
77. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNMC, Delarue J, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24(4):502–9.
78. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery. 1968;64(1):134–42.
79. 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.
80. Kudsk KA, Jonathan E. Rhoads lecture: of mice and men… and a few hundred rats. JPEN J Parenter Enteral Nutr. 2008;32(4):460–73.

81. Jonker MA, Hermsen JL, Gomez FE, Sano Y, Kudsk KA. Injury induces localized airway increases in pro-inflammatory cytokines in humans and mice. Surg Infect (Larchmt). 2011;12(1):49–56.
82. Jonker MA, Hermsen JL, Sano Y, Heneghan AF, Lan J, Kudsk KA. Small intestine mucosal immune system response to injury and the impact of parenteral nutrition. Surgery. 2012;151(2):278–86.
83. Johnson LR, Copeland EM, Dudrick SJ, Lichtenberger LM, Castro GA. Structural and hormonal alterations in the gastrointestinal tract of parenterally fed rats. Gastroenterology. 1975;68(5 Pt 1):1177–83.
84. Kansagra K, Stoll B, Rognerud C, Niinikoski H, Ou CN, Harvey R, et al. Total parenteral nutrition adversely affects gut barrier function in neonatal piglets. Am J Physiol Gastrointest Liver Physiol. 2003;285(6):G1162–70.
85. Heneghan A, Pierre J, Gosain A, Kudsk K. IL-25 stimulation of Parenteral Nutrition (PN) Restores Innate Immune Molecules. Ann Surg. 2014;259(2):394–400.
86. Yang H, Feng Y, Sun X, Teitelbaum DH. Enteral versus parenteral nutrition: effect on intestinal barrier function. Ann N Y Acad Sci. 2009;1165:338–46.
87. Schmitz H, Fromm M, Bentzel CJ, Scholz P, Detjen K, Mankertz J, et al. Tumor necrosis factor-alpha (TNFalpha) regulates the epithelial barrier in the human intestinal cell line HT-29/B6. J Cell Sci. 1999;112(Pt 1):137–46.
88. Zeissig S, Bojarski C, Buergel N, Mankertz J, Zeitz M, Fromm M, et al. Downregulation of epithelial apoptosis and barrier repair in active Crohn's disease by tumour necrosis factor alpha antibody treatment. Gut. 2004;53(9):1295–302.
89. Zeissig S, Bürgel N, Günzel D, Richter J, Mankertz J, Wahnschaffe U, et al. Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. Gut. 2007;56(1):61–72.
90. Buchman AL, Moukarzel AA, Bhuta S, Belle M, Ament ME, Eckhert CD, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. JPEN J Parenter Enteral Nutr. 1995;19(6): 453–60.
91. Pierre JF, Heneghan AF, Meudt JM, Shea MP, Krueger CG, Reed JD, et al. Parenteral nutrition increases susceptibility of ileum to invasion by E coli. J Surg Res. 2013;183(2):583–91.
92. Li J, Kudsk KA, Gocinski B, Dent D, Glezer J, Langkamp-Henken B. Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. J Trauma. 1995;39(1):44–51. discussion-2.
93. Zarzaur B, Fukatsu K, Johnson C, Eng E, Kudsk K. A temporal study of diet-induced changes in Peyer patch MAdCAM-1 expression. Surg Forum. 2001;52:194–6.
94. Gomez FE, Lan J, Kang W, Ueno C, Kudsk KA. Parenteral nutrition and fasting reduces mucosal addressin cellular adhesion molecule-1 (MAdCAM-1) mRNA in Peyer's patches of mice. JPEN J Parenter Enteral Nutr. 2007;31(1):47–52.
95. Ikeda S, Kudsk KA, Fukatsu K, Johnson CD, Le T, Reese S, et al. Enteral feeding preserves mucosal immunity despite in vivo MAdCAM-1 blockade of lymphocyte homing. Ann Surg. 2003;237(5):677–85. discussion 85.
96. 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.
97. Kang W, Kudsk KA, Sano Y, Lan J, Yang-Xin F, Gomez FE, et al. Effects of lymphotoxin beta receptor blockade on intestinal mucosal immunity. JPEN J Parenter Enteral Nutr. 2007;31(5):358–64. discussion 64-5.
98. Hermsen JL, Gomez FE, Maeshima Y, Sano Y, Kang W, Kudsk KA. Decreased enteral stimulation alters mucosal immune chemokines. JPEN J Parenter Enteral Nutr. 2008;32(1):36–44.
99. Alverdy JC, Aoys E, Moss GS. Total parenteral nutrition promotes bacterial translocation from the gut. Surgery. 1988;104(2):185–90.
100. Alverdy JC, Aoys E, Moss GS. Effect of commercially available chemically defined liquid diets on the intestinal microflora and bacterial translocation from the gut. JPEN J Parenter Enteral Nutr. 1990;14(1):1–6.
101. Wu Y, Kudsk KA, DeWitt RC, Tolley EA, Li J. Route and type of nutrition influence IgA-mediating intestinal cytokines. Ann Surg. 1999;229(5):662–7. discussion 7-8.
102. Sano Y, Gomez F, Kang W, Lan J, Maeshima Y, Hermsen J, et al. Intestinal polymeric immunoglobulin receptor is affected by type and route of nutrition. JPEN J Parenter Enteral Nutr. 2007;31(5):351–6. discussion 6-7.
103. Okamoto K, Fukatsu K, Hashiguchi Y, Ueno H, Shinto E, Moriya T, et al. Lack of preoperative enteral nutrition reduces gut-associated lymphoid cell numbers in colon cancer patients: a possible mechanism underlying increased postoperative infectious complications during parenteral nutrition. Ann Surg. 2013;258(6):1059–64.
104. Okamoto K, Fukatsu K, Ueno C, Shinto E, Hashiguchi Y, Nagayoshi H, et al. T lymphocyte numbers in human gut associated lymphoid tissue are reduced without enteral nutrition. JPEN J Parenter Enteral Nutr. 2005;29(1):56–8.
105. Hermsen JL, Gomez FE, Sano Y, Kang W, Maeshima Y, Kudsk KA. Parenteral feeding depletes pulmonary lymphocyte populations. JPEN J Parenter Enteral Nutr. 2009;33(5):535–40.
106. King BK, Li J, Kudsk KA. A temporal study of TPN-induced changes in gut-associated lymphoid tissue and mucosal immunity. Arch Surg. 1997;132(12):1303–9.
107. Sano Y, Gomez FE, Hermsen JL, Kang W, Lan J, Maeshima Y, et al. Parenteral nutrition induces organ specific alterations in polymeric immunoglobulin receptor levels. J Surg Res. 2008;149(2):236–42.

108. Sano Y, Hermsen JL, Kang W, Gomez FE, Lan J, Maeshima Y, et al. Parenteral nutrition maintains pulmonary IgA antibody transport capacity, but not active transport, following injury. Am J Surg. 2009;198(1):105–9.
109. Fukatsu K, Lundberg AH, Hanna MK, Wu Y, Wilcox HG, Granger DN, et al. Increased expression of intestinal P-selectin and pulmonary E-selectin during intravenous total parenteral nutrition. Arch Surg. 2000;135(10): 1177–82.
110. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. National vital statistics reports. 2013;61(4).
111. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med. 1987;317(11):653–8.
112. Kreger BE, Craven DE, McCabe WR. Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med. 1980;68(3):344–55.
113. Kudsk K, Minard G, Croce M, Brown R, Lowrey T, Pritchard F, et al. A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. Ann Surg. 1996;224(4): 531–40. discussion 40-3.
114. 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.
115. Kudsk KA, Li J, Renegar KB. Loss of upper respiratory tract immunity with parenteral feeding. Ann Surg. 1996;223(6):629–35. discussion 35-8.
116. Renegar KB, Johnson CD, Dewitt RC, King BK, Li J, Fukatsu K, et al. Impairment of mucosal immunity by total parenteral nutrition: requirement for IgA in murine nasotracheal anti-influenza immunity. J Immunol. 2001;166(2):819–25.
117. Johnson CD, Kudsk KA, Fukatsu K, Renegar KB, Zarzaur BL. Route of nutrition influences generation of antibody-forming cells and initial defense to an active viral infection in the upper respiratory tract. Ann Surg. 2003;237(4):565–73.
118. Janu P, Li J, Renegar K, Kudsk K. Recovery of gut-associated lymphoid tissue and upper respiratory tract immunity after parenteral nutrition. Ann Surg. 1997;225(6):707–15. discussion 15-7.
119. King BK, Kudsk KA, Li J, Wu Y, Renegar KB. Route and type of nutrition influence mucosal immunity to bacterial pneumonia. Ann Surg. 1999;229(2):272–8.
120. Annane D, Clair B, Mathieu B, Boucly C, Lesieur O, Donetti L, et al. Immunoglobulin A levels in bronchial samples during mechanical ventilation and onset of nosocomial pneumonia in critically ill patients. Am J Respir Crit Care Med. 1996;153(5):1585–90.
121. Niederman MS, Merrill WW, Polomski LM, Reynolds HY, Gee JB. Influence of sputum IgA and elastase on tracheal cell bacterial adherence. Am Rev Respir Dis. 1986;133(2):255–60.
122. Niederman MS, Mantovani R, Schoch P, Papas J, Fein AM. Patterns and routes of tracheobronchial colonization in mechanically ventilated patients. The role of nutritional status in colonization of the lower airway by Pseudomonas species. Chest. 1989;95(1):155–61.
123. Kudsk KA, Hermsen JL, Genton L, Faucher L, Gomez FE. Injury stimulates an innate respiratory immunoglobulin a immune response in humans. J Trauma. 2008;64(2):316–23. discussion 23-5.
124. Jonker MA, Sano Y, Hermsen JL, Lan J, Kudsk KA. Proinflammatory cytokine surge after injury stimulates an airway immunoglobulin a increase. J Trauma. 2010;69(4):843–8.
125. Hermsen J, Sano Y, Gomez F, Maeshima Y, Kang W, Kudsk K. Parenteral nutrition inhibits tumor necrosis factor-alpha-mediated IgA response to injury. Surg Infect (Larchmt). 2008;9(1):33–40.
126. Fukatsu K, Kudsk KA, Zarzaur BL, Wu Y, Hanna MK, DeWitt RC. TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression. Shock. 2001;15(4):318–22.
127. Fukatsu K, Lundberg AH, Hanna MK, Wu Y, Wilcox HG, Granger DN, et al. Route of nutrition influences intercellular adhesion molecule-1 expression and neutrophil accumulation in intestine. Arch Surg. 1999;134(10): 1055–60.
128. Cao Y, Xu Y, Lu T, Gao F, Mo Z. Meta-analysis of enteral nutrition versus total parenteral nutrition in patients with severe acute pancreatitis. Ann Nutr Metab. 2008;53(3-4):268–75.
129. Moore FA, Haenel JB, Moore EE, Whitehill TA. Incommensurate oxygen consumption in response to maximal oxygen availability predicts postinjury multiple organ failure. J Trauma. 1992;33(1):58–65. discussion-7.
130. Friese RS, Rehring TF, Wollmering M, Moore EE, Ketch LL, Banerjee A, et al. Trauma primes cells. Shock. 1994;1(5):388–94.
131. Moore EE, Moore FA, Franciose RJ, Kim FJ, Biffl WL, Banerjee A. The postischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. J Trauma. 1994;37(6):881–7.
132. Magnotti LJ, Deitch EA. Burns, bacterial translocation, gut barrier function, and failure. J Burn Care Rehabil. 2005;26(5):383–91.
133. Deitch EA. Role of the gut lymphatic system in multiple organ failure. Curr Opin Crit Care. 2001;7(2):92–8.

134. Deitch EA, Xu D, Kaise VL. Role of the gut in the development of injury- and shock induced SIRS and MODS: the gut-lymph hypothesis, a review. Front Biosci. 2006;11:520–8.
135. Fukatsu K, Zarzaur BL, Johnson CD, Lundberg AH, Wilcox HG, Kudsk KA. Enteral nutrition prevents remote organ injury and death after a gut ischemic insult. Ann Surg. 2001;233(5):660–8.
136. Li J, Kudsk KA, Hamidian M, Gocinski BL. Bombesin affects mucosal immunity and gut-associated lymphoid tissue in intravenously fed mice. Arch Surg. 1995;130(11):1164–9. discussion 9-70.
137. Janu PG, Kudsk KA, Li J, Renegar KB. Effect of bombesin on impairment of upper respiratory tract immunity induced by total parenteral nutrition. Arch Surg. 1997;132(1):89–93.
138. DeWitt RC, Wu Y, Renegar KB, King BK, Li J, Kudsk KA. Bombesin recovers gut-associated lymphoid tissue and preserves immunity to bacterial pneumonia in mice receiving total parenteral nutrition. Ann Surg. 2000; 231(1):1–8.
139. Hanna M, Zarzaur BJ, Fukatsu K, Chance DeWitt R, Renegar K, Sherrell C, et al. Individual neuropeptides regulate gut-associated lymphoid tissue integrity, intestinal immunoglobulin A levels, and respiratory antibacterial immunity. JPEN J Parenter Enteral Nutr. 2000;24(5):261–8; discussion 8-9.
140. Zarzaur BL, Wu Y, Fukatsu K, Johnson CD, Kudsk KA. The neuropeptide bombesin improves IgA-mediated mucosal immunity with preservation of gut interleukin-4 in total parenteral nutrition-fed mice. Surgery. 2002;131(1):59–65.
141. Genton L, Reese SR, Ikeda S, Le Tho C, Kudsk KA. The C-terminal heptapeptide of bombesin reduces the deleterious effect of total parenteral nutrition (TPN) on gut-associated lymphoid tissue (GALT) mass but not intestinal immunoglobulin A in vivo. JPEN J Parenter Enteral Nutr. 2004;28(6):431–4.

Chapter 3
Assessment of the Patient

Marion F. Winkler, Kenneth A. Lynch Jr., and Stephanie N. Lueckel

Keywords Nutrition risk • Nutrition screening • Nutrition assessment • Body composition • Inflammation • Malnutrition • Nutrition-focused physical exam • Critical care • Intensive care unit

Key Points

- Nutrition assessment should be fully integrated into the comprehensive patient assessment.
- Critically ill patients are at risk for accelerated loss of lean body mass with even greater loss of weight if nutritional intake is poor or absent.
- The physical examination is a key component of any patient assessment.
- Clinical decision making includes recognition of patients who will be unable to eat and the need for initiation of early nutrition support.
- The number of days to initiate oral feeding and timeliness of starting enteral or parenteral nutrition are useful monitoring parameters in the ICU.
- Tests traditionally performed to diagnose malnutrition are reflective of systemic inflammation as opposed to adequacy of intake.
- Relevant components of the nutrition assessment should be discussed daily by the multidisciplinary critical care team.
- The approach to nutrition delivery in the ICU should be based on a multidisciplinary assessment and plan where all providers work in tandem to provide optimal patient care.

M.F. Winkler, PhD, RD, CNSC (✉)
Department of Surgery, Nutrition Support Service, Rhode Island Hospital, Warren Alpert Medical School of Brown University, 593 Eddy Street, NAB 218, Providence, RI 02903, USA
e-mail: mwinkler@lifespan.org

K.A. Lynch, Jr, MS, APRN-CNP
Surgical Critical Care, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI USA

S.N. Lueckel, MD
Division of Trauma and Surgical Critical Care, Department of Surgery, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_3,

Introduction

Nutrition assessment is a means for identifying intensive care unit (ICU) patients at greatest risk for complications. It should include manifestations both of disease-related malnutrition and of nutrient imbalance (e.g., starvation). Patients classified as at risk may have disease processes which interfere with or even prevent nourishment. Additionally, many ICU patients develop intestinal dysfunction and other feeding difficulties. Early identification provides the greatest opportunity for nutritional intervention. Comprehensive patient assessment and multidisciplinary nutrition care helps to ensure the proper route and timing for nutrition therapy and to promote favorable outcomes.

A complete discussion of individual nutrient deficiencies is beyond the scope of this chapter, but an excellent reference tool may be found at http://www.nal.usda.gov/wicworks/Topics/FG/AppendixC_NutrientChart.pdf.

Traditional Methods for Nutrition Assessment

Assessment of the critically ill patient is challenging, particularly when observed findings may be due to alterations in metabolism or inadequate or inappropriate intake. Hemodynamically unstable patients have alterations in cardiac output, oxygen consumption, body temperature, and basal metabolic rate. Normal homeostatic functions are disrupted and there is a marked increase in glucose production due to insulin resistance. Free fatty acid release, proteolysis, and circulating levels of insulin, catecholamines, glucagon, and cortisol are all increased, and patients present clinically with hyperglycemia and increased ureagenesis. Furthermore, the presence of concomitant chronic disease or multi-system organ failure influences nutritional status and nutrient requirements.

Traditional methods of measuring nutritional status, useful in the normal population, are limited in value in those with critical illness. Anthropometric measurements including arm muscle circumference and triceps skinfold thickness, though generally a good index of body protein and energy reserves, are insensitive to nutritional repletion over a relatively short ICU stay and are disrupted by edema [1]. Serum albumin and transthyretin (pre-albumin) levels, while very useful as prognostic indicators, reflect severity of inflammation rather than nutritional status [2] or adequacy of intake [3].

Scoring Systems

Nutrition assessment should be fully integrated into the comprehensive patient assessment. Its purpose is to identify those critically ill patients most likely to benefit from nutrition intervention [4], and to define the degree of urgency with which nutritional intervention should be approached.

Scoring systems, which combine a variety of measurements, have been developed into well-validated prognostic scores [4–15]. Some of these tools are shown in Table 3.1. A recent analysis [16] identified the Malnutrition Screening Tool (MST) [5] as the most reliable instrument for identifying risk in the general acute care setting. The Malnutrition Universal Screening Tool (MUST) [6] is preferable to use in critical care because it includes a factor for acute illness.

A diagnosis of malnutrition identifies the sickest patients, those at risk for both poor clinical outcomes, and those at risk for developing feeding difficulties. Depending on the patient population studied, an estimated 20–50 % of patients in the hospital setting have malnutrition upon admission [17]. Yet, the most recent data from the US Department of Health and Human Services suggests that only 2.8 % of hospitalized patients are diagnosed and coded with malnutrition [18]. The criteria and etiologies for development of malnutrition are discussed in Chap. 1.

Table 3.1 Clinical scoring systems

Screening/assessment tool	Description	Score
Malnutrition Screening Tool (MST) [5]	• Identifies patients at risk of malnutrition • Includes two questions about weight loss in the past 6 months and decreased appetite and poor eating • Validated in adult oncology patients undergoing chemotherapy and radiation	• Score >2 defines nutrition risk • 1 point for weight loss of 2–13 lb • 2 points for weight loss of 14–23 lb • 3 points for weight loss of 24–33 lb • 4 points for weight loss >34 lb • 1 point for decreased appetite and poor eating
Malnutrition Universal Screening Tool (MUST) [6] (www.bapen.org.uk)	• Detects protein calorie malnutrition and risk of developing malnutrition • Criteria includes body mass index (BMI), unplanned weight loss in past 3–6 months, acute disease effect, and lack of nutritional intake >5 days	• Score of 2 indicates high risk, 1 indicates medium risk, 0 indicates low risk • 2 points for BMI < 18.5 m^2/kg • 2 points for weight loss >10 % • 2 points for acute illness with no nutritional intake for >5 days
Mini Nutritional Assessment (MNA) [7–9] (www.mna-elderly.com)	• Evaluates nutritional status of the elderly • Two versions: 18 items and 6 items • Evaluates food intake and weight loss in past 3 months, mobility, presence of psychological stress or acute disease, and neuropsychological problems • Shown to be a good predictor of nutritional imbalance in institutionalized elderly	• Score of 0–7 indicates malnutrition • Score of 8–11 indicates at risk of malnutrition • Score of 12–14 indicates normal nutritional status
Nutritional Risk Index (NRI) [10, 11]	• Evaluates efficacy of perioperative parenteral nutrition in patients undergoing thoracic or abdominal surgery • NRI = 1.519 × serum albumin (g/dL) + 41.7 × (current weight-kg/usual weight-kg) • Reliable prognostic indicator of morbidity and mortality	• <83.5 severe nutrition risk • 83.5–97.5 mild nutrition risk • >97.5 borderline nutrition risk • >100 no nutrition risk
Nutrition Risk Screen-2002 (NRS-2002) [12, 13]	• Identifies patients who are likely to benefit from nutritional support • Recommended by the European Society for Clinical Nutrition and Metabolism • Includes weight loss, BMI, reduced food intake, and severity of disease	• Score of 0–3 for impaired nutritional status based on magnitude and time frame of weight loss, BMI, or reduced food intake • Score of 3 assigned for severe stress and for patients in the intensive care unit (ICU) • A factor is added for age to correct for frailty of elderly
Subjective Global Assessment (SGA) [14] (www.subjectiveglobalassessment.com)	• Used to recognize and document nutritional problems • Includes a dietary and medical history, functional assessment, and physical examination • Good correlation with other clinical scoring systems • Reproducible findings in mechanically ventilated patients [15]	• SGA level C (evident malnutrition) • SGA level B (at nutritional risk) • SGA level A (well nourished)
Nutrition Risk in the Critically Ill Score (NUTRIC) [4]	• Nutritional risk assessment for ICU patients • Helps identify who will benefit from aggressive protein-energy provision • May have utility in the design and interpretation of clinical trials of nutrition therapies in the ICU	• Variables include age, APACHE II, SOFA, # co-morbidities, days from hospital to ICU admission, interleukin-6 (IL-6)

Patient Populations at Risk

Assessment for malnutrition identifies patients who are at highest risk for development of complications. The process includes consideration of the effect of the presenting problem on nutritional intake. For example, the patient who presents to the emergency department with perforated diverticulitis after days of symptoms, and then undergoes a bowel resection may be 5–7 days without oral intake following surgery. Similarly, the multi-system trauma patient who undergoes multiple operative interventions and procedures during hospitalization presents extreme challenges for meeting nutritional goals.

Iatrogenic factors alone, such as scheduled nothing by mouth for planned procedures or surgical interventions, can contribute greatly to caloric debt. In their review of trauma ICU patients in a university-affiliated hospital, Morgan et al. [19] reported that surgery (27 %) and diagnostic procedures (15 %) were the most common reasons for discontinuing tube feeding. Additionally, patients with large draining wounds or entero-atmospheric fistulae are at risk for nutritional deficits [20]. These patients have marked fluid, electrolyte, and protein losses. Further, this fluid loss may contain up to 2 g of nitrogen per liter [21]. It is important to monitor these losses. But, while it is common practice to attempt to replace the protein losses, it is unclear whether very high protein intake improves outcomes.

Patients presenting with acute pancreatitis are a high-risk population that poses significant challenges meeting nutritional goals. These patients often present with some degree of abdominal pain that, depending on disease severity, dictates whether oral, enteral (EN), parenteral (PN), or combinations of nutrition therapies will be required. Patients with mild pancreatitis are usually expected to eat within 5–7 days [22]. Patients with moderate-to-severe pancreatitis may experience significant fluid losses, organ failure, and systemic inflammatory response syndrome, and are less likely to take oral nourishment.

Burn injury patients are also at high risk for malnutrition, especially those with second-degree or greater burns covering more than 40 % of total body surface area [23]. The initial patient presentation is marked by periods of extreme stress, inflammation, and hypermetabolism with an ensuing catabolic state. Gastroparesis is frequent and may influence the ability for the patient to be nourished [24]. Measures of energy expenditure demonstrate a direct relationship with burn size. In patients with severe burns, energy expenditure may reach two times predicted [25]. Newsome et al. [26] found a maximum loss of 22 % body weight after 8 weeks of hospitalization for a major burn. Perhaps the greatest delay in achieving adequate oral intake is seen in burn patients with inhalation injury. Ward et al. [27] and DuBose et al. [28] reported a mean length of 46 ± 31 days and 53 ± 30 days before burn patients who required lengthy mechanical ventilation and tracheostomy were able to eat.

There are many conditions associated with being unable to eat among ICU patients. Boles et al. [29] cited advanced age, dysphagia following stroke, head trauma, pelvic fracture, and the need for emergency abdominal surgery or damage control laparotomy as typical conditions associated with impaired feeding. Zielske et al. [30] demonstrated that severe sepsis and tracheostomy were independent risk factors for severe dysphagia with aspiration. Poor oral intake is also common following mechanical ventilation. Peterson et al. [31] reported that mental status changes, loss of appetite, nausea and vomiting, dislike of food, and difficulty chewing or swallowing were the most frequent reasons for poor oral intake after extubation. Each patient requires careful attention, monitoring, and development of an individual nutrition care plan.

Assessing Intake

The diet history focuses on usual and current intake, food beliefs and practices, food allergies and intolerances, and dietary restrictions. Assessing a patient's "usual" diet, as well as the last time they have taken a full meal, is critical in guiding a nutritional plan. The critically ill patient is frequently

unable to provide a detailed history of usual intake, so this information is often obtained only from family members. It is important to temper wishful thinking that the patient will eat soon and will eat enough. Peterson et al. [31] found that oral intake of ICU patients who were allowed a diet was less than 50 % of requirements in the first 7 days following extubation.

The number of days prior to initiation of nourishment, be it oral, EN, or PN, is a useful clinical and quality parameter to monitor in the ICU. For patients who are eating or were eating prior to their ICU admission, the clinician should explore factors that may contribute to poor nutrient intake such as anorexia, dysgeusia, chewing or swallowing problems, pain, fatigue, depression, and need for assistance with feeding. Direct observation of food intake, such as performing a calorie count, may be useful for quantification of actual intake.

Delays and Obstacles to Feeding in Critical Care

The difference between requirements and intake that occurs throughout an ICU stay may create a substantial cumulative energy deficit. A survey of 66 ICUs in Canada [32] found that ICU patients received only 60 % of their cumulative estimated calorie and protein needs over the course of their ICU stay. Surgical patients in critical care units receive less nutrition when compared to medical patients, especially after gastrointestinal (GI) surgery or cardiovascular surgery [33].

More recent secondary data analyses from large trials have explored the relationship between caloric intake and clinical outcomes. Bellomo et al. [34] found no difference in mean caloric delivery in survivors and non-survivors of acute kidney injury receiving continuous renal replacement therapy. However, intake was low overall (11 kcal/kg/d), and it took 4–5 days to reach stable intake. Conversely, Elke et al. [35] reported that a greater intake of enteral calories (14.5 ± 7.2 kcal/kg) and protein in the early phase of the intensive care episode was associated with lower 60-day mortality and an increase in ventilator-free days. It remains unclear how much intake is adequate, and whether the relationship of calorie deficit to outcome is causal or results from sicker people being harder to feed. That said, an important part of clinical decision making is anticipating which patients will be unable to eat and when to initiate early nutrition support. The timing for initiation of feeding is discussed in subsequent chapters.

Enteral nutrition is frequently stopped or interrupted in the ICU for procedures, surgery, or perceived GI intolerance [19, 36, 37]. However, the definition of intolerance is variable. The incidence of interrupted EN therapy due to intolerance was 30.5 % in a cohort of 1888 ICU patients in the 2009 International Nutrition Study [38]. The most commonly reported intolerances were large gastric residual volumes (61.6 %) and vomiting or diarrhea (36.6 %). Yet, there is no evidence that links gastric residual volumes up to 500 ml with either vomiting or pulmonary complications. Unfortunately, health care providers will turn tube feedings off for subjective patient complaints of feeling nauseous, abdominal pain, vomiting or change in abdominal exam. Table 3.2 lists some of the barriers that delay EN and lead to inadequate calorie administration.

Nutrition-Focused History and Physical Examination

History

Collecting a thorough history, including presenting illness, past history, social and family histories, etc., may help to identify factors that impede adequate nutrient intake, as well as the presence of pre-existing malnutrition. The patient's history provides insight into many nutrition-related problems that arise from weight loss, GI disease, alcohol and drug abuse, elevated metabolic needs, increased

Table 3.2 Barriers for delivering adequate enteral nutrition [19, 36–38]

• Inadequate prescription
• Delayed initiation of feeding
• No feeding tube in place
• Lack of formula or pump on nursing unit
• Feeding tube malposition
• Frequent interruption due to:
Feeding tube problem (patency)
Elevated gastric residual volumes
Gastrointestinal intolerance (abdominal distension, vomiting/emesis, diarrhea, subject discomfort)
Procedure/surgery
Hemodynamic instability
Airway management
Daily care of patient
• Delay in initiating motility agents
• Risk of aspiration
• Lack of algorithm or protocol
• Staffing
• Attitudes toward nutrition practice

nutrient losses, chronic disease-related catabolic response, and recent major surgery. Socioeconomic status may reflect the ability to purchase and prepare food. Living alone and social isolation, and physical or mental handicaps all add to the risk of inadequate nutrition intake. Cultural and religious values may also influence eating behavior. These elements of the nutrition-related medical history are important to consider in ICU patients, particularly those who present with pre-existing malnutrition.

Medications

A thorough review and documentation of a patient's home medications is required for all patients. With the potential for adverse events associated with bleeding and synergistic, additive, or antagonistic drug interactions, the history must also elicit use of herbal remedies and over-the-counter or prescribed vitamin and mineral supplements [39, 40]. Patients often do not disclose self-prescribed complementary or alternative medicine (CAM) therapies, particularly without direct questions. Patients fear judgmental responses, believe their clinicians do not need to know, or are never asked about CAM use [41].

Documentation of all medications including herbal products and over-the-counter supplements should be conducted to screen for potential drug-drug interactions and drug-induced nutritional deficiencies. For example, bleeding has been anecdotally associated with consumption of certain dietary supplements [42]. Long term use of proton pump inhibitors may predispose patients to fractures because of their interaction with mineral absorption, particularly calcium, iron and magnesium [43]. Polypharmacy, especially among the elderly, plays a significant role in unintentional weight loss as many drugs impact the intake, absorption, metabolism, and excretion of nutrients [44].

There are numerous medications that impair intake by altering appetite and taste (Table 3.3). Phenytoin and certain antibiotics including macrolides, sulfonamides, and tetracyclines are associated with anorexia, while anticholinergics and sympathomimetics induce early satiety. Metronidazole, calcium channel blockers, and angiotensin-converting enzyme inhibitors (ACEIs) decrease taste sensation.

Table 3.3 Medication side effects and influence on ability to eat [43–45]

Side effect	Drug or medication category
Ability to feed self	Sedatives, opiates, psychotropic agents
Anorexia	Antibiotics, digoxin
Constipation	Opiates, iron supplements, diuretics
Diarrhea	Laxatives, antibiotics
Dysphagia	Potassium supplements, nonsteroidal anti-inflammatory agents (NSAIDs), bisphosphonates
Early satiety	Anticholinergic drugs, sympathomimetic agents
Impaired taste	Metronidazole, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), metformin
Increased energy expenditure	Thyroxine, ephedrine
Nausea and vomiting	Antibiotics, opiates, digoxin, theophylline, NSAID
Decreased splanchnic blood flow	Vasopressors

Table 3.4 Review of systems with nutritional implications[a]

General/constitutional
Average weight, weight loss or gain, general state of health, sense of well-being, ability to conduct usual activities, exercise tolerance (strength) (stamina) (endurance), weakness or fatigue
Skin
Pigmentation, moisture or dryness, texture, changes in hair growth or loss, nail changes, non-healing wounds, pressure ulcers
Eyes/ears/nose/mouth/throat
Vision, tooth decay, ill-fitting dentures, gingival bleeding, difficulty swallowing, altered taste (dysgeusia) and smell (parosmia), oral lesions (angular stomatitis, cheilitis, mucositis), problems eating
Gastrointestinal
Appetite, indigestion, abdominal pain, heartburn, nausea, vomiting, jaundice, constipation, or diarrhea, abnormal stools (clay colored, tarry, bloody, greasy, foul smelling), flatulence, recent changes in bowel habits
Musculoskeletal
Pain, swelling, limitation of motion, muscular weakness, decreased muscle mass, cramps
Neurologic/psychiatric
Anxiety, depression, paresthesia, gait disturbances, neuropathy
Allergic/immunologic/lymphatic/endocrine
Reactions to food

[a]Modified from [90]

Narcotic use induces anorexia, worsens gastroparesis and constipation, and leads to decreased feeding ability. Laxative use and antibiotics cause or exacerbate diarrhea. Certain foods and timing of meals can also alter the effect of specific drug therapy and should be taken into consideration [45].

Review of Systems

Symptoms elicited during the review of systems (ROS) (Table 3.4) can reflect both the presence of deficiencies and the risk for deficiencies for which further assessment is needed. It is a crucial component of the nutritional assessment, but often impossible, other than by proxy, in the critically ill patient. An effort should be made to obtain the nutrition-related ROS from family members and caregivers.

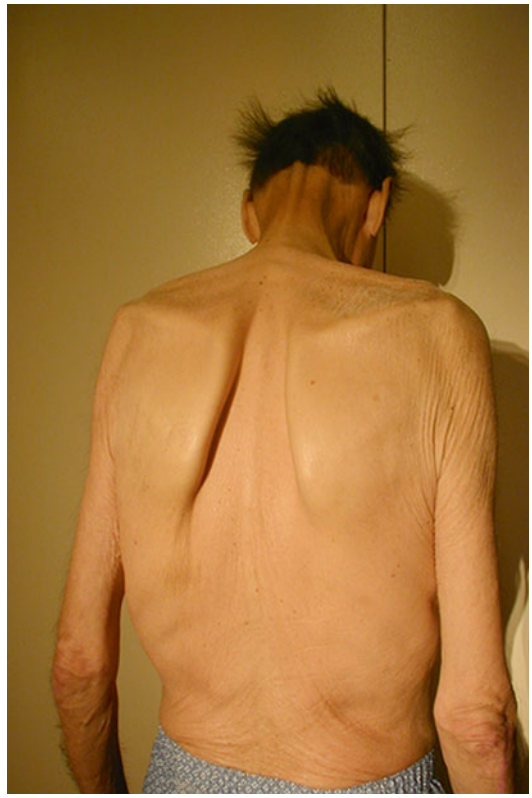


Fig. 3.1 Severe muscle and fat wasting. Photo courtesy of Betty Hagan, RN

Physical Examination

It is certainly important to discover and treat significant deficiencies and starvation in the critically ill. However, it is equally important to understand the body composition of these patients to better contextualize laboratory tests that are significantly impacted by such things as muscle mass. For example, the cachectic elderly patient with a creatinine that rises from 0.2 to 0.4 mg/dl may be in acute renal failure, despite the creatinine still being below normal.

The nutrition-focused components of the physical exam should be standard in any complete physical exam that is performed on any patient. These include an overall assessment for calorie balance and catabolism, as well as a search for signs of specific deficiencies.

There are multiple observations made at a glance, such as the presence of cachexia or morbid obesity. It is easy to recognize diminished body composition in an underweight frail patient who has lost either, or both, fat and muscle. Generalized muscle wasting, especially around the temples and triceps, as well as clavicular protrusion can be readily apparent on physical exam in these patients (Fig. 3.1). However, the loss of lean body mass (LBM), as occurs in the catabolic but adequately fed patient, may be obscured in the obese patient when the losses are predominantly muscular, the so-called obesity sarcopenia. Even fat loss may be difficult to identify in these patients when they are particularly obese. Careful examination of muscle size and tone by thorough palpation of such places as the upper arm and thigh may help discover muscle mass loss. Edema is a common physical finding in ICU patients that may also mask loss of LBM and weight.

The clinician should assess the patient's level of consciousness and ability to safely eat. For example, a patient with a recent traumatic head injury may not be able to protect the airway, increasing the risk for aspiration. Whether assessment of swallowing function diminishes the incidence of pneumonia remains controversial.

Examining the head and face will reveal numerous clues to nutritionally relevant disease or deficiency, for example icterus in the patient with underlying liver disease. Inspection of the patient's mouth may help in identification of deficiencies, but also the patient's ability to eat food or swallow. The examination includes assessment for the quality of dentition, cheilosis, angular stomatitis, glossitis, mucositis, thrush, and hydration.

The patient's hemodynamic status may impact the ability to feed, and should be included in the assessment. The presence of shock and level of vasopressors are of particular concern when considering enteral nutrition (see Chap. 4). Other critical illness-related concerns, which impact on the delivery of nourishment, include volume overload or restrictions, and the ease of enteral access or presence of mechanical ventilation.

Assessment of work of breathing (respiratory rate and volume) has been proposed as a component of the nutrition-related physical examination as it may be reflective of an increase in calorie consumption. However, increasing the calorie prescriptions to compensate may not be advisable as overfeeding increases CO_2 production, which may also increase work of respiration. The presence of noninvasive positive pressure ventilation is often thought to be a risk for aspiration due to gastric distension. Frequent venting of the feeding tube may attenuate this concern.

The abdominal exam is, of course, critical. Tenderness, guarding, or distention may preclude enteral feeding. The presence of all ostomies, drains, or feeding tube, and the presence and status of wounds must be noted and monitored. Other considerations related to enteral access are addressed in Chap. 5.

Assessment of the patient's extremities includes observing skin color and temperature, hair, presence of any lesions or ulcers as well as an exam of the nail beds. The clinician should take note of the more subtle features of the patient such as spoon-shaped nails; presence of lanugo; and hair growth, distribution, quality, and pigmentation. The clinician should be able to recognize the more common physical manifestations of nutrient deficiencies seen in patients with malnutrition. Representative examples are listed in Table 3.5.

Table 3.5 Clinical signs with nutritional implications and significance in physical examination

General	Obesity, edema, cachectic appearance
Skin	Rashes, xerosis, follicular hyperkeratosis (vitamin A), flaky dermatitis (niacin, riboflavin, zinc), pallor (iron), ecchymosis (vitamin K), venous ulcers or pressure sores, slow healing wounds, dryness, perifollicular petechiae (vitamin C)
Hair	Dyspigmentation, easy pluckability, thinning, straightness, lack of luster (protein)
Nails	Spoon shaped (iron), brittle, transverse lines (protein), splinter hemorrhages (vitamin C)
Head/neck	Temporal muscle wasting, parotid enlargement, goiter (iodine)
Eyes	Pale, dull conjunctiva, scleral xerosis, Bitot's spots, night blindness (vitamin A)
Mouth	Condition of teeth, edentulous, state of dentures, bleeding gums (vitamin C)
Lips	Cheilosis (riboflavin), angular stomatitis (riboflavin)
Tongue	Glossitis (B vitamins), edema, fissuring (niacin), atrophic lingual papillae
Abdomen	Abdominal distension, ascites, hepatomegaly
Extremities	Edema, subcutaneous fat excess or loss, ataxia
Neurological	Irritable, weakness, loss of deep tendon reflex, sensory loss, asterixis (B vitamins), tetany (calcium, magnesium)

The extremity exam also allows the clinician to assess the patient's muscle mass, strength and tone. Sarcopenia, the age-related loss of muscle without loss of fat, can occur in both normal and overweight patients and can further complicate recovery [46]. The critically ill patient may be bedridden for extended periods of time. Bed rest in healthy older adults contributes to loss of muscle mass and significant functional decline within 10–21 days [47], while these same consequences in sick hospitalized patients may occur with 5–7 days [48]. Coupled with the stress of illness and injury, critically ill patients are at risk for accelerated loss of LBM. Patients who suffer loss of muscle mass have an increased susceptibility for ICU-acquired weakness, persistent functional disability, and loss of independence [49, 50].

Pressure ulcers are associated with increased morbidity, mortality, and length of hospital stay [51]. While there are both intrinsic (age, mobility, hydration) and extrinsic (pressure or friction) factors that lead to the development of pressure ulcers, poor nutritional status and inadequate nutritional intake have a direct correlation with their development [52]. Banks et al. [53] found malnutrition associated with a high risk of having a pressure ulcer in an acute care setting and with stage and severity of pressure ulcers. As stated previously, the definitions of malnutrition tend to be self-referential in the acutely ill. Randomized controlled trials of nutritional intervention to prevent pressure ulcers have failed to demonstrate a benefit. Despite this, we believe that early and aggressive nutrition therapy may help minimize the development and severity of pressure ulcers.

Objective Tests in Nutritional Assessment

Laboratory Evaluation

Abnormal serum concentrations of essential nutrients can be due to dietary deficiency or poor absorption, but more often reflect redistribution, impaired transport, abnormal utilization, or a combination of any of these in the acutely ill. Choice and interpretation of nutrient levels is difficult, especially in the presence of inflammation.

In the critically ill patient, interpretation of serum protein concentrations has long been confused with reflecting adequacy of intake. There is a weak relationship or none at all between protein levels and intake [3]. Koretz [54] demonstrated the inability to predict the direction of change in serum protein levels, change in anthropometrics, weight loss, or clinical outcomes based on nutrition intervention. For all their lack of reliability, however, alterations in these biologic markers are useful in predicting patients at highest risk for complications and death.

Interpretation of serum albumin is affected by its long half-life, large body pool, intercompartmental fluid shifts due, usually, to inflammation, and the provision of exogenous albumin [55, 56]. Septic patients have significantly lower levels of retinol-binding protein (RBP) and transthyretin (prealbumin) than do non-septic patients [29]. Decreasing carrier protein levels lowers, for example, fat-soluble vitamin levels. But these lower levels may or may not have clinical relevance. As inflammation subsides, changes in RBP and transthyretin have been proposed to represent a rapid and persistent response to nutrition therapy [57–59]. This relationship, however, has been dismissed based on technical review [54]. Positive acute-phase reactants, such as C-reactive protein (CRP), help detect presence and resolution of an inflammatory state. CRP characteristically rises within hours after an acute stimulus and returns to near normal levels with resolution of systemic inflammation. Interpretation of transthyretin levels in conjunction with CRP in burn patients have been proposed as a means to distinguish an acute-phase effect from poor intake [60], but this is untested in prospective randomized trials. Given the lack of relationship between transthyretin and intake, this is unlikely to add anything to the assessment of adequacy of intake. A decrease in CRP of ≥50 mg/L in ICU patients predicts recovery [61]. Use of ratios, such as CRP to albumin and CRP to transthyretin, shows promise as more

sensitive predictors of overall outcome than any single protein parameter. However, there are no data correlating these ratios to nutrient intake [62, 63].

Cytokines have also been evaluated as markers of inflammation and predictors of mortality in the acute care setting. Interleukin 6 (IL-6), in particular, has been independently associated as a marker for malnutrition as defined by Subjective Global Assessment (SGA) [14], in patients with end-stage renal disease [64]. While cytokines are certainly reflective of systemic inflammation, and are used in the definition of malnutrition, they are not very useful in assessment of adequacy of nutrient intake.

Nitrogen balance studies have long been promoted as a means to estimate protein metabolic rates. The magnitude of nitrogen loss in critically ill patients reflects severity of illness or injury. Nutrition intervention alone does not ameliorate the characteristic negative nitrogen balance associated with the hypermetabolic response to injury. Impaired intake and poor absorption may further complicate estimation of protein requirements. Additionally, abnormal nitrogen losses from burn wound exudate, wound vacuum systems, fistulas, GI drains, diarrhea, and dialysis must be considered.

In his review, Stroud [65] points out that increasing protein intake in critically ill patients to achieve positive nitrogen balance has not proven to alter clinical outcomes. He further explains that although high nitrogen intake reduces net nitrogen losses, there are no studies to suggest doing so results in any clinical benefits and cautions it might do harm. Conversely, Hoffer and Bistrian [66] conducted a comprehensive systematic review of protein requirements in critical illness and concluded that high protein intake is safe and may be optimal for most critically ill patients except for those with refractory hypotension, overwhelming sepsis, or severe liver disease. Existing studies are flawed in design and are biased toward achieving positive nitrogen retention by delivering high-calorie diets. Measurement of urinary nitrogen and provision of a high protein intake remain the standard of care and are recommended by national guidelines [67]. However, these practices need further study.

Height, Weight, and Body Mass Index

The expansion of extracellular water in trauma and septic patients may mask loss of body cell mass in the initial days following injury. Anthropometric measurements are insensitive to acute changes, and are difficult to perform and interpret following fluid resuscitation, or when a patient has generalized edema or anasarca. Rapid changes in body weight are most reflective of alterations in total body water. In a study of ten critically injured and 12 severely septic patients over a 3–4-week period, Hill [68] documented a net accumulation of 4.73 and 12.5 L of total body water, respectively. Most of the changes in body weight could be accounted for by changes in extracellular water.

Height and actual body weight must be obtained on all patients admitted to the ICU. Measurement of both height and weight is important for calculating body surface area and body mass index (BMI), dosing of medications, and assessing renal function. Obtaining an accurate height on patients admitted to the ICU can be difficult, as patients are bedridden and use of a stadiometer is not feasible. While there is no standardized well-validated approach to measuring height in the critical care setting, acceptable alternatives include measurements of knee height, arm span length, and recumbent height for wheelchair-bound patients [69–71]. Self-reporting may be helpful if the patient is awake and alert, however patients frequently overestimate height and underestimate body weight [72]. Clinicians may be required to rely on family members, caregivers, or medical records to provide approximated height and weight history.

Despite the challenges in interpretation, weight is important, not only as part of the patient assessment, but as a baseline to determine trends that occur during hospitalization. Daily weights are recommended for most ICU patients. As most modern ICU beds have built in scales, this should be an easy measurement to obtain. It is our experience, however, that the quality of bed-scale measurements is highly operator dependent. Furthermore, it is difficult to control for the added weight of tubing and

equipment on the bed, particularly in patients on mechanical ventilators. Staff education on zeroing of the bed scale prior to admission, positioning of the bed and accounting for bed linens while weighing is mandatory. Documentation of unplanned weight loss of >2 % in 1 week, >5 % in 1 month, or >7.5 % in 3 months in the context of acute injury or illness are consensus diagnostic criteria for severe malnutrition [73].

Recognizing unintentional weight loss prior to admission to the acute care setting identifies patients at higher risk for postoperative complications. In an examination of nearly 900,000 surgical patients treated at 1368 hospitals, there was a two- to threefold risk of developing *Clostridium difficile* enterocolitis, surgical-site infection or pneumonia, and greater than a fivefold higher risk of developing mediastinitis after coronary artery bypass or catheter-associated urinary tract infection if malnutrition or weight loss were among the pre-existing conditions [74].

Body Composition Assessment

There are many quantitative methods to augment the physical examination for determining body composition. Most will report adipose mass, lean or fat-free mass, and bone mass. However, methods including underwater weighing, air displacement plethysmography, dual-energy X-ray absorptiometry (DEXA), in vivo neutron activation analysis, and isotope dilution are impractical in ICU patients and applicable only in research settings. There are, however, techniques that may be useful at the bedside to augment physical examination.

Bio-impedance analysis (BIA) estimates body composition by using the differences in the passage of an electrical current between lean tissue and fatty tissue. An electrical current is passed through parts of the body (arm to leg, across one limb or trunk). Lean tissue is less resistant to the passage of the electrical current than the fatty tissue. Fat-free mass can be estimated and subtracted from body weight to determine total body fat. Difference in impedance can be detected in intracellular and extracellular fluid compartments by using multiple frequencies so that determination of fluid distribution is possible. This method has been primarily studied and validated in healthy patients. A few studies show the effectiveness of BIA in surgical patients [75]. Of all the body composition techniques, it is most portable and least invasive—it is performed by placing electrodes on the hands and feet and running a low current out of a handheld meter. However there are no studies looking at the utility of BIA in the critically ill. It can be inferred by the nature of the test that those with edema, cachexia, obesity, and/or patients with ascites or requiring dialysis will not have reliable impedance measurements. Therefore, this method of body composition assessment may have very limited use in the critically ill.

Aside from body composition analysis, there are other procedures to assess functional status that are validated to predict outcome and are included in the nutritional assessment because of their crossover with muscle mass and inflammation. Handgrip strength (HGS) is one of these techniques. Guerra et al. [76] showed that when controlling for age, BMI, sex, and degree of illness, patient-generated SGA scores were associated with HGS and thus reinforced the value of HGS as a measure of risk. However, HGS may be difficult to assess in the critically ill due to sedation, impaired cognition, or paralysis. If a critically ill patient is able to participate, HGS is an easy way to assess strength and function and is a recommended monitoring technique [73].

There are also emerging applications for older diagnostic studies. For example, computed tomography (CT) or magnetic resonance (MRI) scans and ultrasounds can be employed to determine body composition. CT scans have been utilized to quantify skeletal muscle mass, visceral adipose tissue, and subcutaneous and intramuscular adipose tissue, and to monitor loss of tissue mass in critically ill patients [77]. The abundance of CT scans obtained on the critically ill could make these types of measurements routine in the assessment of body composition and functional status. For example, psoas muscle thickness has prognostic value in cirrhotic patients waiting for liver transplantation [78],

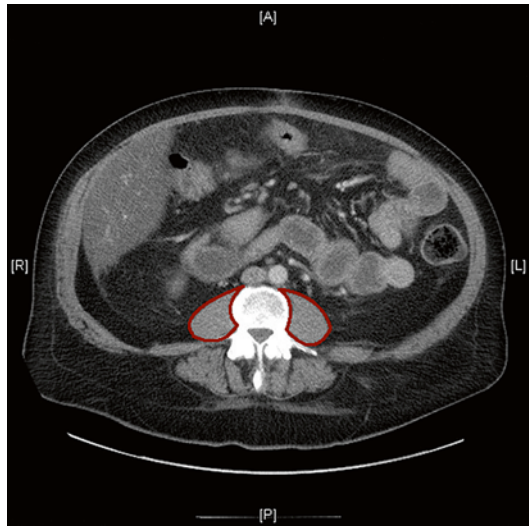


Fig. 3.2 Psoas muscle on CT imaging in a patient with malnutrition. Psoas muscle from CT imaging in a 60-year-old obese male who lost 25 kg over 6 months due to recurrent bowel obstruction and inability to eat. Body mass index changed from 46 to 38 kg/m^2. The *red* area denotes cross-sectional image of the left and right psoas at the level of the fourth lumbar vertebral body. Note, as well, the small size and heterogeneous appearance of the longissimus muscles due to replacement of muscle by fat.

patients undergoing abdominal aortic aneurysm repair [79], and critically ill mechanically ventilated adults [80]. Experienced clinicians can calculate the area of the psoas muscle or the psoas:lumbar vertebral index [81] from cross-sectional imaging (Fig. 3.2).

Ultrasound has also been validated for evaluating body composition, specifically fat mass [82]. Tillquist et al. [83] showed that an ultrasound could be easily used to measure the thickness of the quadriceps muscle in healthy individuals. This bedside technique might be practical in the future to identify the presence of skeletal muscle wasting among critically ill patients.

Energy Expenditure

Body composition is important to help determine energy requirements and interpret measures of energy expenditure. The major determinants of metabolic rate are (1) the amount of metabolically active tissue mass, (2) the effect of physical activity, (3) diet induced thermogenesis and (4) illness hypermetabolism. Together, these comprise the total daily energy consumption [84]. Indirect calorimetry (IC) is considered the gold-standard method for establishing energy expenditure in the clinical setting, and its use is recommended in guidelines, particularly for patients with severe malnutrition, obesity, or inflammatory states where there is less correlation between measured energy expenditure and commonly used predictive equations [67]. Prescribing calories based on IC has been studied as a method to improve clinical outcomes in comparison to other techniques; however, there are limited data in support of this recommendation [85]. By properly measuring energy expenditure, it is hoped that the sequelae of overfeeding, including hyperglycemia, metabolic disturbances, hypercarbia, longer mechanical ventilation, and liver dysfunction, may be avoided. In the absence of IC, variations of the Penn State Equation are recommended for critically ill mechanically ventilated adults [84, 86]. Another common approach for estimating energy requirements is to use 25–30 kcal/kg/day for normal weight adults and 11–14 kcal/kg for critically ill obese patients [67].

Conclusion

We admit patients to the ICU with everything from starvation to obesity. Many ICU patients are hypermetabolic. All need to be fed. But their diseases range from simple postoperative care to full-blown multiple organ failure. Assessing this very diverse group of patients requires an organized approach. Patients are admitted to ICUs with underlying malnutrition, made worse by acute inflammation, hemodynamic instability, marked catabolism, and alterations in energy expenditure and negative nitrogen balance. It is vital to obtain as much information as possible from the medical history, review of symptoms, physical examination, and diagnostic studies. The number of days prior to initiation of nourishment and actual intake from food, EN, or PN are especially important. Finally, the nutritional assessment should be updated daily during critical care team rounds.

Malnutrition in the critically ill correlates highly with adverse clinical outcomes, hospital length of stay, readmission rates, morbidity, mortality, and health care costs [74, 87]. Although up to 50 % of patients presenting to acute care centers have malnutrition [17], clinicians correctly document it only occasionally. Early identification and diagnosis of malnutrition helps to ensure that individualized nutritional goals are met and sustained throughout the patient's entire hospitalization. As has been noted, "nutrition therapy is a marathon and not a sprint" [88]. Adequate energy and nutrient intake is important not only in the ICU, but during recovery and rehabilitation. Ongoing assessment of nutrition adequacy should continue throughout hospitalization, and be included in discharge plans [89].

References

1. Gray GE, Gray LK. Anthropometric measurements and their interpretations: principles, practices and problems. J Am Diet Assoc. 1980;77:534–9.
2. Jensen GL, Wheeler D. A new approach to defining and diagnosing malnutrition in adult critical illness. Curr Opin Crit Care. 2012;18:206–11.
3. Seres DS. Surrogate nutrition markers, malnutrition, and adequacy of nutrition support. Nutr Clin Pract. 2005;20:308–13.
4. Heyland DK, Dhaliwal R, Jian X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care. 2011;15:R 268–80.
5. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. Nutrition. 1999;15:458–64.
6. Stratton RJ, King CL, Stroud MA, Jackson AA, Elia M. Malnutrition Universal Screening Tool predicts mortality and length of hospital stay in acutely ill elderly. Br J Nutr. 2006;95:325–30.
7. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci. 2001;56A:M366–77.
8. Vellas B, Villars H, Abelian G, Soto ME, Rolland Y, Guigoz Y, et al. Overview of the MNA-its history and challenges. J Nutr Health Aging. 2006;10:456–65.
9. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the mini nutritional assessment short form (MNA-SF): a practical tool for identification of nutritional status. J Nutr Health Aging. 2009;13:782–8.
10. Perioperative total parenteral nutrition in surgical patients: The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med. 1991;325:525–32.
11. Aziz EF, Javed F, Pratap B, Musat D, Nader A, Pulimi S, et al. Malnutrition as assessed by nutritional risk index is associated with worse outcome in patients admitted with acute decompensated heart failure: an ACAP-HF data analysis. Heart Int. 2011;632:3–8.
12. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22:321–36.
13. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22:415–21.
14. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewall J, et al. Nutritional assessment: a comparison of clinical judgment and objective measurements. N Engl J Med. 1982;16:969–72.

15. Sheean PM, Peterson SJ, Gurka DP, Braunschweig CA. Nutrition assessment: the reproducibility of SGA in patients requiring mechanical ventilation. Eur J Clin Nutr. 2010;64:1358–64.
16. Skipper A, Ferguson M, Thompson K, Castellanos VH, Porcari J. Nutrition screening tools – an analysis of the evidence. JPEN J Parenter Enteral Nutr. 2012;35:292–8.
17. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr. 2008;27:5–15.
18. U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. Statistics on hospital stays, 2009. http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed 6 Mar 2014.
19. Morgan LM, Dickerson RN, Alexander KH, Brown RO, Minard G. Factors causing interrupted delivery of enteral nutrition in trauma intensive care units. Nutr Clin Pract. 2004;19:511–7.
20. Majercik S, Kinikini M, White T. Enteroatmospheric fistula: from soup to nuts. Nutr Clin Pract. 2012;27:507–12.
21. Cheatham ML, Safcsak K, Brzezinski SJ, et al. Nitrogen balance, protein loss, and the open abdomen. Crit Care Med. 2007;35:127–31.
22. Mirtallo JM, Forbes A, McClave SA, Jensen GL, Waitzberg DL, Davies AR. International consensus guidelines for nutrition therapy in pancreatitis. JPEN J Parenter Enteral Nutr. 2012;36:284–91.
23. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. Lancet. 2004;363:1895–902.
24. Jacobs DG, Jacobs DO, Kudsk KA, Moore FA, Oswannski MF, Poole VG, et al. Practice management guidelines for nutritional support of the trauma patient. J Trauma. 2004;57:660–79.
25. Shields BA, Doty KA, Chung KK, Wade CE, Aden JK, Wolf SE. Determination of resting energy expenditure after severe burn. J Burn Care Res. 2013;34:e22–8.
26. Newsome TW, Mason AD, Pruitt BA. Weight loss following thermal injury. Ann Surg. 1973;178(2):215–7.
27. Ward EC, Uriarte M, Sppath B, Conroy AL, Sppatht B. Duration of dysphagic symptoms and swallowing outcomes after thermal burn injury. J Burn Care Rehabil. 2001;22:441–53.
28. DuBose CM, Groher MG, Mann GC, Mozingo DW. Pattern of dysphagia recovery after thermal burn injury. J Burn Care Rehabil. 2005;26:233–7.
29. Boles JM, Garre MA, Youinou PY, Mialon P, Menez JF, Jouquan J, et al. Nutritional status in intensive care patients: evaluation in 84 unselected patients. Crit Care Med. 1983;11:87–90.
30. Zielske J, Bohne S, Brunkhorst FM, Axer H, Guntinas-Lichius O. Acute and long-term dysphagia in critically ill patients with severe sepsis: results of a prospective controlled observational study. Eur Arch Otorhinolaryngol. 2014. doi:10.1007/s00405-014-3148-6. 27 June.
31. Peterson SJ, Tsai AA, Scala CM, Sowa DC, Sheean PM, Braunschweig CL. Adequacy of oral intake in critically ill patients 1 week after extubation. J Am Diet Assoc. 2010;110:427–33.
32. Heyland DK, Schroter-Noppe D, Drover JW, Jain M, Keefe L, Dhaliwal R, et al. Nutrition support in the critical care setting: current practice in Canadian ICUs—opportunities for improvement? JPEN J Parenter Enteral Nutr. 2003;27:74–83.
33. Drover JW, Cahill NE, Kutsogiannis J, Pagliarello G, Wischmeyer P, Wang M, et al. Nutrition therapy for the critically ill surgical patient. We need to do better! JPEN J Parenter Enteral Nutr. 2010;34:644–52.
34. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, et al. Calorie intake and patient outcomes in severe acute kidney injury: findings from the randomized evaluation of normal vs. augmented level of replacement therapy (RENAL) study trial. Crit Care. 2014;18:R45. doi:10.1186/cc13767.
35. Elke G, Wang M, Weiler N, Day AG, Heyland DK. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care. 2014;18:R29. doi:10.1186/cc13720.
36. 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;27:702–13.
37. Cahill NE, Murch L, Cook D, Heyland DK. Barriers to feeding critically ill patients: a multicenter survey of critical care nurses. J Crit Care. 2012;27(6):72–34.
38. Gungabissoon U, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr. 2014. doi:10.1177/0148607114526450. March 17.
39. Norred CL. A follow-up survey of the use of complementary and alternative medicines by surgical patients. AANA J. 2002;70:119–25.
40. Gulla J, Singer AJ. Use of alternative therapies among emergency department patients. Ann Emerg Med. 2000;35:226–8.
41. Robinson A, McGrail MR. Disclosure of CAM use to medical practitioners: a review of qualitative and quantitative studies. Complement Ther Med. 2004;12:90–8.
42. Stanger MJ, Thompson LA, Young AJ, Lieberman HR. Anticoagulant activity of selected dietary supplements. Nutr Rev. 2012;70:107–17.
43. Insogna KL. The effect of proton pump-inhibiting drugs on mineral metabolism. Am J Gastroenterol. 2009;104:S2–4.

44. Visvanathan R, Newbury JW, Chapman I. Malnutrition in older people-screening and management strategies. Aust Fam Physician. 2004;33:799–805.
45. White R. Drugs and nutrition: how side effects can influence nutritional intake. Proc Nutr Soc. 2010;69:558–64.
46. Jeejeebhoy KN. Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. Curr Opin Clin Nutr Metab Care. 2012;15:213–9.
47. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA. 2007;297:1769–74.
48. Puthucheary Z, Harridge S, Hart N. Skeletal muscle dysfunction in critical care: wasting, weakness, and rehabilitation strategies. Crit Care Med. 2010;38(Suppl):S676–82.
49. DeJonghe B, Bastuji-Garin S, Durand M-C, Malissin I, Rodrigues P, Cerf C, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med. 2007;35:2007–15.
50. Ali NA, O'Brien JM, Hoffmann SP, Phillips G, Garland A, Finley JCW, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med. 2008;178:261–8.
51. Redelings MD, Lee NE, Sorvillo F. Pressure ulcers: more lethal than we thought? Adv Skin Wound Care. 2005;18:367–72.
52. Ek AC, Unosson M, Larsson J, Von Schenck H, Bjurulf P. The development and healing of pressure ulcers related to the nutritional state. Clin Nutr. 1991;10:245–50.
53. Banks M, Bauer J, Graves N, Ash S. Malnutrition and pressure ulcer risk in adults in Australian health care facilities. Nutrition. 2010;26:896–901.
54. Koretz RL. Death, morbidity and economics are the only end points for trials. Proc Nutr Soc. 2005;64:277–84.
55. Rothschild MA, Oratz M, Schreiber SS. Albumin synthesis. N Engl J Med. 1972;286:748–57.
56. Carpentier YA, Bruyns J, Barthel J. Plasma protein concentration in nutritional assessment. Proc Nutr Soc. 1972;41:405–17.
57. Winkler MF, Gerrior SA, Pomp A, Albina JE. Use of retinol binding protein and prealbumin as indicators of the response to nutrition therapy. J Am Diet Assoc. 1989;89:684–7.
58. Tuten MB, Wogt S, Dasse F, Leider Z. Utilization of prealbumin as a nutritional parameter. JPEN J Parenter Enteral Nutr. 1984;9:709–11.
59. Vanlandingham S, Spiekerman AM, Newmark SR. Prealbumin: a parameter of visceral protein levels during albumin infusion. JPEN J Parenter Enteral Nutr. 1982;6:230–1.
60. Prelack K, Dylewski M, Sheridan RL. Practical guidelines for nutritional management of burn injury and recovery. Burns. 2007;33:14–24.
61. Reny J-L, Vuagnat A, Ract C, Benoit M-O, Safar M, Fagon J-Y. Diagnosis and follow-up of infections in intensive care patients: value of C-reactive protein compared with other clinical and biological variables. Crit Care Med. 2002;30:529–35.
62. Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8:359321. 10/1371/journal.pone.0059321. Epub 2013 Mar 12.
63. Xie Q, Zhou Y, Xu Z, Yang Y, Kuang D, You H, et al. The ratio of CRP to prealbumin levels predict mortality in patients with hospital-acquired acute kidney injury. BMC Nephrol. 2011. doi:10.1186/1471-2369-12-30. June 29.
64. Honda H, Qureshi AR, Heimburger O, Barany P, Wang K, Pecoits-Filho R, et al. Serum albumin, c-reactive protein, interleukin 6, and fetuin A as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis. 2006;47:139–48.
65. Stroud M. Protein and the critically ill; do we know what to give? Proc Nutr Soc. 2007;66:378–83.
66. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr. 2012;96:591–600.
67. McClave SA, Martindale RG, Vanek VW, Roberts P, Taylor B, Ochoa JB, 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.
68. Hill GL. Implications of critical illness, injury, and sepsis on lean body mass and nutritional needs. Nutrition. 1998;14:557–8.
69. Chumlea WC, Roche AF, Steinbaugh ML. Estimating stature from knee height for persons 60 to 90 years of age. J Am Geriatr Soc. 1985;33:116–20.
70. Brown JK, Feng JY, Knapp TR. Is self-reported height or arm span a more accurate alternative measure of height? Clin Nurs Res. 2002;11:417–32.
71. Froehlich-Grobe K, Nary DE, Van Sciver A, Lee J, Little TD. Measuring height without a stadiometer: empirical investigation of four height estimates among wheelchair users. Am J Phys Med Rehabil. 2011;90:658–66.
72. Haverkort EB, de Haan RJ, Binnekade JM, van Bokhorst-de van der Schueren MAE. Self-reporting of height and weight: valid and reliable identification of malnutrition in preoperative patients. Am J Surg. 2012;203:700–7.

73. White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy Malnutrition Work Group, et al. 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;36:275–83.
74. Fry DE, Pine M, Jones BL, Meimban RJ. Patient characteristics and the occurrence of never events. Arch Surg. 2010;145:148–51.
75. Hannan WJ, Cowen SJ, Plester C, Fearon KCH. Proximal and distal measurements of extracellular and total body water by multi-frequency bio-impedance analysis in surgical patients. Appl Radiat Isot. 1998;49:621–2.
76. Guerra RS, Fonseca I, Pichel F, Restivo MT, Amaral TF. Handgrip strength and associated factors in hospitalized patients. JPEN J Parenter Enteral Nutr. 2013;39(3):322–30.
77. Braunschweig CA, Sheean PM, Peterson SJ, Perez SG, Freels S, Troy KL, et al. Exploitation of diagnostic computed tomography scans to assess the impact of nutritional support on body composition changes in respiratory failure patients. JPEN J Parenter Enteral Nutr. 2014;38(7):880-85.
78. Durand F, Buyse S, Francoz C, Laouenan C, Bruno O, Beighiti J, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. J Hepatol. 2014;60:1151–7.
79. Lee JS-J, He K, Harbaugh CM, Schaubel DE, Sonnenday CJ, Wang SG, et al. Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. J Vasc Surg. 2011;53:912–7.
80. Weijs PJ, Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. Crit Care. 2014;18:R12. doi:10.1186/cc13189.
81. Ebbeling L, Grabo DJ, Shashaty M, Dua R, Sonnad SS, Sims CA, et al. Psoas:lumbar vertebra index: central sarcopenia independently predicts morbidity in elderly trauma patients. Eur J Trauma Emerg Surg. 2014;40:57–65.
82. Pineau JC, Guihard-Costa AM, Bocquet M. Validation of ultrasound techniques applied to body fat measurement. A comparison between ultrasound techniques, air displacement plethysmography and bioelectrical impedance vs. dual-energy X-ray absorptiometry. Ann Nutr Metab. 2007;51:421–7.
83. Tillquist M, Kutsogiannis DJ, Wischmeyer PE, Kummerlen C, Leung R, Stollery D, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. JPEN J Parenter Enteral Nutr. 2014; 38(7):886-90.
84. Frankenfield DC, Ashcraft CM. Estimating energy needs in nutrition support patients. JPEN J Parenter Enteral Nutr. 2011;35:563–70.
85. Dhaliwal R, Cahill N, Lemieux M, Heyland DK. The Canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. Nutr Clin Pract. 2014;29:29–43.
86. 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.
87. Mogensen K, Christopher K. The association of malnutrition and 30-day post discharge hospital readmission in ICU survivors: a registry based cohort study. SCCM 2013; Abstract 54.
88. Braunschweig CA, Sheean PM, Peterson SJ. Examining the role of nutrition support and outcomes for hospitalized patients: putting nutrition back in the study design. J Am Diet Assoc. 2010;110:1646–9.
89. Tappenden KA, Quatrara B, Parkhurst ML, Malone AM, Fanjian G, Ziegler TR. Critical role of nutrition in improving quality of care: an interdisciplinary call to action to address adult hospital malnutrition. JPEN J Parenter Enteral Nutr. 2013;37:482–97.
90. Hark L, Morrison G. Medical nutrition and disease: a case based approach. 4th ed. Hoboken, NJ: John Wiley & Sons; 2009.

Chapter 4
Timing and Indications for Enteral Nutrition in the Critically Ill

Philippa T. Heighes, Gordon S. Doig, and Fiona Simpson

Keywords Enteral nutrition • Enteral feeding • Enteral timing • Enteral indications • Nutrition support • Intensive care • Critical illness

Key Points

- Enteral nutrition should be commenced within the first 24 h of admission to an ICU.
- The provision of early enteral nutrition has been shown to reduce mortality, reduce gut dysfunction, prevent ventilator associated pneumonia and shorten the duration of mechanical ventilation and ICU stay.
- Early enteral nutrition is indicated in all patients who are likely to require ICU care for longer than 2 days.
- Enteral nutrition may be initiated as soon as shock is stabilised:
  - Shock Index ≤1 for at least 1 h (heart rate ÷ systolic blood pressure = Shock Index)
- Studies consistently fail to document harmful effects arising from early enteral nutrition.

Introduction

Up to 50 % of critically ill patients have malnutrition at the time of their admission to the intensive care unit (ICU) [1–3], with an additional 38 % at risk of developing malnutrition by the time they are discharged [4]. It has long been recognised that malnutrition in critical illness is associated with decreased immune function, an increased risk of nosocomial infections, impaired respiratory function and an increased risk of death [5].

P.T. Heighes, MNE • G.S. Doig, PhD (✉) • F. Simpson, MND
Intensive Care Research Unit, Northern Clinical School, Royal North Shore Hospital, University of Sydney, Pacific Highway, St. Leonards NSW 2065, Australia
e-mail: gdoig@med.usyd.edu.au

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_4,

Despite relatively uniform recommendations on the appropriate timing of enteral nutrition (EN) in the ICU from professional societies internationally, there is widespread variation and inconsistency in practice around the world. All major clinical practice guidelines recommend starting nutrition support soon after admission to an ICU [6–11]. The provision of nutrition support to critically ill patients has been recognised as a standard of care and a basic human right [12].

A large international survey of nutrition practices demonstrated that 35 % of ICU patients remain unfed for 2 or more days after admission to the ICU [13]. Other studies report that up to 25 % of ICU patients who should be fed are *never* fed during their ICU stay [6]. The purpose of this chapter is to summarise the evidence related to the timing of initiation and indications for enteral nutrition in the ICU.

Benefits of Early Enteral Nutrition

International evidence-based nutrition guidelines recommend the initiation of early EN in critically ill patients. The European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines on Enteral Nutrition in Intensive Care [8] state "EN should be given to all ICU patients who are not expected to be taking a full oral diet within 3 days. It should have begun during the first 24 h" (Grade C). The Australian and New Zealand (ANZ) Nutrition Guidelines (Grade B+) [7], the Canadian Clinical Practice Guidelines (not graded) [10], and the joint American Society for Parenteral and Enteral Nutrition (ASPEN) and Society for Critical Care Medicine (SCCM) Guidelines for the Provision and Assessment of Nutrition Support (level C) [14] also all recommend early EN in critically ill patients. See Table 4.1 for a summary of these clinical recommendations.

The initiation of EN early in the care of critically ill patients is possible. For example, in clinical trials involving major trauma patients, feeding was commenced "immediately after resuscitation", with an average time from ICU admission to commencement of EN of approximately 4 h [15, 16]. Likewise in a clinical trial involving patients with major burns of 25–60 % total body surface area (TBSA), where feeding was commenced "immediately after hospitalisation," a 4-h time frame from admission to initiation of EN was achieved [17]. In a large observational study of nutritional practices from around the world, top-performing ICUs demonstrated their ability to consistently deliver EN soon after admission, with four of the top ten hospitals able to provide enteral nutrition to *95 % of their patients* within 48 h of admission to the ICU [13]. These studies serve to reinforce that, even in the demanding and complex critically ill patient, the early delivery of EN can be achieved.

Furthermore, results from clinical trials and meta-analyses provide strong evidence that patients benefit from the early provision of EN: The delivery of early EN has been found to significantly reduce mortality. In 2009 Doig et al. [18] conducted a rigorous literature search to identify

Table 4.1 Summary of recommendations regarding early EN from international guidelines

International guideline	Recommendation
ESPEN Guidelines on Enteral Nutrition [8]	EN should be given to all ICU patients who are not expected to be taking a full oral diet within 3 days. It should have begun during the first 24 h using a standard polymeric formula
Australian and New Zealand Nutrition Guidelines [7]	At ICU admission if patient not expected to be tolerating adequate oral intake within next day commence EN within 24 h
ACCEPT Nutrition Guidelines [9]	At ICU admission if patient not expected to be tolerating adequate oral intake within next day commence EN within 24 h
Canadian Clinical Practice Guidelines [10]	We recommend the use of a standard polymeric enteral formula that is initiated within 24–48 h after admission to ICU
SCCM/ ASPEN Guidelines [14]	In critically ill adults expected to stay > 2 or 3 days, EN should be started early within the first 24–48 h following admission

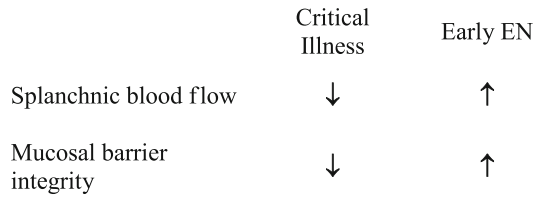


Fig. 4.1 Physiological effects of critical illness and early EN on the gut

methodologically sound randomised controlled trials (RCTs) free of major flaws (failure to maintain allocation concealment and excessive loss to follow-up >10 %) that addressed the question of timing of initiation of EN in critically ill patients. Trials included in the systematic review were conducted in diverse groups of critically ill ICU patients: patients with major burns of 25–60 % TBSA; severe pancreatitis and peritonitis; major trauma with Injury Severity Score (ISS) >20 and mixed medical/surgical ICU patients. When all reported mortality events were pooled from all trials, the primary meta-analysis demonstrated a statistically significant reduction in mortality of 10 % ($P=0.02$) when EN was initiated early, within 24 h of ICU admission or injury [18].

Alongside a reduction in mortality, other important clinical benefits have also been reported. The provision of early EN led to a statistically significant reduction in the incidence of ventilator-acquired pneumonia (VAP) by 27 % ($p=0.01$) [18]. The delivery of nutrients via the enteral route is known to have positive effects on splanchnic blood flow (Fig. 4.1), maintaining the functional integrity of the gastrointestinal tract and supporting the natural immune function of the gut, an important defence mechanism for the critically ill [19, 20]. Maintenance of gut immune function, combined with a reduction in gut dysfunction and aspiration, could explain the associated reduction in VAP. Strong trends towards reduced need for mechanical ventilation and reduced ICU stay [21] are also consistent with the physiological benefits arising from providing nutrients to the gut.

Furthermore, these improved outcomes result in a reduction in the overall costs of care. A recently published full economic analyses considered the costs of providing extra days of EN and costed the reductions in healthcare resource consumption arising from fewer days of mechanical ventilation and earlier ICU discharge. The analyses demonstrated that the provision of early EN, within 24 h of ICU admission, significantly reduced overall hospital costs by US$14,462 (95 % CI $5,464–$23,669) for each patient who received early EN [21].

ICU patients are not the only patient groups to show benefits from receiving early EN. Meta-analyses of clinical trials conducted in patients undergoing major elective intestinal surgery demonstrated statistically significant mortality reductions attributable to early feeding [22]. Technical review of clinical trials conducted in acutely ill patients who required care on the hospital ward reported early EN significantly reduced infectious complications [23]. Early feeding also resulted in significantly reduced length of hospital stay in both of these groups of patients [22, 23]. Finally, it is important to note that a systematic overview of all reviews of clinical trials of early EN failed to find any evidence of harm documented in any patient group [24].

Indications for Early Enteral Nutrition (<24 h from ICU Admission)

The Australian and New Zealand guideline for nutrition support in critical illness recommends that early EN is indicated in all critically ill patients who are expected to remain in the ICU at least 2 days and are not expected to commence an oral diet within 2 days of ICU admission [6, 7, 25]. The ESPEN guidelines also make broad recommendations for EN within 24 h of ICU admission, stating that early EN is indicated in "all ICU patients who are not expected to be taking a full oral diet within 3 days" [8]. In Canada,

a large-scale cluster-randomised controlled trial involving 499 critically ill patients from 14 different hospitals evaluated the effects of implementing these broad recommendations and demonstrated a significant reduction in mortality with the initiation of EN within 24 h of ICU admission [9].

Enteral Formula Choice

There are a large number of commercial enteral nutrition formulas available for use in adult ICUs around the world. Most commercial formulas are lactose and often gluten free, and all contain added vitamins, minerals and trace elements. The ideal combination of protein, carbohydrate and lipid for the critically ill patient remains unknown. As such we therefore recommend any standard formula as the first choice for the majority of patients in the ICU, thus encouraging EN to commence early (see Chap. 10).

Absolute Contraindications to Early Enteral Nutrition

There is general agreement in the literature over only two *absolute* contraindications to early EN: (1) Current active treatment for gastrointestinal (GI) obstruction and (2) multiple sequential surgical procedures scheduled at time of initial ICU admission, with less than 12 h between each procedure [26, 27].

Overcoming Common Barriers to Early Enteral Nutrition

Clinical Shock/Haemodynamic Instability

EN can be commenced as soon as shock is *stable*. Unstable shock is a life-threatening condition requiring immediate medical treatment and can lead to multiple organ damage and death. Clinical trials involving major trauma patients have provided a clear working definition of stable shock, that is, Shock Index ≤ 1 for at least 1 h (heart rate ÷ systolic blood pressure = Shock Index). This definition of stable shock does not require the patient to be weaned off vasoactive drugs or for lactates to be returned to normal. Using this definition, clinical trials were able to safely commence early EN an average of 9–10 h after major trauma or 4–5 h after ICU admission [15, 16].

Clinicians often express concern regarding the delivery of early EN to critically ill patients with shock states requiring treatment with vasopressors (i.e. systolic blood pressure <90 mmHg not responsive to fluid bolus). A large systematic review evaluating early EN in critically ill patients requiring vasopressors demonstrated that early EN was well tolerated in this patient group [28]. Furthermore, a prospective review of 1174 mechanically ventilated patients treated with vasopressors found a beneficial mortality effect of early feeding, which was in fact more evident in the sickest patients being treated with multiple vasopressors [29].

The use of vasopressors to treat systemic shock results in blood flow being shunted away from the gut, and some clinicians express concern that providing nutrients to an under-perfused gastrointestinal tract may lead to an increased risk of non-occlusive mesenteric ischemia or non-occlusive bowel necrosis. Interestingly, a major review of all available evidence failed to demonstrate any relationship

between delivering enteral nutrition and subsequent increased risk of non-occlusive mesenteric ischemia or non-occlusive bowel necrosis [28]. Indeed, current evidence suggests that splanchnic blood flow *increases* in response to intestinal delivery of nutrients in the critically ill patient [30, 31]. Thus, the delivery of early EN may actually protect the gut from early ischemia-reperfusion injuries related to shock and major surgery.

Waiting for Bowel Sounds, Passage of Flatus or Stool

Major clinical practice guidelines make strong recommendations *against* waiting for bowel sounds, passage of flatus or stool prior to starting EN in critically ill patients [14]. The presence or absence of bowel sounds does not correlate with subsequent bowel function. Despite a historical reliance on the presence of bowel sounds being used as an indicator that it is "safe" to feed patients, clinical studies demonstrate that EN commenced before the return of bowel sounds may actually decrease subsequent GI dysfunction in the medical or surgical ICU patient [32]. Furthermore, clinical trials conducted in patients undergoing gastrointestinal surgery demonstrate that early EN commenced well before the return of bowel sounds results in a significant mortality reduction and found no evidence to support keeping patients nil by mouth after gastrointestinal surgery until the return of bowel sounds [22].

Gastric Residual Volume Assessed Before Starting EN

High gastric residual volumes (GRV) do not predict subsequent aspiration or aspiration related pneumonitis [33]. No major clinical practice guideline recommends checking GRVs before commencing EN. Large cluster randomised trials, conducted to evaluate both the Canadian Guideline and the Australian and New Zealand Guideline, demonstrate not checking GRVs before commencing EN is safe [6, 9, 34].

Furthermore, a major clinical trial has demonstrated that after EN is commenced, accepting GRVs as high as 500 ml is safe [35], with a more recent clinical trial reporting no increase in the incidence of aspiration or other related complications when GRVs were never measured [36]. This challenges the traditional belief that regular GRV monitoring may prevent or reduce the incidence of complications such as VAP in patients receiving EN. In fact, studies suggest that there is no clear correlation between increased GRV, vomiting, aspiration events and VAP [33, 36].

Patients Managed with an Open Abdomen After Major Surgery

A recent large observational study of 597 patients with open abdomen after surgery for major trauma suggests that these patients benefit from early EN. After appropriate statistical control for severity of illness, patients who received EN before the first attempt at abdominal closure experienced: significantly reduced times to definitive fascial closure; a significant reduction in other major complications and a significant reduction in mortality [37]. Although there are no randomised controlled trials with a focus on this patient group, the promising results of this large observational study demonstrate that early EN is safe, and that potential benefits are meaningful to patients.

Considerations for Practice: Preparing to Commence Enteral Nutrition

Obtain Enteral Access

The nasogastric route is usually the first choice of access device for commencement of EN. Delays in commencement of feeding can be avoided by the routine placement of nasogastric tubes in most patients in conjunction with artificial airway insertion. Tube position *must* be confirmed with a chest X-ray prior to commencement of feeding. Complications, such as incorrect tube positioning in the lung, may cause significant harm. Alternative measures, such as testing of the pH of a sample of aspirate from the tube and auscultation over the epigastrium of air injected through the NG tube can be misleading and should not be considered as a definitive method of confirming tube position. In patients with base of skull or severe facial fractures, nasogastric tubes are contraindicated and other feeding tube placement options should be considered. Orogastric tubes are frequently used as an early first choice because nasogastric tube insertion may lead to intracranial placement.

Other feeding tube types such as nasojejunal tubes, surgically or endoscopically placed gastrostomy and jejunostomy tubes are reasonable alternatives depending on clinical need.

Implement a Guideline

An evidence-based guideline (EBG) is a systematically developed document that provides guidance and support in clinical decision making for specific clinical circumstances based upon recommendations for interventions with proven clinical benefits [38]. The active implementation of an evidence based nutritional support guideline can overcome barriers to practice change [39], resulting in improvements in the provision of nutritional support [6] that can translate to improved patient outcomes [9]. Guideline implementation and practice change processes should involve multiple interventions including education, timely audit and feedback and reminders [6].

A simple guideline should contain focused recommendations for a broad indication promoting the commencement of EN within 24 h of ICU admission. Placing posters around your ICU to promote knowledge of the benefits of the early initiation of feeding is a useful initial step to engage clinicians and raise awareness. The delivery of regular in-services, along with audit and feedback of current performance, is also useful strategies in overcoming barriers to practice change [39].

Conclusion

Early EN is indicated in all patients who are likely to require ICU care for longer than 2 days and should be commenced within the first 24 h of admission to an ICU. The provision of early EN has been shown to reduce mortality, reduce gut dysfunction, prevent ventilator associated pneumonia and shorten the duration of mechanical ventilation and ICU stay. Studies consistently fail to document any harmful effects arising from early EN.

References

1. Sungurtekin H, Sungurtekin U, Oner O, Okke D. Nutrition assessment in critically ill patients. Nutr Clin Pract. 2008;23(6):635–41.

2. Sheean PM, Peterson SJ, Chen Y, Liu D, Lateef O, Braunschweig CA. Utilizing multiple methods to classify malnutrition among elderly patients admitted to the medical and surgical intensive care units (ICU). Clin Nutr. 2013;32(5):752–7.
3. Fontes D, Generoso SV, Toulson Davisson Correia MI. Subjective global assessment: a reliable nutritional assessment tool to predict outcomes in critically ill patients. Clin Nutr. 2014;33(2):291–5.
4. 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.
5. 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.
6. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA. 2008;300(23):2731–41.
7. Doig GS, Simpson F. Evidence-based guidelines for nutritional support of the critically ill: results of a bi-national guideline development conference. Evidence based decision making website 2005. Accessed 20 May 2014 from http://www.evidencebased.net/files/EBGforNutSupportofICUpts.pdf.
8. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25(2):210–23.
9. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). CMAJ. 2004;170(2):197–204.
10. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27(5):355–73.
11. 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.
12. Kondrup J. Proper hospital nutrition as a human right. Clin Nutr. 2004;23(2):135–7.
13. Heyland DK, Heyland RD, Cahill NE, Dhaliwal R, Day AG, Jiang X, et al. Creating a culture of clinical excellence in critical care nutrition: the 2008 “Best of the Best” award. JPEN J Parenter Enteral Nutr. 2010;34(6):707–15.
14. 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.
15. Kompan L, Kremzar B, Gadzijev E, Prosek M. Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. Intensive Care Med. 1999;25(2):157–61.
16. Kompan L, Vidmar G, Spindler-Vesel A, Pecar J. Is early enteral nutrition a risk factor for gastric intolerance and pneumonia? Clin Nutr. 2004;23(4):527–32.
17. Chiarelli A, Enzi G, Casadei A, Baggio B, Valerio A, Mazzoleni F. Very early nutrition supplementation in burned patients. Am J Clin Nutr. 1990;51(6):1035–9.
18. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 hours of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med. 2009;35(12):2018–27.
19. 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.
20. Correia MI, da Silva RG. The impact of early nutrition on metabolic response and postoperative ileus. Curr Opin Clin Nutr Metab Care. 2004;7(5):577–83.
21. Doig GS, Chevrou-Severac H, Simpson F. Early enteral nutrition in critical illness: a full economic analysis using US costs. Clinicoecon Outcomes Res. 2013;5:429–36.
22. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. J Gastrointest Surg. 2009;13:569–75.
23. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29(12):2264–70.
24. Heighes PT, Doig GS, Sweetman EA, Simpson F. An overview of evidence from systematic reviews evaluating early enteral nutrition in critically ill patients: more convincing evidence is needed. Anaesth Intensive Care. 2010;38(1):167–74.
25. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Cluster randomized clinical trial of Algorithms for Critical Care Enteral and Parenteral Therapy (ACCEPT). CMAJ. 2004;170(2):197–204.
26. 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.
27. Doig GS, 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.

28. Yang S, Wu X, Yu W, Li J. Early enteral nutrition in critically ill patients with hemodynamic instability: an evidence-based review and practical advice. Nutr Clin Pract. 2014;29(1):90–6.
29. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. Am J Crit Care. 2010;19(3):261–8.
30. Revelly JP, Tappy L, Berger MM, Gersbach P, Cayeux C, Chiolero R. Early metabolic and splanchnic responses to enteral nutrition in postoperative cardiac surgery patients with circulatory compromise. Intensive Care Med. 2001;27(3):540–7.
31. Berger MM, Berger-Gryllaki M, Wiesel PH, Revelly JP, Hurni M, Cayeux C, et al. Intestinal absorption in patients after cardiac surgery. Crit Care Med. 2000;28(7):2217–23.
32. Warren J, Bhalla V, Cresci G. Postoperative diet advancement: surgical dogma vs evidence-based medicine. Nutr Clin Pract. 2011;26(2):115–25.
33. McClave SA, Lukan JK, Stefater JA, Lowen CC, Looney SW, Matheson PJ, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. Crit Care Med. 2005;33(2):324–30.
34. 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.
35. Montejo JC, Minambres E, Bordeje L, Mesejo A, Acosta J, Heras A, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. Intensive Care Med. 2010;36(8):1386–93.
36. Reignier J, Mercier E, Le GA, Boulain T, Desachy A, Bellec F, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309(3):249–56.
37. Burlew CC, Moore EE, Cuschieri J, Jurkovich GJ, Codner P, Nirula R, et al. Who should we feed? 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.
38. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ. 1999;318(7182):527–30.
39. Simpson F, Doig GS. The relative effectiveness of practice change interventions in overcoming common barriers to change: a survey of 14 hospitals with experience implementing evidence-based guidelines. J Eval Clin Pract. 2007;13(5):709–15.

Chapter 5
Access and Complications of Enteral Nutrition Support for Critically Ill Patients

Tushar D. Gohel and Donald F. Kirby

Keywords Enteral access • Enteral nutrition • Parenteral nutrition • Nasal feeding tube • Percutaneous gastrostomy tube • Endoscopy • Jejunostomy • Intensive care • Nutrition support • Prepyloric • Postpyloric • Surgical gastrostomy

Key Points

- Enteral nutrition is the preferred means for nourishing eligible critically ill patients.
- Access for enteral nutrition is often complex and not without complications, particularly in the critically ill.
- Options for enteral feeding in the ICU include: nasal and oral feeding tubes, or tubes placed endoscopically, radiologically, or surgically.
- Complications associated with enteral feeding and access for enteral feeding are often preventable and familiarity with and close monitoring for these is required.
- There are important clinical factors to consider before making decisions related to the type of enteral access chosen.

Introduction and Historical Perspective

Tube feeding has been practiced for more than 400 years. Wilhelm His utilized a hollow tube attached to a bladder to deliver a feeding into the esophagus in 1598 [1]. Following that, the monk Aquapendente used a silver tube passed through a nostril into the pharynx for feeding tetanus patients. In the seventeenth and eighteenth centuries, flexible leather tubes were placed in the esophagus and were used as

T.D. Gohel, MD (✉)
Department of Gastroenterology, Cleveland Clinic,
9500 Euclid Avenue, Mail Code A51, Cleveland, OH 44195, USA
e-mail: gohelt@ccf.org

D.F. Kirby, MD, FACP, FACN
Center for Human Nutrition, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_5,

nasogastric tubes for enteral feeding [1]. Nasogastric intubation became commonplace in the twentieth century, using tubes made of rubber and later plastic. Specialized nutrition support, however, showed little progress until the 1960s when intensive care units (ICUs) began to be constructed in large hospitals. With the development of intensive care medicine came the realization that technology was required for the nutrition support of ICU patients.

In 1967, Dudrick et al. demonstrated that a central venous cannula could be used to deliver a concentrated mixture of protein hydrolysate and glucose [2]. Parenteral (or intravenous) nutrition was refined and found extensive clinical use in the 1970s. Nonetheless, the advantages of enteral over parenteral nutrition were recognized from the beginning of intensive nutrition support [3, 4], and documented repeatedly over time [5, 6]. Since then, the variety and quality of enteral formulas as well as the methods of delivery have all improved dramatically.

Enteral nutrition (EN) refers to the delivery of nutrients and fluids directly to the gastrointestinal (GI) tract for digestion and absorption. Enteral preparations are formulated to optimize digestion, but no benefit is realized unless substrate absorption is achieved. Even if the GI tract is shortened or altered by disease or operations, the digestive system has a very large functional reserve. Today, the major indication for parenteral nutrition is lack of a functioning gut. Thus, most patients can be fed enterally.

If the patient can absorb nutrients through the intestine, the advantages of enteral nutrition over parenteral nutrition in providing nutrition to surgical and critically ill patients are now well appreciated. Comparative outcome studies have shown that enteral nutrition is associated with increased GI anastomotic strength [7], fewer nosocomial infections [8], and decreased risk of gastrointestinal bleeding [9, 10], as compared with parenteral nutrition. Cost-benefit analyses as well favor enteral over parenteral nutrition [11, 12]. Additionally, a number of biologic markers which have been associated with better outcomes are improved, including attenuation of the metabolic response to stress [13, 14], improved nitrogen balance [8, 15, 16], better glycemic control [17], enhanced visceral blood flow [18], and increased visceral protein synthesis [19, 20].

Feeding device selection should be based on duration of use and where the patient will be fed, taking into account the patient's underlying condition. In this chapter, we highlight the present options for obtaining enteral access in critically ill patients, and the complications that can be encountered. Gaining enteral access can be challenging, costly, and sometimes, even life threatening. Options for enteral access include: blind placement of nasal and oral feeding tubes, ending in the stomach or further into the small intestine, and facilitated placement of nasal feeding tubes, gastrostomy, or jejunostomy tubes. These latter are placed using endoscopic, radiologic, laparoscopic, or open surgical techniques. This overview will discuss the general characteristics of feeding devices and the methods of their placement and use. The selection of a specific device will be based, in part, on whether the patient will be fed into the stomach (prepyloric feeding) or the small bowel (postpyloric feeding), and whether the patient is likely to need short-term (i.e., <4 weeks) or long-term (≥4 weeks) enteral access.

Overview of Device Selection and Access Adequacy

A clear rationale for enteral feedings, potential length of therapy, and a plan for enteral access placement must be determined to assist the clinician in determining the optimal type of enteral access device to place. Factors important in selecting enteral access in critically ill patients are shown in Table 5.1. Figure 5.1 shows options for enteral access and factors important in selecting enteral access in critically ill patients.

Table 5.1 Important factors to consider before selection of enteral access in critically ill patients

Considerations impacting enteral access selection
Mental status
Presenting condition
Current and past medical and surgical history
Anatomy and function of upper airway and GI tract (especially recent orofacial injuries)
Presence of a functional GI tract
Hemodynamic stability
Concurrent medications (opiates, vasopressors, anticholinergics, antidepressants)
Anticipated length of time that enteral nutrition is required
Predicted prognosis
Ethical considerations, specifically regarding patients' expressed wishes
Patient and family expectations
Local expertise available for placement

Short-Term EN Considerations

The estimated duration of EN therapy is the main factor in determining whether a nasal/oral versus feeding enterostomy (e.g., PEG) is desired. It is important to note that a cutoff based on duration for nasal tubes is arbitrary and based on opinion [21]. Most of the concerns about use of nasal tubes for longer periods stem from mechanical issues caused by stiff larger bore sump tubes, and may not apply to smaller feeding tubes or to Silastic tubes. Prospective randomized clinical studies, albeit few, have failed in the aggregate to demonstrate a difference in complication rates between nasal tubes and gastrostomies in long-term use [22].

Generally, tubes used for short term therapy (<4 weeks) are placed nasally (or in some cases orally) at the bedside, or with endoscopic, electromagnetic, or fluoroscopic assistance [23, 24]. These tubes may terminate in the stomach, duodenum, or jejunum (e.g., nasogastric [NGT], nasoduodenal [NDT], nasojejunal [NJT] tubes). For long-term placement (>4 weeks), enterostomy tubes can be placed in the stomach and small intestine using endoscopic, fluoroscopic, laparoscopic, and open laparotomy approaches. Nasal feeding tubes can provide an opportunity to assess tolerance of enteral feeding before placement of a percutaneous enterostomy, if longer access is required.

Many critically ill patients will have a larger bore sump tube inserted nasally or orally for gastric decompression, especially if they show signs of gastric distension. When patients no longer require gastric decompression, these tubes may be used for medication administration or, for the short term, enteral feeding. These may then be replaced with a smaller-bore, flexible nasal feeding tube. It is theorized that these smaller, softer tubes improve patient comfort and safety, but data is scant. Oral insertion may be preferred in patients with facial or sinus fractures. However, orally placed tubes are often limited to those patients who are either comatose or being sedated for mechanical ventilation so that the gag reflux is suppressed.

If the decision has been made to feed beyond the stomach, it is recommended that the feeding tip be placed at or beyond the ligament of Treitz. This has been suggested as a means to decrease the risk of duodenogastric reflux, which could increase the risk of tube feeding related aspiration. However, this benefit is not well proven [25, 26].

Finally, when patients ha ve been undernourished for any length of time, and in particular if they have electrolyte losses, they are at risk for developing refeeding syndrome. This is discussed in Chapter 7. It is composed of any one or combination of hypokalemia, hypophosphatemia, hypomagnesemia, and Wernicke's, and may be fatal if not treated preemptively. Shifts in glycemic control and volume must also be monitored carefully when initiating EN.

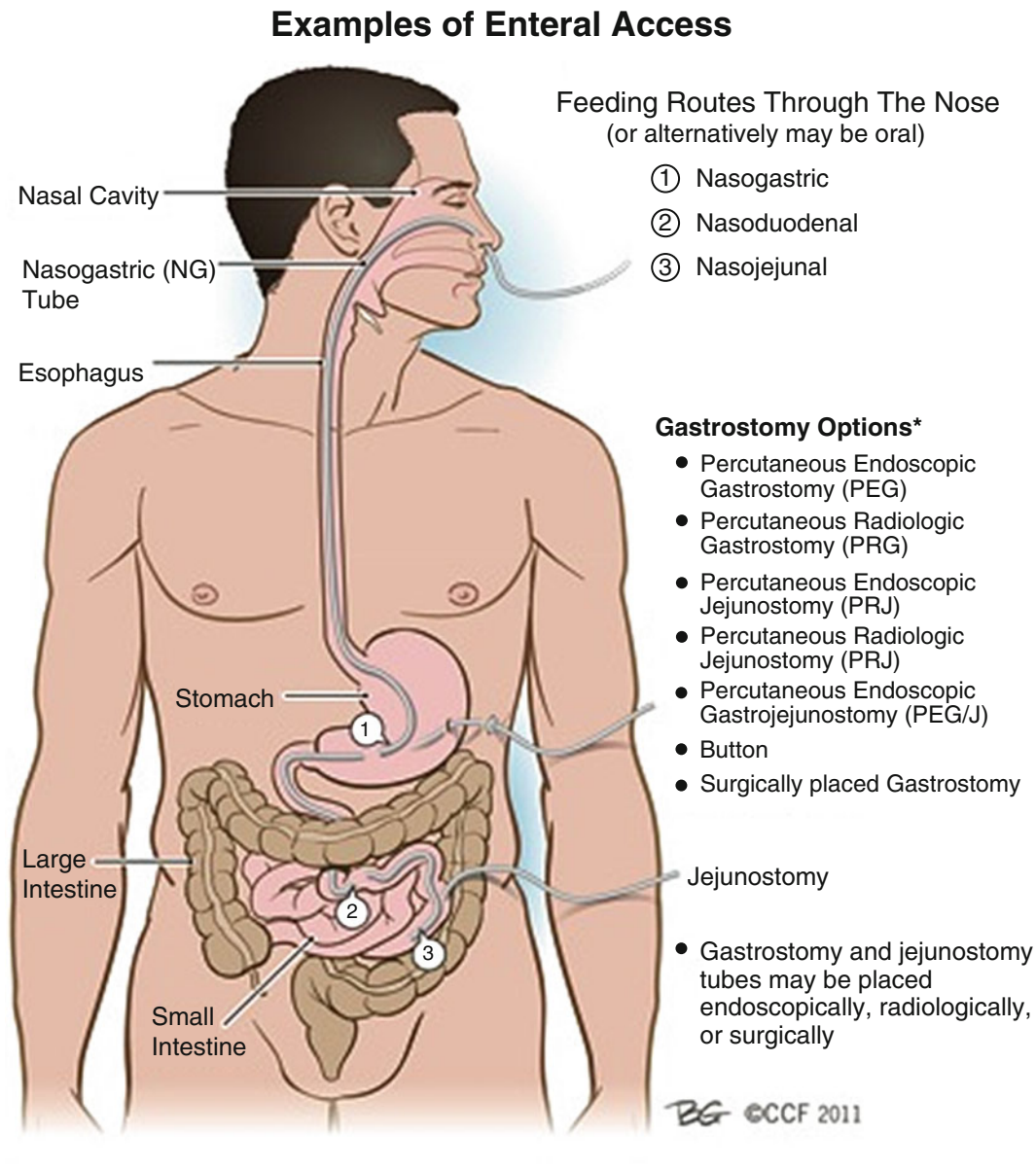


Fig. 5.1 Examples of enteral access routes. Reprinted with the permission, Cleveland Clinic Center for Medical Art & Photography © 2011–2012. All Rights Reserved

Long-Term EN Considerations

When long-term EN access is needed, the condition of the anterior abdominal wall, presence of coagulopathies, and patient tolerance to anesthesia and/or conscious sedation must be assessed. Assessment of the abdominal wall for open wounds and fistulas, future ostomy or surgical (e.g., gastric pull-up) requirements, or necessary percutaneous or intraabdominal infusion devices and peritoneal dialysis catheters must be known and become part of the decision-making process. Further, the presence of ascites or tumors may preclude the placement of a percutaneous or surgical feeding device. Overall patient prognosis should also always be considered.

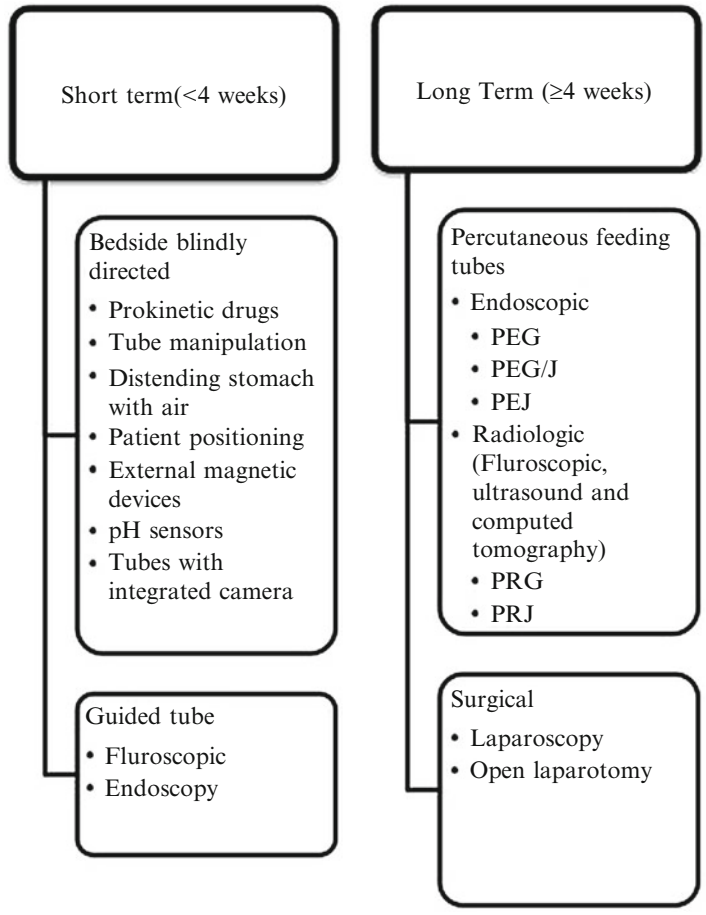


Fig. 5.2 List of the options for short- and long-term enteral access

Currently, the most common technique used for long term EN therapy is the percutaneous endoscopic gastrostomy (PEG). A radiologically guided percutaneous gastrostomy (PRG) is an alternative to the PEG technique. Historically, PRG has been associated with a greater frequency of complications [27, 28]. However, this bias has never been tested in a randomized trial. Furthermore, PRG is often reserved for patients failing or having contraindications to PEG placement, so any increase in complication rate is more likely due to patient selection bias. A PRG may be the preferred technique in patients with pharyngeal or esophageal abnormalities that preclude endoscopic tube placement. Surgical gastrostomy tubes can be performed by either open laparotomy or laparoscopic approaches. Figure 5.2 lists the options for short- and long-term enteral access. This is followed by a decision-making algorithm (Fig. 5.3) that can be adjusted for institutional experience and expertise.

Gastric Versus Small Bowel Access for Enteral Nutrition

There is considerable debate regarding the best site for feeding ICU patients, specifically whether the distal tip should be prepyloric versus postpyloric [25]. The decision to place an enteral device prepylorically or postpylorically is based on gastric motility, gastric aspiration risk, alteration of GI

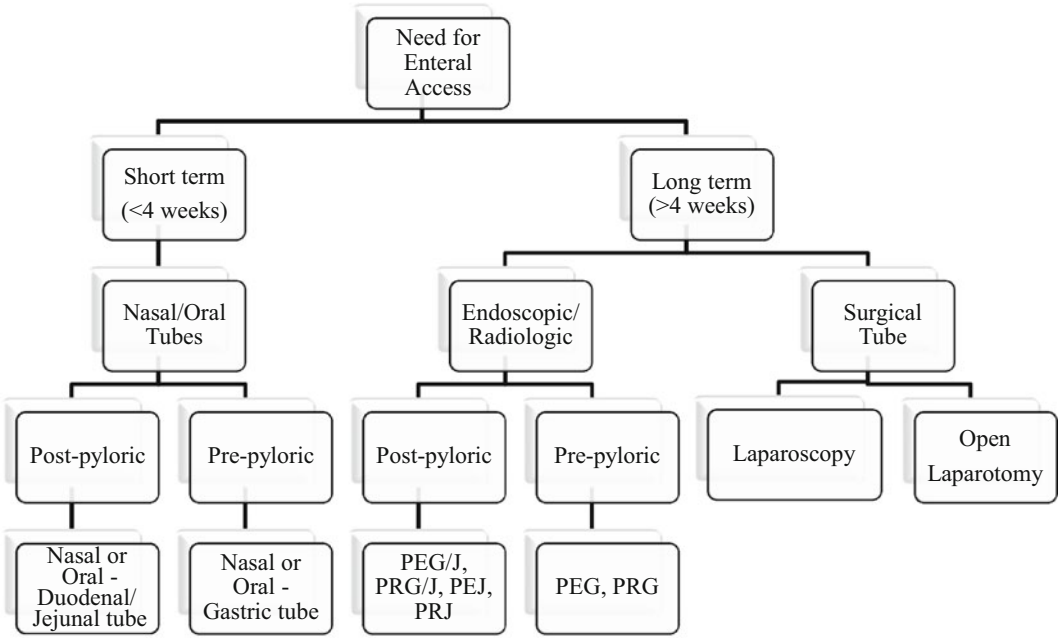


Fig. 5.3 Algorithm for tube selection

anatomy (i.e., postoperative), and coexisting medical conditions. Small bowel feedings are the preferred choice in the presence of conditions such as gastric outlet obstruction, gastroparesis, and in patients at increased risk of aspiration. However, it should be noted that small bowel feeding is no guarantee against aspiration [25]. The use of a gastrojejunal tube system, which allows for simultaneous gastric decompression and small bowel feedings, may be useful for gastric outlet obstruction, severe gastroesophageal reflux disease, gastroparesis, and early (postoperative) feeding. Use of small bowel feeding to reduce aspiration pneumonia continues to be recommended without the support of good studies. Although older data from small studies and technical reviews suggest this may be of benefit, newer, larger studies do not support this finding [29–32].

The theoretical advantages of gastric feeding include utilization of the reservoir function of the stomach, the capability to bolus feed, the ease of tube placement for short-term and early access, the need for less equipment (such as a feeding pump for continuous feeding), and decreased costs.

Tube Selection

Nasal and Oral Feeding Tubes

Nasal and oral feeding tubes are usually inserted when short-term need for enteral access is anticipated (see section "Short-Term EN Considerations"). Practically speaking, the nasal approach may be better tolerated than oral tube placement in patients who are not mechanically ventilated and sedated. In theory, the gag reflex is suppressed and both the nasal and oral approaches should be equally well tolerated in intubated patients. Requirements for nasal feeding include accessibility (e.g., no nasal obstruction), a functional gut, no contraindications (i.e., intestinal obstruction), and a relatively shorter

estimated length of use. As previously stated, many guidelines suggest limiting nasal tube use to 2–6 weeks of EN support [21, 33, 34]. But this recommendation is generally based on opinion, and not supported by recent technical review [22]. In fact, the New York State Department of Health policy (for patients in nursing homes) allows for nasal tubes to remain for 96 days before consideration of a feeding gastrostomy is required [35].

Nasal and oral tubes are often placed first while future need for long-term access is being considered. Nasal feeding tubes are commonly made of polyurethane or silicone, both of which remain soft and flexible over time.

Delayed gastric emptying has been shown in 50–80 % of critically ICU patients and can lead to high gastric residuals and intolerance of nasogastric feeding [36, 37]. When this occurs, it may be appropriate to consider postpyloric feeding. In addition, concomitant use of promotility agents and enteral feeds may be beneficial in providing nutrition to mechanically ventilated patients [38, 39]. Metoclopramide is occasionally administered to ICU patients to improve gastric motility. Erythromycin, while not FDA approved for gastroparesis, is used frequently as an off-label medication and may improve gastric motility in critically ill patients [39, 40]. It should be noted that monitoring gastric residuals has not proven to decrease ventilator associated pneumonia in patients on mechanical ventilation [41].

Nasal feeding tubes may be placed blindly or facilitated by means of an electromagnetic enteral access monitoring system (Cortrak®, Corpak Medsystems, Inc., Buffalo Grove, IL), magnetically guided feeding tubes (Gabriel, Syncro Medical Innovations, Inc., Macon, GA), or with fluoroscopic or endoscopic assistance [42]. Feeding tubes with an optical system including a light source, camera and a lens are being developed for placement under direct visualization. Success rates may vary widely as a result of operator skill, tube type, available equipment, patient's mental status and willingness to cooperate, and anatomy. For example, Ugo et al. attempted postpyloric placement of 8- and 10 Fr-weighted feeding tubes at the bedside in 103 patients in an ICU [43]. Postpyloric placement was achieved in 83 % of patients. However, only 43 % of the tubes were in the preferred position, in the third portion of the duodenum or beyond.

Fluoroscopically guided placement of nasal feeding tubes can be performed in the ICU, with a portable C-arm fluoroscopy device or the patient can be transferred to the radiology suite. The average fluoroscopic-guided placement has been reported to take 10–20 min [44, 45]. Radiologic placements of postpyloric feeding tubes have success rates comparable with endoscopically placed tubes [44, 45]. Without bedside fluoroscopy, we perceive that it is less safe and more labor and cost intensive to transport critically ill patients to a fluoroscopy unit.

Endoscopic placement of nasal feeding tubes is another technique to provide EN to patients. There have been numerous modifications to the original "drag-and-pull" endoscopic method, including a push technique with a stiffened tube, and use of distal suture ties or clips. Patrick et al. evaluated 54 consecutive critically ill patients referred for endoscopic NJT placement [46]. The NJT with guide wire was advanced under direct visualization, through the pylorus and to the appropriate position in the small bowel. An X-ray was obtained after each case to confirm placement on days 1, 3, and 7, and weekly thereafter. Placement was successful in 94 % of cases with few minor complications. The authors concluded that endoscopic placement of tubes in critically ill patients offered several advantages, including the ability to directly visualize tube placement and reduced need for repeat radiographs to confirm correct placement, ease of beside execution of the procedure, and a high success rate with low procedure time (average of 12 min).

Nasal feeding tubes can be fairly easily displaced [47]. Taping may not be protective and suturing tubes to the nose, which seems rather barbaric, has been done. The nasal bridle (Figs. 5.4 and 5.5) is a good alternative to tape or sutures. It is less invasive, more comfortable and is easily placed. The bridle consists of an umbilical tape looped behind the nasal septum, which is then clipped to the nasal feeding tube. It has been shown to diminish the likelihood of tube dislodgement. This in turn may reduce restraint use, patient discomfort, and overall health care costs. Popovich et al. reported use of

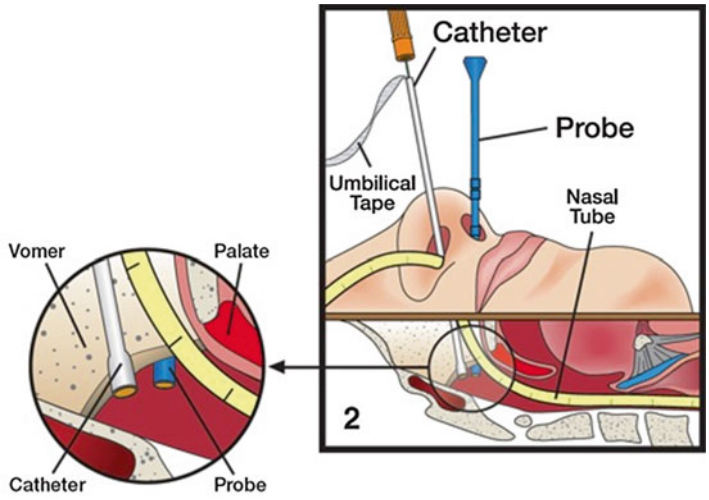


Fig. 5.4 Nasal bridal tube placement technique, demonstrating catheter magnet mechanism behind nasal septum. Reprinted with permission from Applied Medical Technology (AMT), Inc. Brecksville, OH

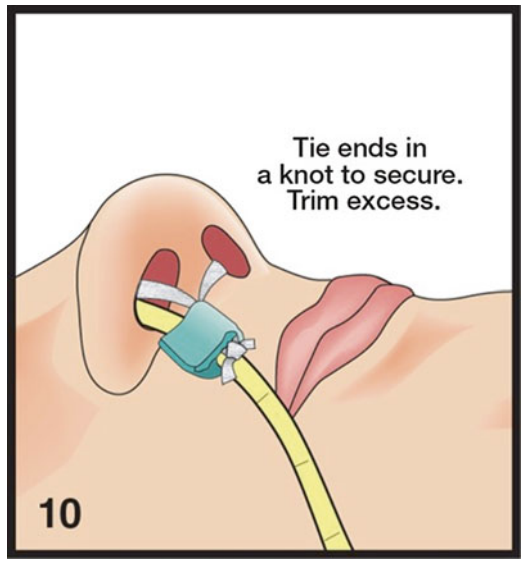


Fig. 5.5 Method of securing tube with bridle clip on feeding tube and umbilical tape, previously placed around nasal septum. Reprinted with permission from Applied Medical Technology (AMT), Inc. Brecksville, OH

an umbilical tape bridle procedure in 26 critically ill patients who received enteral nutrition and either had removed or were at risk for removing their nasal feeding tubes [48]. There were no episodes of bleeding, infection, sinusitis, or nasal septum trauma caused by this technique. Complications associated with bridle procedures have included mild epistaxis and superficial nasal ulceration. Bridling in critically ill patient is a low-morbidity practice that reduces the rate of accidental tube dislodgement (18 vs. 63 % compared to unbridled tubes), and thus may improve caloric intake [49].

Enterostomy Tubes

There are three main percutaneous approaches for nutritional support: endoscopic, radiologic, and surgical. Gastrostomies may be used for administering nutrition in patients who lack adequate caloric intake, have difficulty or are unable to swallow, or are at higher risk for oropharyngeal aspiration [50]. Surgical gastrostomy or endoscopic gastrostomy may also be necessary for gastric decompression in patients with gastric outlet obstruction or small bowel obstruction, functional obstruction, or enteric fistulae.

Percutaneous endoscopic gastrostomy (PEG), first described by Gauderer et al. in 1980, is now a widely accepted procedure for long-term enteral feeding [51], and the most commonly used technique for long-term feeding [50, 52]. Decisions for PEG placement are dependent on many factors, including underlying diagnosis, risk of aspiration, presence of gastroparesis, need for gastric decompression, and any prior surgery. The risks of sinusitis and nasal or pharyngeal injuries are also eliminated by replacing nasal tubes with enterostomies [22], although these are likely less of an issue with the smaller softer tubes currently in use.

A PEG with jejunal extension (PEG/J or JET PEG) may be useful for patients with gastroparesis. A PEG/J has two external ports, one for gastric decompression and/or access and the other for jejunal feeding. Depending on its size, a preexisting PEG may need to be exchanged for a larger PEG—usually a 24 Fr PEG and a 12 Fr jejunal extension. However, extension placement is more difficult and always requires endoscopic or fluoroscopic expertise for the procedure. Decompression of the stomach while feeding distally has been proposed to decrease the incidence of aspiration, but has not been proven in a randomized trial to decrease pneumonia. The longer, thinner tube required to access the jejunum through a gastrostomy may be at higher risk for clogging, may limit feeding rate, and the jejunal extension might "flip back" into the stomach. Further, patients fed into the jejunum may not tolerate bolus feeding which may be desirable if tube feeding is required in the longer term.

Absolute contraindications of endoscopic tube enterostomy include the inability to bring the anterior gastric wall in apposition with the abdominal wall, pharyngeal or esophageal obstruction, uncorrected coagulopathy, mechanical obstruction of GI tract (unless the procedure is indicated for decompression), active peritonitis, and intestinal ischemia. Relative contraindications include ascites, peritoneal carcinomatosis, previous gastric surgeries, marked hepatomegaly, facial fractures, and high cervical fractures [21, 53]. In patients with peritoneal carcinomatosis and malignant ascites, an enterostomy tube can be used if ascites volume is low, accumulates slowly, and is drained before PEG placement [54].

There are several techniques available for placing endoscopic enterostomies (pull, push, and introducer). Occasionally, surgical or endoscopic placement of enterostomies may be done while the patient is undergoing other surgical procedures. Gastrostomies have also been safely placed via a percutaneous technique in critically ill patients [55], but the indications for this practice are unclear. Further, where a nasal option exists, the clinical team should be circumspect when choosing percutaneous options and exposing already critically ill patients to unnecessary procedures [56].

Jejunostomy is employed as a feeding route for patients who are undergoing surgeries for gastroesophageal disease or for abdominal trauma and for those who are at increased risk for gastric aspiration [57]. Advantages include a theoretical decrease in risk of aspiration and provision of continued feeding despite gastric dysfunction [57]. Disadvantages include more difficult placement and more frequent clogging of the thinner tube. As mentioned, this approach usually requires continuous drip infusions and use of small-bore tubing and precludes rapid bolus feeding.

Direct percutaneous endoscopic jejunostomy (PEJ) has been also used in the critical care setting, but should be rarely necessary. Patients with severe acute pancreatitis who have high gastric residual, prior gastrectomy, esophagectomy and/or gastric pull-up surgery, history of Roux-en-Y surgery for weight loss, and gastric dysmotility may benefit from a PEJ tube. Gastric outlet obstruction is another potential indication for direct J tube feeding if the endoscope can be passed beyond the obstruction. Fan et al. compared PEJ tube with PEG/J in 116 patients requiring long-term jejunal feeding [58]. While there were no outcomes differences reported in this retrospective observation, they found

significantly longer feeding tube patency (number of days from established jejunal access to first endoscopic reintervention) (13.5 vs 55.9 %) and fewer endoscopic reinterventions (5 vs. 19) for tube dysfunction with PEJ compared to PEG/J tubes [58]. PEG/J was successfully placed in 27 patients with severe brain injury (Glasgow Coma Scale ≤8). The tube migrated into the stomach in two patients, and technical difficulties precluded insertion in three patients [59].

Radiologically/Fluoroscopically Placed Gastrostomy and Jejunostomy Tubes

Specific problems that may preclude endoscopy-guided placement include facial fracture, certain skull fractures with leakage of cerebral fluid, high cervical fractures, and upper GI obstruction. In these cases, image-guided gastrostomy placement may be successful. Also, some centers may have less access to endoscopists, and an interventional radiologist may offer similar expertise. These are rarely performed in ICU setting [60]. Radiologically placed tubes have become more widely used with increasingly available resources [61]. However, in critically ill patients, this approach can be difficult as it may require patients to be transferred to a radiological unit and also requires the available expertise of a skilled interventional radiologist. Contraindications for radiologic placement of tubes include unfavorable anatomy (i.e., high-laying stomach), previous gastrectomy, gastric neoplasm, peptic ulcer, and gastric varices [53].

Surgical Gastrostomy and Jejunostomy

A gastrostomy or jejunostomy tube inserted using the laparoscopic or open (laparotomy) method is performed in the operating room usually under general anesthesia. Surgical placement of feeding tubes is used when patients are undergoing another abdominal operation, when endoscopic and radiologic attempts fail, and/or in the presence of upper GI tract obstruction or facial trauma.

Surgical tubes placed in the jejunum are believed to decrease the risk of aspiration because they bypass the stomach [62], but this is unproven. Complications (i.e., wound dehiscence, tube dislodgement, or anesthesia related) of surgical enterostomy may be higher as they require operative placement. These tubes are not easy to replace and are very cumbersome to place in critically ill patients with multiple comorbidities. Surgically placed tubes cost more to place and have the longest recovery time [63].

Complications

Table 5.2 shows many potential complications that can occur with enteral tube feeding. Complications can be secondary to the procedure, to the tubes, or secondary to enteral feeding itself. In this section we focus on complications secondary to procedures and from the tube itself. We discuss the complications which are common to all feeding access procedures, and then highlight the complications seen with the different categories of access.

General Complications

Many of the complications occur regardless of method. For example, any sedation provided for patient comfort may be associated with cardiopulmonary issues.

Table 5.2 Complications associated with enteral access[a]

Enteral access	Complications
Nasal and oral feeding tubes (NGT, NDT, NJT, OGT)	*Minor Complications*: Local oral or nasal irritation, epistaxis, sinusitis, tube dislodgement, tube malposition, tube clogging, tube kinking, feeding intolerance *Major Complications*: Arrhythmia, esophageal perforation, duodenal perforation, gastric rupture, aspiration, tracheoesophageal fistula, pneumothorax, tube feeding into pulmonary tree
Percutaneous gastrostomy and gastrojejunostomy (PEG/J)	*Minor Complications*: Stoma leakage, wound infection, bleeding, tube dislodgement, pain, gastroesophageal reflux, tube blockage, ileus *Major Complications*: Gastrocolocutaneous fistula, necrotizing fasciitis, tumor implantation at the stoma site, cardiac failure with hypoxia, bowel obstruction, small bowel perforation, subcutaneous emphysema, volvulus, gastric hemorrhage, peritonitis, cellulitis, hematoma, internal bleeding, catheter dislodgement into the peritoneal cavity, buried bumper syndrome, pressure necrosis from internal or external bumpers, aspiration pneumonia
Radiological and surgical gastrostomy and jejunostomy	Surgical and anesthesia complications, otherwise same as above

[a]Adapted with permission from Handbook of Clinical Nutrition and Stroke (p. 216) by Mandy L. Corrigan, Arlene A Escuro and Donald F. Kirby, 2013, New York, NY, Springer Science + Business Media. Copyright 2013

Bleeding may occur in the critically ill population. With nasal and oral tubes, bleeding may range from minor epistaxis to severe nasopharyngeal hemorrhage that may require nasal packing or cautery. Acute bleeding during PEG placement is uncommon and occurs in approximately 1 % of cases [64]. A review of 1338 patients reported that fewer than 0.5 % of cases requiring blood transfusion and/or surgery [65] Bleeding occurring late after PEG tube placement is reported to complicate 0.3–1.2 % of PEGs [66]. Late bleeding is typically caused by traumatic erosions (from the internal bolster), ulceration, or peptic ulcer disease [64, 65, 67]. Barkmeier et al. compared PRG, PEGs, and surgical gastrostomy tubes in 1998 and found no significant difference in the complication rates among three groups [63].

Tube blockage and clogging are common to all tubes and is partially a function of the tube size, but also what is infused through the tube. Inappropriate medication choices that include fiber supplements, bile sequestrants, exchange resins or viscous meds like sucralfate are poor choices for feeding tubes because of their propensity to cause clogging. Inadequately crushed medications, inadequate flushing, and precipitation or curdling of the tube feeding can cause tube blockage [68].

Methods used for unclogging clogged tubes include warm water, carbonated beverages, pancreatic enzymes, and declogging plastic brush devices [57, 69]. Ideally, tubes should be flushed before and after use. Aspiration of gastric contents is a significant risk for clogging of tubes, likely due to curdling of the feed product by gastric contents [70]

Tube displacement/dislodgement can occur with any device. Patients may pull out any of the devices. Iatrogenic dislodgement is common in our experience, and occurs in such settings as when patients are being rolled or transferred. As previously discussed, nasal bridles may be useful for securing nasal tubes. Abdominal binders may decrease access for the patient to pull on enterostomy tubes, but care must be taken not to create lateral torque on the tube as any deviation from the angle of the ostomy passage may enlarge the ostomy and create leaking.

Reflux esophagitis and aspiration can occur in any patient receiving tube. Protocols to limit these are suggested and likely in place in individual ICUs, but are poorly supported by research. Data are conflicting as to whether gastroesophageal reflux may occur more frequently when a feeding tube is used in supine position [71, 72].

Complications of Nasal and Oral Feeding Tubes

Misplacement of a nasal or oral tube into the bronchopulmonary tree is one of the most severe complications. This occurs in 2–4 % of nasal feeding tube placements. When it does occur, however, it is unsuspected in 80 % of occurrences and results in pneumothorax in up to 50 % of incidents [73, 74]. A radiograph is the gold standard for ensuring correct placement and should be performed before the feeding tube is used for any purpose. Bedsides electromagnetic imaging systems, however, may obviate the need for radiographic confirmation [23].

Nasopharyngeal discomfort due to the physical presence of the tube in the throat is common. Theremay be a deficiency in saliva production due to mouth breathing and the absence of chewing. Sore mouth, dysphagia, sensation of thirst, and dry mucous membrane are recognized as minor complications [75].

Pleuropulmonary complications include pneumomediastinum, subcutaneous emphysema, pneumothorax, pneumonitis, pulmonary hemorrhage, pleural effusion, emphysema, hemothorax, and perforation of the esophagus. Major risk factors for pleuropulmonary complications include depressed sensorium, impaired gag reflex, recent endotracheal intubation, decreased laryngeal sensitivity, esophageal stricture, enlarged heart, and neuromuscular blocking drugs [76–78]. Rarely, a tracheoesophageal fistula may develop when large-bore nasal feeding tubes are used with an endotracheal tube or a tracheostomy tube in place. The fistula can develop from pressure necrosis of the esophageal and trachea [79]. Endobroncheal tube placement is most common in those with altered swallowing or a reduced gag reflex in the ICU [80]. Intrapulmonary infusion of an enteral diet can be fatal, if not recognized. The operator's familiarity, nonforceful insertion, careful observation for distress, and dependence on a chest and abdomen radiograph after placement reduce these complications [80].

Complications of Enterostomy Tubes

Endoscopic gastrostomies have a lower morbidity and mortality, generally do not need general anesthesia, and are less expensive to perform than surgical gastrostomies [63]. The procedure related mortality rate is negligible (<1 %) (81). Koc et al. studied 31 patients who underwent PEG tube placement in a neurosurgical ICU. Procedure-related mortality was 0 %. The authors concluded that PEG was a safe and well-tolerated method for neurosurgical ICU patients [82]. Zippi et al. studied 36 ICU patients who underwent PEG tube placement. All 36 PEG tubes (16 or 20 Fr) were placed bedside in an ICU with the assistance of an anesthetist using propofol. All tubes were inserted by the pull method. Procedure-related mortality was 0 %. The most common complication was tube clogging, which occurred in 11 % of patients [83].

Pneumoperitoneum is usually benign and its rate varies from 5 to 16 % in ICU patients [84–86]. Pneumoperitoneum following PEG tube does not necessitate surgical intervention in all patients; however, the higher incidence of mortality and complications requiring intervention associated with post PEG pneumoperitoneum suggest the need for further investigation and vigilance among ICU patients with this finding [84]. Subcutaneous emphysema has also been described after PEG placement. It occurs from air being introduced between the cutaneous and subcutaneous tissues. In the absence of other findings, it is inconsequential and should not preclude feeding [87]. It may, however, signal a surgical emergency if the patient becomes at all unstable.

Gastrocolocutaneous fistula occurs rarely after PEG placement, and results from interposition of bowel, usually splenic fixture, between the anterior abdominal wall and gastric wall [51]. Peritonitis is a rare, but serious, complication that most often results from leakage of gastrointestinal contents or infusion of enteral feeds into the peritoneal cavity via a displaced feeding tube [88]. Deep tissue infections are less common (<1 %) and are typically treated with broad-spectrum antibiotics [88].

Peristomal leakage of tube feeding and/or gastric contents around the tube site has been reported to occur in 1–2 % of patients and can be a significant management problem leading to abdominal wall burns and requiring surgical intervention [89]. Enterostomy tube bolsters should be loosened, and all efforts made to minimize any lateral tension to the stoma. These maneuvers allow the stoma to close around the tube, effecting a seal and stopping leakage. Stoma adhesive powder or zinc oxide can be applied to the site of peristomal leakage to prevent local skin irritation. Foam dressing rather than gauze can help reduce local skin irritation caused by gastric contents. Replacement of the gastrostomy tube with a larger one, or tightening of the bolster, often results in worsening the leakage around a stoma made larger by these interventions [67].

Complications of Radiologically Placed Enterostomy Tubes

Percutaneously placed radiological enterostomy (PRG) tubes are reported to have higher complication rates than PEGs, but this data, as discussed earlier, is observational and subject to significant selection bias [90]. Galaski et al. retrospectively reviewed 30 PEG and 44 PRG. Minor complications were comparable in both groups, and no procedure related mortality was found in either group [27]. Overall, radiographically placed tubes may be useful in patients who cannot undergo endoscopic placement or where endoscopic expertise is unavailable.

Complications of Surgical Enterostomy Tubes

Surgical insertion of feeding ostomy tubes is a relatively safe procedure. Mechanical complications include intestinal obstruction, intraperitoneal leakage, local abscess collection, and intestinal necrosis. Dwyer et al. showed that surgical gastrostomy tube placement had higher complications compared to PEG tube placement [91]. Han-Geurts et al. described leakage from the jejunostomy site, requiring re-exploration in 1 in 79 patients undergoing jejunostomy [92]. In another series of 262 patients undergoing feeding Jejunostomy during esophagectomy, 1.5 % of patients experienced major complications requiring re-operation [93]. Ryan et al. in their experience of 8 years reported a relaparotomy rate of 1.4 % as a result of jejunostomy [94]. In one study of 43 laparoscopically placed jejunostomies, dislodgement occurred in 20 % of the patients [95]. While in different study by Wakefield et al. reported only 2 % of dislodgment in patients undergoing intraoperative open jejunostomy [96]. The rate of minor complications varies in different series from 14 to 35 % [95–98]. Yagi et al. reported a 4 % increase of skin excoriation as a result of feeding tube [97]. Surgically placed tubes may also be associated with more serious complications such as intussusception, volvulus, and possibly intestinal ischemia requiring operative intervention or resulting in death [99–101].

Decreasing Complications and Improving Delivery

Many factors contribute towards inadequate delivery of enteral nutrition. These factors include delay in starting and advancement of feeding, frequent interruption in feeding and under-ordering [76]. In multiple studies, superior results have been reported by implementing a standardized feeding protocol [102, 103].

Determining EN tolerance is often difficult, especially in ICU patients where the abdominal exam may be confounded by paralysis, mechanical ventilation, bulky dressings, and an open abdomen.

Conclusion

Enteral feeding in critically ill patients requires a functional GI tract and appropriate access. This chapter has discussed the numerous routes by which EN can be delivered and the potential complications associated with each. Deciding on appropriate enteral access in critically ill patients depends ultimately on the patient's clinical condition, surgical history, length of anticipated feeding time, as well as risk associated with the various enteral access devices and local expertise. It is essential that the patient or surrogate and the physician together assess the risks and benefits of enteral access options in all critically ill patients.

References

1. Chernoff R. An overview of tube feeding: from ancient times to the future. Nutr Clin Pract. 2006;21(4):408–10.
2. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery. 1968;64(1):134–42.
3. Burt ME, Stein TP, Brennan MF. A controlled, randomized trial evaluating the effects of enteral and parenteral nutrition on protein metabolism in cancer-bearing man. J Surg Res. 1983;34(4):303–14.
4. Borzotta AP, Pennings J, Papasadero B, Paxton J, Mardesic S, Borzotta R, et al. Enteral versus parenteral nutrition after severe closed head injury. J Trauma. 1994;37(3):459–68.
5. Chrysomilides SA, Kaminski Jr MV. Home enteral and parenteral nutritional support: a comparison. Am J Clin Nutr. 1981;34(10):2271–5.
6. Kudsk KA, Stone JM, Carpenter G, Sheldon GF. Enteral and parenteral feeding influences mortality after hemoglobin-E. coli peritonitis in normal rats. J Trauma. 1983;23(7):605–9.
7. Moss G, Greenstein A, Levy S, Bierenbaum A. Maintenance of GI function after bowel surgery and immediate enteral full nutrition. I. Doubling of canine colorectal anastomotic bursting pressure and intestinal wound mature collagen content. JPEN J Parenter Enteral Nutr. 1980;4(6):535–8.
8. 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.
9. Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. Crit Care Med. 1999;27(12):2812–7.
10. 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(4):313–8.
11. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. Crit Care Med. 2001;29(2):242–8.
12. Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. Am J Gastroenterol. 2002;97(9):2255–62.
13. 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.
14. Fong YM, Marano MA, Barber A, He W, Moldawer LL, Bushman ED, et al. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. Ann Surg. 1989;210(4):449–56. discussion 456-7.
15. Chiarelli A, Enzi G, Casadei A, Baggio B, Valerio A, Mazzoleni F. Very early nutrition supplementation in burned patients. Am J Clin Nutr. 1990;51(6):1035–9.
16. Hasse JM, Blue LS, Liepa GU, Goldstein RM, Jennings LW, Mor E, et al. Early enteral nutrition support in patients undergoing liver transplantation. JPEN J Parenter Enteral Nutr. 1995;19(6):437–43.
17. Vernet O, Christin L, Schutz Y, Danforth Jr E, Jequier E. Enteral versus parenteral nutrition: comparison of energy metabolism in healthy subjects. Am J Physiol. 1986;250(1 Pt 1):E47–54.
18. Bengmark S, Gianotti L. Nutritional support to prevent and treat multiple organ failure. World J Surg. 1996;20(4):474–81.
19. Kudsk KA, Minard G, Wojtysiak SL, Croce M, Fabian T, Brown RO. Visceral protein response to enteral versus parenteral nutrition and sepsis in patients with trauma. Surgery. 1994;116(3):516–23.
20. Suchner U, Senftleben U, Eckart T, Scholz MR, Beck K, Murr R, et al. Enteral versus parenteral nutrition: effects on gastrointestinal function and metabolism. Nutrition. 1996;12(1):13–22.

21. Jain R, Maple JT, Anderson MA, Appalaneni V, Ben-Menachem T, ASGE Standards of Practice Committee, et al. The role of endoscopy in enteral feeding. Gastrointest Endosc. 2011;74(1):7–12.
22. Gomes Jr CA, Lustosa SA, Matos D, Andriolo RB, Waisberg DR, Waisberg J. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for adults with swallowing disturbances. Cochrane Database Syst Rev. 2012;3:CD008096.
23. 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.
24. Vanek VW. Ins and outs of enteral access. Part 1: short-term enteral access. Nutr Clin Pract. 2002;17(5):275–83.
25. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. Crit Care. 2003;7(3):R46–51.
26. 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.
27. Galaski A, Peng WW, Ellis M, Darling P, Common A, Tucker E. Gastrostomy tube placement by radiological versus endoscopic methods in an acute care setting: a retrospective review of frequency, indications, complications and outcomes. Can J Gastroenterol. 2009;23(2):109–14.
28. Silas AM, Pearce LF, Lestina LS, Grove MR, Tosteson A, Manganiello WD, et al. Percutaneous radiologic gastrostomy versus percutaneous endoscopic gastrostomy: a comparison of indications, complications and outcomes in 370 patients. Eur J Radiol. 2005;56(1):84–90.
29. Montecalvo MA, Steger KA, Farber HW, Smith BF, Dennis RC, Fitzpatrick GF, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. Crit Care Med. 1992;20(10):1377–87.
30. Adam MD, Rupinder D, Andrew GD, Emma JR, Andrew RD, Daren KH. Comparisons between intragastric and small intestinal delivery of enteral nutrition in the critically ill: a systematic review and meta-analysis. Crit Care. 2013;17(3):R125.
31. Montejo JC, Grau T, Acosta J, Ruiz-Santana S, Planas M, Garcia-De-Lorenzo A, et al. Multicenter, prospective, randomized, single-blind study comparing the efficacy and gastrointestinal complications of early jejunal feeding with early gastric feeding in critically ill patients. Crit Care Med. 2002;30(4):796–800.
32. Davies AR, Morrison SS, Bailey MJ, Bellomo R, Cooper DJ, Doig GS, et al. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. Crit Care Med. 2012;40(8):2342–8.
33. Kirby DF. Decisions for enteral access in the intensive care unit. Nutrition. 2001;17(9):776–9.
34. Park RH, Allison MC, Lang J, Spence E, Morris AJ, Danesh BJ, et al. Randomised comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding in patients with persisting neurological dysphagia. BMJ. 1992;304(6839):1406–9.
35. New York State Department of Health Policies. Section 415.12 – Quality of care. 01/13/93;C.
36. Kao CH, ChangLai SP, Chieng PU, Yen TC. Gastric emptying in head-injured patients. Am J Gastroenterol. 1998;93(7):1108–12.
37. Tarling MM, Toner CC, Withington PS, Baxter MK, Whelpton R, Goldhill DR. A model of gastric emptying using paracetamol absorption in intensive care patients. Intensive Care Med. 1997;23(3):256–60.
38. Chapman MJ, Fraser RJ, Kluger MT, Buist MD, De Nichilo DJ. Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. Crit Care Med. 2000;28(7):2334–7.
39. Reignier J, Bensaid S, Perrin-Gachadoat D, Burdin M, Boiteau R, Tenaillon A. Erythromycin and early enteral nutrition in mechanically ventilated patients. Crit Care Med. 2002;30(6):1237–41.
40. Jackson MD, Davidoff G. Gastroparesis following traumatic brain injury and response to metoclopramide therapy. Arch Phys Med Rehabil. 1989;70(7):553–5.
41. Reignier J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309(3):249–56.
42. Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, et al. Enteral nutrition practice recommendations. JPEN J Parenter Enteral Nutr. 2009;33(2):122–67.
43. Ugo PJ, Mohler PA, Wilson GL. Bedside postpyloric placement of weighted feeding tubes. Nutr Clin Pract. 1992;7(6):284–7.
44. Foote JA, Kemmeter PR, Prichard PA, Baker RS, Paauw JD, Gawel JC, et al. A randomized trial of endoscopic and fluoroscopic placement of postpyloric feeding tubes in critically ill patients. JPEN J Parenter Enteral Nutr. 2004;28(3):154–7.
45. Fang JC, Hilden K, Holubkov R, DiSario JA. Transnasal endoscopy vs. fluoroscopy for the placement of nasoenteric feeding tubes in critically ill patients. Gastrointest Endosc. 2005;62(5):661–6.
46. Patrick PG, Marulendra S, Kirby DF, DeLegge MH. Endoscopic nasogastric-jejunal feeding tube placement in critically ill patients. Gastrointest Endosc. 1997;45(1):72–6.
47. Gunn SR, Early BJ, Zenati MS, Ochoa JB. Use of a nasal bridle prevents accidental nasoenteral feeding tube removal. JPEN J Parenter Enteral Nutr. 2009;33(1):50–4.

48. Popovich MJ, Lockrem JD, Zivot JB. Nasal bridle revisited: an improvement in the technique to prevent unintentional removal of small-bore nasoenteric feeding tubes. Crit Care Med. 1996;24(3):429–31.
49. Seder CW, Stockdale W, Hale L, Janczyk RJ. Nasal bridling decreases feeding tube dislodgment and may increase caloric intake in the surgical intensive care unit: a randomized, controlled trial. Crit Care Med. 2010;38(3):797–801.
50. Larson DE, Burton DD, Schroeder KW, DiMagno EP. Percutaneous endoscopic gastrostomy. Indications, success, complications, and mortality in 314 consecutive patients. Gastroenterology. 1987;93(1):48–52.
51. Gauderer MW, Ponsky JL, Izant Jr RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. J Pediatr Surg. 1980;15(6):872–5.
52. Gauderer MW. Percutaneous endoscopic gastrostomy and the evolution of contemporary long-term enteral access. Clin Nutr. 2002;21(2):103–10.
53. Itkin M, DeLegge MH, Fang JC, McClave SA, Kundu S, Janne d'Othee B, et al. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). J Vasc Interv Radiol. 2011;22(8):1089–106.
54. Baltz JG, Argo CK, Al-Osaimi AM, Northup PG. Mortality after percutaneous endoscopic gastrostomy in patients with cirrhosis: a case series. Gastrointest Endosc. 2010;72(5):1072–5.
55. Yarmus L, Gilbert C, Lechtzin N, Imad M, Ernst A, Feller-Kopman D. Safety and feasibility of interventional pulmonologists performing bedside percutaneous endoscopic gastrostomy tube placement. Chest. 2013;144(2):436–40.
56. Slattery E, Seres DS. Just because we can does not mean we should: a perspective on combined tracheostomy and percutaneous endoscopic gastrostomy tube insertion. Chest. 2014;145(2):421–2.
57. Metheny NA, Stewart BJ, McClave SA. Relationship between feeding tube site and respiratory outcomes. JPEN J Parenter Enteral Nutr. 2011;35(3):346–55.
58. Fan AC, Baron TH, Rumalla A, Harewood GC. Comparison of direct percutaneous endoscopic jejunostomy and PEG with jejunal extension. Gastrointest Endosc. 2002;56(6):890–4.
59. Kirby DF, Clifton GL, Turner H, Marion DW, Barrett J, Gruemer HD. Early enteral nutrition after brain injury by percutaneous endoscopic gastrojejunostomy. JPEN J Parenter Enteral Nutr. 1991;15(3):298–302.
60. DiSario JA, Baskin WN, Brown RD, DeLegge MH, Fang JC, Ginsberg GG, et al. Endoscopic approaches to enteral nutritional support. Gastrointest Endosc. 2002;55(7):901–8.
61. Duszak Jr R, Mabry MR. National trends in gastrointestinal access procedures: an analysis of Medicare services provided by radiologists and other specialists. J Vasc Interv Radiol. 2003;14(8):1031–6.
62. Freeman C, Delegge MH. Small bowel endoscopic enteral access. Curr Opin Gastroenterol. 2009;25(2):155–9.
63. Barkmeier JM, Trerotola SO, Wiebke EA, Sherman S, Harris VJ, Snidow JJ, et al. Percutaneous radiologic, surgical endoscopic, and percutaneous endoscopic gastrostomy/gastrojejunostomy: comparative study and cost analysis. Cardiovasc Intervent Radiol. 1998;21(4):324–8.
64. Amann W, Mischinger HJ, Berger A, Rosanelli G, Schweiger W, Werkgartner G, et al. Percutaneous endoscopic gastrostomy (PEG). 8 years of clinical experience in 232 patients. Surg Endosc. 1997;11(7):741–4.
65. Mamel JJ. Percutaneous endoscopic gastrostomy. Am J Gastroenterol. 1989;84(7):703–10.
66. Jarnagin WR, Duh QY, Mulvihill SJ, Ridge JA, Schrock TR, Way LW. The efficacy and limitations of percutaneous endoscopic gastrostomy. Arch Surg. 1992;127(3):261–4.
67. Schapiro GD, Edmundowicz SA. Complications of percutaneous endoscopic gastrostomy. Gastrointest Endosc Clin N Am. 1996;6(2):409–22.
68. Mathus-Vliegen LM, Koning H. Percutaneous endoscopic gastrostomy and gastrojejunostomy: a critical reappraisal of patient selection, tube function and the feasibility of nutritional support during extended follow-up. Gastrointest Endosc. 1999;50(6):746–54.
69. Marcuard SP, Stegall KL, Trogdon S. Clearing obstructed feeding tubes. JPEN J Parenter Enteral Nutr. 1989;13(1):81–3.
70. Powell KS, Marcuard SP, Farrior ES, Gallagher ML. Aspirating gastric residuals causes occlusion of small-bore feeding tubes. JPEN J Parenter Enteral Nutr. 1993;17(3):243–6.
71. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999;354(9193):1851–8.
72. Castel H, Tiengou LE, Besancon I, Joubert C, Fatome A, Piquet MA. What is the risk of nocturnal supine enteral nutrition? Clin Nutr. 2005;24(6):1014–8.
73. Odocha O, Lowery Jr RC, Mezghebe HM, Siram SM, Warner OG. Tracheopleuropulmonary injuries following enteral tube insertion. J Natl Med Assoc. 1989;81(3):275–81.
74. Rassias AJ, Ball PA, Corwin HL. A prospective study of tracheopulmonary complications associated with the placement of narrow-bore enteral feeding tubes. Crit Care. 1998;2(1):25–8.
75. Hoffmann S, Koller M, Plaul U, Stinner B, Gerdes B, Lorenz W, et al. Nasogastric tube versus gastrostomy tube for gastric decompression in abdominal surgery: a prospective, randomized trial comparing patients' tube-related inconvenience. Langenbecks Arch Surg. 2001;386(6):402–9.

76. McClave SA, Sexton LK, Spain DA, Adams JL, Owens NA, Sullins MB, et al. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. Crit Care Med. 1999;27(7):1252–6.
77. Lee SS, Mathiasen RA, Lipkin CA, Colquhoun SD, Margulies DR. Endoscopically placed nasogastrojejunal feeding tubes: a safe route for enteral nutrition in patients with hepatic encephalopathy. Am Surg. 2002;68(2): 196–200.
78. Damore 2nd LJ, Andrus CH, Herrmann VM, Wade TP, Kaminski DL, Kaiser GC. Prospective evaluation of a new through-the-scope nasoduodenal enteral feeding tube. Surg Endosc. 1997;11(5):460–3.
79. Wood DE, Mathisen DJ. Late complications of tracheotomy. Clin Chest Med. 1991;12(3):597–609.
80. Marderstein EL, Simmons RL, Ochoa JB. Patient safety: effect of institutional protocols on adverse events related to feeding tube placement in the critically ill. J Am Coll Surg. 2004;199(1):39–47. discussion 47-50.
81. Dewald CL, Hiette PO, Sewall LE, Fredenberg PG, Palestrant AM. Percutaneous gastrostomy and gastrojejunostomy with gastropexy: experience in 701 procedures. Radiology. 1999;211(3):651–6.
82. Koc D, Gercek A, Gencosmanoglu R, Tozun N. Percutaneous endoscopic gastrostomy in the neurosurgical intensive care unit: complications and outcome. JPEN J Parenter Enteral Nutr. 2007;31(6):517–20.
83. Zippi M, Fiorani S, De Felici I, Febbraro I, Mattei E, Traversa G, et al. Percutaneous endoscopic gastrostomy (PEG) in critically ill patients performed at bed in intensive care unit: report of our experience. Clin Ter. 2009;160(5):359–62.
84. Nazarian A, Cross W, Kowdley GC. Pneumoperitoneum after percutaneous endoscopic gastrostomy among adults in the intensive care unit: incidence, predictive factors, and clinical significance. Am Surg. 2012;78(5):591–4.
85. Milanchi S, Allins A. Early pneumoperitoneum after percutaneous endoscopic gastrostomy in intensive care patients: sign of possible bowel injury. Am J Crit Care. 2007;16(2):132–6.
86. Gottfried EB, Plumser AB, Clair MR. Pneumoperitoneum following percutaneous endoscopic gastrostomy. A prospective study. Gastrointest Endosc. 1986;32(6):397–9.
87. Stathopoulos G, Rudberg MA, Harig JM. Subcutaneous emphysema following PEG. Gastrointest Endosc. 1991;37(3):374–6.
88. Gossner L, Keymling J, Hahn EG, Ell C. Antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): a prospective randomized clinical trial. Endoscopy. 1999;31(2):119–24.
89. Lin HS, Ibrahim HZ, Kheng JW, Fee WE, Terris DJ. Percutaneous endoscopic gastrostomy: strategies for prevention and management of complications. Laryngoscope. 2001;111(10):1847–52.
90. Burkitt P, Carter LM, Smith AB, Kanatas A. Outcomes of percutaneous endoscopic gastrostomy and radiologically inserted gastrostomy in patients with head and neck cancer: a systematic review. Br J Oral Maxillofac Surg. 2011;49(7):516–20.
91. Dwyer KM, Watts DD, Thurber JS, Benoit RS, Fakhry SM. Percutaneous endoscopic gastrostomy: the preferred method of elective feeding tube placement in trauma patients. J Trauma. 2002;52(1):26–32.
92. 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.
93. Sica GS, Sujendran V, Wheeler J, Soin B, Maynard N. Needle catheter jejunostomy at esophagectomy for cancer. J Surg Oncol. 2005;91(4):276–9.
94. Ryan AM, Rowley SP, Healy LA, Flood PM, Ravi N, Reynolds JV. Post-oesophagectomy early enteral nutrition via a needle catheter jejunostomy: 8-year experience at a specialist unit. Clin Nutr. 2006;25(3):386–93.
95. Jenkinson AD, Lim J, Agrawal N, Menzies D. Laparoscopic feeding jejunostomy in esophagogastric cancer. Surg Endosc. 2007;21(2):299–302.
96. Wakefield SE, Mansell NJ, Baigrie RJ, Dowling BL. Use of a feeding jejunostomy after oesophagogastric surgery. Br J Surg. 1995;82(6):811–3.
97. Yagi M, Urade M, Takamura H, Hasebe K. Mechanical complications associated with the tube for enteral nutrition. Nihon Rinsho. 2001;59 Suppl 5:345–8.
98. Yagi M, Hashimoto T, Nezuka H, Ito H, Tani T, Shimizu K, et al. Complications associated with enteral nutrition using catheter jejunostomy after esophagectomy. Surg Today. 1999;29(3):214–8.
99. Sivasankar A, Johnson M, Jeswanth S, Rajendran S, Surendran R. Small bowel volvulus around feeding jejunostomy tube. Indian J Gastroenterol. 2005;24(6):272–3.
100. Holmes 4th JH, Brundage SI, Yuen P, Hall RA, Maier RV, Jurkovich GJ. Complications of surgical feeding jejunostomy in trauma patients. J Trauma. 1999;47(6):1009–12.
101. Tapia J, Murguia R, Garcia G, de los Monteros PE, Onate E. Jejunostomy: techniques, indications, and complications. World J Surg. 1999;23(6):596–602.
102. Spain DA, McClave SA, Sexton LK, Adams JL, Blanford BS, Sullins ME, et al. Infusion protocol improves delivery of enteral tube feeding in the critical care unit. JPEN J Parenter Enteral Nutr. 1999;23(5):288–92.
103. Mackenzie SL, Zygun DA, Whitmore BL, Doig CJ, Hameed SM. Implementation of a nutrition support protocol increases the proportion of mechanically ventilated patients reaching enteral nutrition targets in the adult intensive care unit. JPEN J Parenter Enteral Nutr. 2005;29(2):74–80.

Chapter 6
Timing and Indication for Parenteral Nutrition in the Critically Ill

Jan Gunst and Michael P. Casaer

Key Points

- Parenteral nutrition increases risk of infectious and other complications in critical illness in a time and dose dependent manner.
- There is no strong evidence for improved clinical outcome with enhanced nutrition early in critical illness.
- A pragmatic approach to parenteral nutrition in the intensive care unit would be to administer it only after day 7 in patients with a persistent failure for enteral nutrition.
- Refeeding syndrome in the intensive care unit is an iatrogenic complication that should be prevented at all times by administration of parenteral thiamine, phosphate and potassium as indicated.
- Further research is required to determine an individualized optimal time point for initiation of parenteral nutrition.

Introduction: The History of Parenteral Nutrition: From Puppies to the ICU

Until the 1960s, patients with permanent gastrointestinal failure, due to major intestinal resection, fistulae or agenesis, faced an inevitable death by starvation, which urged the development of parenteral nutrition (PN) as a rescue therapy. However, the development of both effective and safe PN formulations was cumbersome and hampered by several factors:

- Lack of a reliable and durable intravenous (IV) central venous access (metal needles in large arm veins).
- Lack of knowledge how to prepare energy-dense (parenteral) preparations, necessitating infusions of large fluid amounts.
    - Lack of expertise and machinery for the sterile and apyrogenic preparation of PN.
    - Unavailability of stable preparations of trace elements, vitamins and lipids for parenteral infusion.

J. Gunst, MD, PhD
Intensive Care Medicine, University Hospitals Leuven, Herestraat 49, Leuven 3000, Belgium

M.P. Casaer, MD, PhD (✉)
Intensive Care Medicine, University Hospitals Leuven, Herestraat 49, Leuven 3000, Belgium

Burn Unit, University Hospitals Leuven, Herestraat 49, Leuven 3000, Belgium
e-mail: Michael.casaer@uzleuven.be

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_6,

The heroic process of trial and error that resulted in a safe and effective parenteral nutrition practice was described in detail in a review by the original clinical investigators [1, 2]. In a first milestone experiment, six puppies not only survived more than 7 months nourished exclusively parenterally, they also had comparable growth as controls receiving oral nutrition. Subsequently, the feasibility of this parenteral nutrition strategy was demonstrated in severely malnourished patients and in an infant with short bowel syndrome [1, 2]. Although the first infant eventually died, several months of PN resulted in growth, weight gain and wound closure and reversed weight loss in adults in this obviously non-controlled experiment.

The safety and feasibility of the clinical use of PN gradually improved thanks to the introduction of central venous access, the development of atraumatic, non-pyrogenic, and biocompatible infusion catheters, the preparation of PN solutions in lamellar airflow chambers and the increased availability of commercial, ready-to-use macronutrient and micronutrient preparations. When reconsidering the indications of (supplemental) PN in critical illness today, we should never forget the undisputable life-saving contribution of the PN pioneers to patients with permanent loss of the gastrointestinal tract, surviving today thanks to home PN.

Feeding Policies in the ICU Until the Publication of Recent RCTs

While it is incontrovertible that, without parenteral nutrition, patients with chronic gut failure would starve, the indications for use of PN in the ICU are less clear. Due to the lack of large randomized controlled trials (RCTs) on the optimal timing and indication of PN in critically ill patients, the use of PN in the ICU has varied considerably among centers. This is illustrated by the divergent professional guidelines on timing and indication of (supplemental) PN in critically ill patients and by the use of PN in recent large clinical studies in the field of critical care.

Whereas both European and American feeding guidelines recommended the early institution and buildup of enteral nutrition (EN), an intervention that may promote intestinal integrity and immune defense [3, 4] (see also Chap. 2), the recommended timing of initiating supplemental PN varied considerably. The European ESPEN guidelines recommended early (i.e., within 2 or 3 days after ICU admission) institution of supplemental PN when enteral nutrition was deemed insufficient to cover the metabolic requirements [5, 6]. In contrast, the American ASPEN/SCCM guidelines recommended withholding supplemental PN until 1 week after ICU admission [4].

Hence, in the German VISEP trial, a RCT in patients with severe sepsis, patients received EN with early institution of supplemental PN. On average, more than 50 % of total calorie intake was provided by the parenteral route during the first week in ICU [7]. Likewise, in the Scandinavian Glutamine trial, including general ICU patients, early supplemental PN was provided. This resulted in administration of more than 70 % of the total calorie intake by the parenteral route in the first week [8]. In sharp contrast, 74 % of critically ill patients never received PN in a large observational study including mainly North American and Australian ICUs [9]. A recent high-quality survey of the evolution in PN use in the USA in almost 400, 000 ICU patients even showed a decline in the proportion of patients receiving PN, from 7.2 % in 2001–2002 to 5.5 % in 2007–2008. However, in patients receiving PN it was started much earlier than suggested by the American guidelines; median 2 days (IQR 1–3) after admission [10].

As mentioned before, the substantial worldwide variation in feeding policies for the same diseases—critical illness and sepsis—is likely attributable to the lack of solid evidence, which should ultimately be delivered by large RCTs. Hence, professional guidelines were largely based on observational studies and expert opinion. In the absence of large RCTs, every approach had potential theoretical advantages and downsides.

The early administration of supplemental PN, as advocated by European guidelines, was intended to prevent the accumulation of caloric and protein deficit. Indeed, buildup of such a deficit has been associated with adverse outcome in several large observations. In an international multicenter observational analysis, every 1000 kcal increase in average daily energy intake was associated with a shorter duration of mechanical ventilation and a 25 % relative reduction in 60 days mortality [9]. Likewise, the incidence of new infections was found to be lower in patients with a lower energy debt [11]. However, the observational nature of these studies precludes an estimation whether these associations were causal or casual. Indeed, the adequacy of feeding, especially the adequacy of EN, depends on the severity of illness. The buildup of a caloric deficit may to some extent reflect a higher disease severity rather than being detrimental by itself. Moreover, a number of observational analyses of the relation between nutrient intake and outcome were flawed by time bias and/or informative censoring [12]. A reliable estimation of the impact of early, full nutritional support including early administration of supplemental parenteral nutrition requires an adequately powered methodologically sound randomized controlled trial [13, 14].

In contrast to the European guidelines, the American guidelines recommended withholding parenteral nutrition until 1 week after ICU admission. This policy allows accumulation of energy deficit in a considerable number of patients, as EN is often insufficient to meet the caloric requirements, especially in the acute phase of illness. In the absence of RCTs, this approach was justifiable. Compared with EN, administration of PN has been associated with an increased risk of complications, such as hyperglycemia, infectious complications and hyperbilirubinemia. Theoretically, administration of supplemental PN could offset potential benefits of more energy and protein delivery with increased complications.

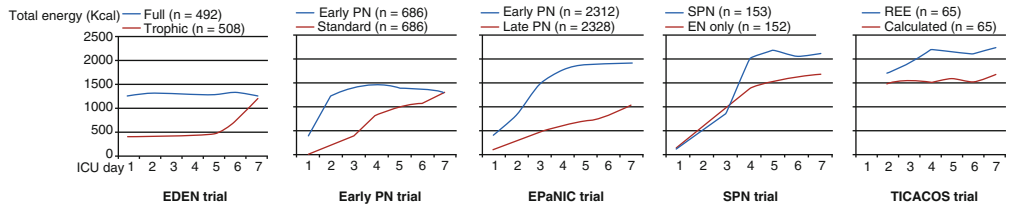
Another factor contributing to the difference in the American versus the European approach with regard to timing of supplemental PN may have been the long-standing unavailability of newer PN preparations containing less inflammatory lipids in the USA. Indeed, for decades, only soybean oil based preparations were approved by the American Food and Drug Administration (FDA). The feared delayed hypersensitivity reactions reported with the cottonseed oil emulsions of the early 1960s are very uncommon with soybean oil-based preparations [15]. In any case, the clinical superiority of different lipid compositions in PN remains to be established [16].

In summary, an important discrepancy between European and American PN practices has existed for decades. Recently, both strategies have been compared in several high quality randomized controlled trials [17–19]. In the following section we will provide a balanced overview of the published RCTs in order to put the results in a broader perspective.

Results from Recent RCTs Studying the Time of PN Initiation in the ICU

Over the last years, three (large) RCTs have studied the timing of supplemental parenteral nutrition, the EPaNIC, SPN and Early PN trial respectively. The study design varied among the different studies, with different inclusion criteria and different interventions started at different time points in the first week of critical illness (Fig. 6.1). These three trials, altogether involving more than 6000 patients, unequivocally showed that early administration of supplemental PN did not have a clinical benefit. Moreover, one RCT, the EPaNIC study, even showed net harm by early administration of supplemental PN.

The most recent RCT, the Australian Early PN trial (see Fig. 6.1), studied the initiation of supplemental parenteral nutrition very early in the disease course, within a few hours after ICU admission, in patients with a relative and rather short—48 h—contraindication for enteral nutrition [18]. The nutrition



Patients	Medical (ALI) Eligible for EN	Mixed medical/surgical EN relatively contraindicated (Short term)	Mixed medical/surgical (unselected) With nutritional risk (NRS≥3)	Mixed medical/surgical (on day 4) Eligible for EN but <60% target	Mixed medical/surgical
New infections in ICU	Unaffected	Unaffected	More with Early PN	Between day 9 and day 28: Less with SPN From randomization to day 28: Unaffected	More with REE
Duration of mechanical ventilation	Unaffected	Shorter with Early PN	Longer with Early PN	Unaffected	Longer with REE
ICU Length of stay	Unaffected	Unaffected	Longer with Early PN	Unaffected	Longer with REE
ICU Mortality	Unaffected	Unaffected (60 day mortality: unaffected)	Unaffected	Unaffected	Unaffected (Trend towards reduced hospital mortality)

Fig. 6.1 Comparative graph: Comparison of energy and outcome in five recent RCTs. The outcomes for new infections, duration of mechanical ventilation, duration of stay in the ICU, and ICU mortality are depicted as only these were available for all five trials The *underlined* outcome measure represents the predefined primary endpoint of each trial. The comparison reveals no benefit of enhanced macronutrient delivery early during critical illness on survival or on intensive care dependency. It may be that the apparent differences among the studies for other outcomes are related to the differences in dose of macronutrients or the route of macronutrient delivery. *Filled lines* represent days where, according to the study protocols, patients were *not* allowed to receive parenteral nutrition. *Dashed lines* represent days where patients were allowed to receive parenteral nutrition. All cartoons were drafted based on the data reported in the original publications. The *lines* represent mean values for total energy intake. For the SPN trial, only % of target was available. Based on the published results, average energy intake between day 4 and 8 was 28 kcal/day in the SPN arm, which for the average patient bodyweight (74.8 kg) resulted in 2094 kcal corresponding to approximately 100 % of target. *N* the number of patients randomized per arm, *ALI* acute lung injury, *EN* enteral nutrition, *ICU* intensive care unit, *NRS* nutritional risk score, *PN* parenteral nutrition. Reprinted from Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014 Jun 19;370(25):2449–50; with permission from NEJM 2014

therapy in control patients was left to the discretion of the treating physician. The protocol did not allow PN administration before day 3 in these patients. This resulted in more than one third of control patients also receiving PN in the first week of critical illness, either as total parenteral nutrition or as a supplement to enteral nutrition. Unfortunately, data on the relative contribution of EN and PN to total energy intake in both groups are not available. The resulting energy intake in both groups differed only modestly (see Fig. 6.1). The primary endpoint, mortality at 60 days, was unaffected, as were most secondary endpoints. There were similar incidences of new infections, no impact on organ failure and comparable ICU and hospital length of stay. The investigators found a small apparent benefit of early PN on other secondary endpoints. In the ICU, a small reduction in time on mechanical ventilation was found (0.4 days/10 ICU stay days reduction). However, this did not translate in a reduction in ICU stay. Second, manual palpation and judgment of muscle volume during ICU stay also suggested less muscle wasting in Early PN patients. However, this subjective assessment has been demonstrated to be unreliable in critically ill patients, and even more so in a non-blind blinded not "blinding" setting [20]. And finally, there was a statistically significant difference in perceived quality of life at 60 days by early PN, but the difference was so small that it was judged clinically meaningless by the investigators. The authors also

published a model based health economy analysis in order to predict possible cost reductions with early PN based on the estimated clinical effect size [21]. In this model, early PN initiation generated a significant reduction of healthcare costs. Of note, this analysis is not based on true healthcare costs data obtained from the individual patients (invoices) but is an extrapolation based on the reported differences in clinical outcome and their assumed price [22].

In summary, in the early PN trial, initiation of PN within a few hours after ICU admission was compared to later initiation of PN, which could be as early as after 2 days. It did not affect clinical outcome despite a small but statistically significant reduction in the duration of mechanical ventilation.

The Swiss SPN trial (see Fig. 6.1) focused on a different and smaller patient group [17]. SPN patients were enrolled on day 3 after ICU admission if they received less than 60 % of target by EN at that time and were expected to stay in ICU for more than 5 days. In the SPN group, supplemental PN was started at day 4, whereas PN was withheld until day 9 in the control arm. Energy target was based on Resting Energy Expenditure, which was determined by indirect calorimetry and effectively measured in two thirds of the patients. In the remaining patients, energy target was calculated. The included patients received a fairly large but still below 60 % of target amount of enteral nutrition on day 3 of critical illness. Control patients had their EN gradually increased to about 80 % of target by the end of the first week in ICU. SPN patients additionally received a small dose of PN increasing total energy intake close to 100 % of target. The limited difference in energy intake was reflected by identical insulin needs in both study groups. In the original paper, a reduction in the acquisition of new infections with SPN was reported [17]. However, this claim was based on the infection rate occurring after day 9 in ICU, hence ignoring a potential impact of the intervention during the first 5 days after randomization [23]. This methodological choice is particularly problematic, as not attributing all events observed after randomization to the randomized intervention significantly increases the risk of bias, which has been shown decades ago by the FDA in the context of the Anturane Reinfarction trial [24]. Indeed, when taking into account all infections occurring after randomization in the SPN trial—the primary endpoint as reported on clinicaltrials.gov—the incidence of infections was identical in both groups [25]. Also, secondary endpoints, including the duration of mechanical ventilation, ICU and hospital length of stay and ICU and hospital mortality were unaffected by the intervention.

Summarizing, in the SPN trial, adding a low dose of PN to rather successful EN between days 4 and 8 did not provoke harm nor generate substantial benefit.

Finally, the Belgian EPaNIC study (see Fig. 6.1) randomized general ICU patients to Early or Late PN. In all patients, initiation of EN was attempted if oral intake was not expected. In order to attenuate the rapidly accumulating energy deficit during the first days in ICU, early PN patients received dextrose 20 % aimed at achieving 400 and 800 kcal total energy intake (including EN) on, respectively, days 1 and 2. If EN was insufficient on day 3, parenteral nutrition was initiated targeted at achieving, together with EN, 100 % of energy target by the end of day 4. Late PN patients received dextrose 5 % and no PN before day 8 in ICU, even if EN was insufficient. Potassium, phosphate and micronutrients were administered to all patients until adequate EN was achieved, in order to prevent refeeding syndrome [26]. The EPaNIC study enrolled all patients at nutritional risk, as defined by the nutritional risk score (NRS). This circumvented the difficulty in predicting a prolonged ICU stay and/or subsequent failure to achieve adequate enteral intake. The achieved difference in energy intake between patients in the two randomization groups after 1 week was substantial [27]. In contrast to what was expected from the above cited observational studies, the prevention of a caloric deficit by early parenteral nutrition increased ICU length of stay, the primary endpoint, and increased overall hospital length of stay as well. Mortality was similar in both groups, but the incidence of new infections, in particular airway, bloodstream, and wound infections, was higher in the early PN group. There were also increases in duration of mechanical ventilation, duration of renal replacement therapy, and duration of acute kidney injury stage two [28]. While hyperbilirubinemia was less frequent, other markers

of cholestasis and hepatocellular damage (gamma glutamyl transferase, alkaline phosphatase and alanine amino transferase) increased more in early PN patients. Moreover, early PN increased the incidence of biliary sludge in patients with prolonged ICU stay [29]. Early PN increased hospital expenditures [30]. The incidence of ICU-acquired muscle weakness (ICU AW) in patients staying more than 7 days in ICU was higher with early as compared to late PN. Early PN slowed the recovery from ICU AW [31].

In summary, the three recent feeding trials (EPaNIC, SPN and Early PN trial) demonstrated that early PN, initiated at day 1, 3, or 4 in the ICU, did not improve clinical outcome and may even be harmful (see Fig. 6.1).

While the SPN and Early PN results—neutral and hence less against the existing bias—have been easily accepted, a number of opinion papers have been written aimed at explaining or refuting the EPaNIC results. Specifically, the patient selection, the PN composition and the energy target have been questioned. These critiques are hypothesis-generating and could be the subject of future clinical trials. However, preplanned subgroup analyses together with extensive post-hoc investigations of the EPaNIC study largely opposed these arguments as explanation for the observed negative effects of early PN in the trial.

A first concern regarding the generalizability of the EPaNIC results was the patient selection. Some experts were particularly worried by the relatively high proportion of cardiac surgery patients (approximately 60 % of the total study population). This critique assumes that cardiac surgery patients would react differently to feeding than any other critically ill patient. Berger and Mustafa concluded in their review that cardiac surgery patients indeed often have relatively short ICU stays and have an acceptable premorbid nutritional status if the cardiac function is not compromised [32]. However, the effect of the randomized intervention was comparable in cardiac surgery versus the 1822 “other patients” included in EPaNIC [19, 33] (Fig. 6.2).

A second concern was that a hypothesized beneficial effect of supplemental PN in the sickest patients would have been obscured by an untoward effect of PN in less severely ill patients. Of note, mean APACHE-II scores in EPaNIC were comparable as in the SPN or Early PN trial. A post-hoc analysis of the impact of early versus late PN on the likelihood of an earlier discharge alive from ICU and on the risk for acquisition of a new infection in ICU refuted this hypothesis (see Fig. 6.2). When the impact of the intervention was studied in separate quartiles of APACHE-II scores, there was no identifiable subgroup of illness severity in which early PN had a beneficial impact.

Some experts attributed the unfavorable outcome with early PN rather to the Dextrose 20 % (given on day 1 and 2) than to the 5 days of PN thereafter. In addition, the amino acid intake was suggested to be too low to allow benefit from supplemental PN. However, post hoc analysis of the relative glucose versus protein doses in EPaNIC revealed that higher protein to glucose ratios were associated with a lower likelihood of earlier alive discharge from ICU [33].

Another suggested criticism was that the achieved energy intake by early PN in the EPaNIC trial may have been above the optimal level. In order to detect an intermediate energy intake associated with better outcome, we performed an observational analysis of the relation between cumulative energy intake up to a given day in ICU and the likelihood of an earlier ICU discharge in the upcoming days. An inverse relationship was found. Even in late PN patients receiving only EN, all energy intervals higher than the lowest energy intake were associated with longer ICU stays [33]. As mentioned before, this finding is hypothesis-generating and should ultimately be confirmed by an RCT allocating patients to different energy doses rather than by an observational analysis of the relationship between nutrient dose and recovery. The results of the EDEN trial, a RCT investigating the impact of 1 week of full EN versus restricted, “trophic” EN in ARDS patients are consistent with these findings [34]. In this study, early full EN, although recommended by all professional societies, did not provide any short- or long-term clinical benefit (see Fig. 6.1) [35].

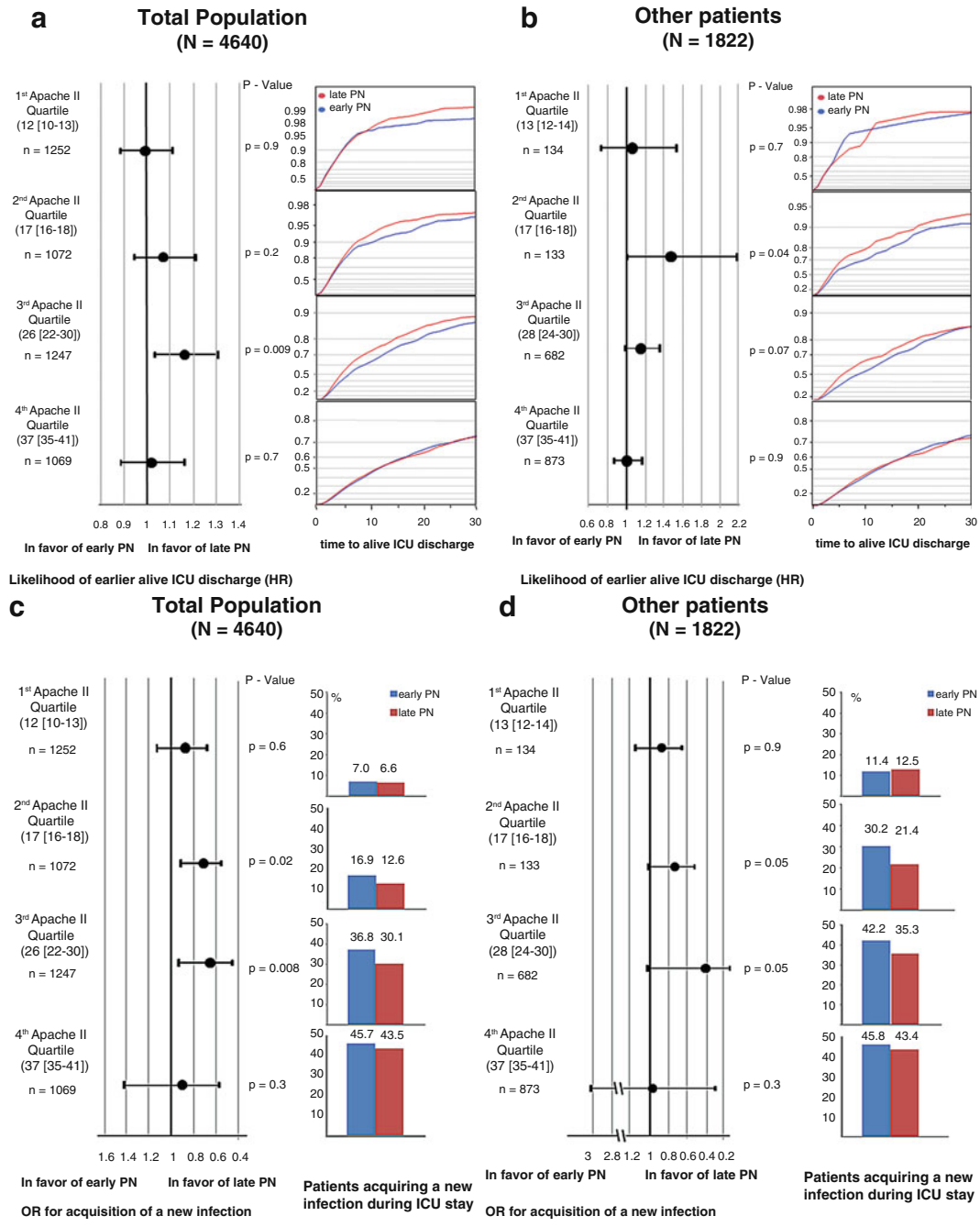


Fig. 6.2 Blue journal subgroups analyses. Time to live discharge from the intensive care unit (ICU) and acquisition of a new infection with early parenteral (early PN) versus late PN (no PN during the first week in the ICU) in different-severity-of-illness subgroups. (**a**, **b**) *Left*: Hazard ratios (HRs) and confidence intervals (CIs) (plus *P* value) for an earlier alive-ICU-discharge with early versus late PN in patient quartiles defined by APACHE II score. (**a**, **b**) *Right*: Kaplan–Meier curves depicting the proportion of patients discharged alive from the ICU on ICU Days 1–30. (**c**, **d**) *Left*: Odds ratios (ORs) and CIs for acquisition of a new infection in ICU with early versus late PN (plus *P* value). (**c**, **d**) *Right*: Crude proportion of patients acquiring a new infection in the ICU. (**a**, **c**) Total study population. (**b**, **d**) Other patients; these are the patients admitted to the medical ICU, admitted for medical reasons after surgery, or admitted after complex surgery (including trauma and burns). Whereas Kaplan–Meier curves depict only the first 30 days in ICU, the hazard ratios, in contrast, are based on every patient's entire ICU stay. *APACHE* acute physiology and chronic health evaluation. Reprinted with permission of the American Thoracic Society, Copyright © 2014 American Thoracic Society. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. 2013. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med, 187, 247–55

Some experts have suggested that only indirect calorimetry-guided nutritional strategies will improve outcome and avoid harm by overfeeding. The measurement of REE would allow to administer no more energy than is expended by the patient. An increased respiratory quotient would allow the clinician to detect overfeeding [36]. Unfortunately, current nutritional regimens in critical care have been found to insufficiently suppress endogenous tissue breakdown and gluconeogenesis [37]. Hence, the provided nutrients are administered on top of an unknown and insufficiently suppressed endogenous nutrient mobilization, so that overfeeding remains plausible, even when patients are fed no more than measured REE [37–39]. Moreover, the measurement of REE is difficult, and even more so when patients are more severely ill (presence of chest drains, high FiO2) [36, 40]. Even in the most experienced hands, as was the case in the SPN trial, REE was effectively measured only in 65 % of patients, in which the intervention also did not offer clinical benefit [17]. A recent comparison of 3 different indirect calorimeters also casted doubt on the reliability of the tool, with inter-instrument differences in measured REE up to 400 kcal [41]. A pilot RCT comparing artificial nutrition guided by indirect calorimetry (IC) versus "calculation based feeding" showed more infections, a longer duration of mechanical ventilation and a prolonged ICU stay in the IC guided patients. Of note, IC guided feeding resulted in a higher nutritional intake and particularly more PN administration [42]. Hence, there is currently no convincing evidence in favor of IC-guided feeding in the acute phase of critical illness.

Patients with Strong and Prolonged Contraindication for EN

While the Australian Early PN trial focused on patients with a short and relative contraindication for EN, patients with a true contraindication for EN were excluded. As specified in the online supplement, patients could only be included if "not expected to receive enteral, parenteral or oral nutrition today or tomorrow" and were excluded if "long-term contraindications to enteral or oral nutrition" were present [18]. Also in other RCTs, such patients were mostly excluded. Indeed, many investigators judged the randomization of such patients to "PN" versus "no PN" to be unethical as the latter group would be intentionally starved. However, there is no hard evidence that artificial feeding would be superior to short-term starvation in the ICU [43]. Therefore, these patients were not excluded in the EPaNIC trial. In this study, more than 500 patients with a surgical contraindication for EN were included. They were recognizable upon ICU admission, having undergone pulmonary, esophageal, abdominal or pelvic surgery. Patients in this subgroup received a mean EN energy intake of 0 kcal on day 7. With virtually no nutritional supply by EN in the first week in both randomization groups, this EPaNIC subgroup represents the extremes of the randomized intervention, i.e., early, total parenteral nutrition in the Early PN group, versus 1 week of relative starvation in the Late PN group. Of note, patients in the Late PN group received a minimum parenteral amount of glucose in the first week to prevent hypoglycemia, and also electrolytes, vitamins and trace elements were administered early to prevent refeeding syndrome. Nevertheless, the harmful effect of early PN was even more pronounced than in the total study population. Indeed, delaying PN beyond the first week in ICU substantially reduced the incidence of new infections and increased the likelihood of a shorter stay in ICU [19]. Hence, this subgroup analysis of the EPaNIC trial suggests that patients who intuitively would benefit the most from early PN actually experienced most harm.

Patients with Severe Malnutrition

This remains an area of uncertainty. Patients with malnutrition were also included in the three aforementioned feeding trials (EPaNIC, SPN and Early PN). In the EPaNIC trial, however, patients with a body mass index (BMI) below 17 were excluded, which equals approximately 1 % of screened

patients. Nevertheless, patients in the highest nutritional risk scores with BMI above or equal to 17 were included in EPaNIC, in which subgroup the harmful effect of early PN was equally present. The SPN and Early PN trial did include patients with the lowest BMI categories. Unfortunately, however, no information was provided on the impact of the intervention in these subgroups.

There is very weak evidence that the most severely malnourished patients may benefit from earlier supplementation of PN. This exception is based on the Veterans Affairs study, in which the impact of 7–15 days of PN preoperatively, followed by 3 days PN postoperatively, was investigated versus no PN. This RCT showed a numerical, albeit nonsignificant reduction in noninfectious complications only in the patients with the most severe malnutrition. Nevertheless the same intervention provoked a significant increase of postoperative infectious complications in the patients with mild to moderate malnutrition [44]. The reader is reminded that any of these post hoc analyses may induce bias and are not definitive evidence.

Mechanisms for Harm by Parenteral Nutrition

Several factors may account for the increased harm observed with early PN. Two potential theoretical explanations emerge. On the one hand, parenteral nutrition-related complications may be responsible. Alternatively, an increased nutrient intake per se (regardless of the route of administration) may be harmful. A post hoc analysis of the EPaNIC study found that the lowest dose of delivered macronutrients was associated with the fastest recovery, both in the late and early PN group and also in prolonged critically ill patients [33]. Higher doses of macronutrients, administered parenterally or enterally, were associated with progressively more delayed recovery. This analysis suggests that not or not only the parenteral route by itself was responsible for the deleterious effects of early PN, but also the increased nutritional supply. This hypothesis is supported by the results of the recent CALORIES trial. In this large ($N=2600$) pragmatic RCT patients were randomized to receive either EN or PN for the first 5 days in ICU or until oral intake was resumed, whichever came first [45]. Feeding in both arms was isocaloric and below nutritional target. It is unclear why PN didn't reach the preset target. The primary endpoint of 30 day mortality was unaffected. Likewise, there was no impact on secondary endpoints, except for more vomiting with EN and a trend towards more liver enzyme elevations with PN. As clinical outcome in both groups was comparable, this study suggests that harm with PN observed in the EPaNIC and Veterans trials was rather dose- than route-related [19, 42, 44].

One emerging mechanism which may explain these findings is the inhibition of autophagy by more intense feeding [46]. Autophagy, a cellular housekeeping process that is crucial for self-maintenance by clearing cellular damage, is strongly inhibited by feeding. The process of autophagy involves the digestion of intracellular content within lysosomes. In this process, substrate is delivered to the lysosome via an intermediate organelle, the autophagosome. The crucial importance of autophagy in maintaining cellular homeostasis is illustrated by the severe phenotypes that develop when autophagy is selectively knocked out in animal models [47–49]. Animals with a tissue-specific, inducible knockout in key autophagic proteins progressively develop severe organ failure, even under basal, unstressed circumstances. In addition, these animals are more vulnerable to stress conditions. This is explained by the fact that autophagy can clear most intracellular damage, and is the only pathway able to clear certain macromolecular structures such as potentially toxic protein aggregates and damaged organelles. Besides a role in cellular homeostasis, autophagy plays a crucial role in the starvation response, which explains why autophagy is potently inhibited by feeding.

Recent human and animal studies have identified autophagy as a potentially important pro-survival and organ-protective pathway in critically ill states. Stimulation of autophagy has been shown to be protective against organ failure and mortality, whereas inhibition of autophagy had the opposite effects [50–53]. In a critically ill animal model, it was shown that early PN suppressed autophagy in critically ill states, which related to more severe mitochondrial damage and increased vital organ

damage. As autophagy also has an important role in innate immunity, autophagy suppression by feeding could theoretically also have contributed to the increased infection rate observed with early supplemental PN [54–56].

Besides an impact on autophagy, several other factors may account for the increased infectious risk with early parenteral nutrition [19, 42, 44]. Bloodstream infections may be provoked in a direct manner by PN administration. Indeed, PN infusion bags may be contaminated, particularly if they contain lipids, as these increase the pH of the solution [57, 58]. However, the incidence of such contamination related bloodstream infections might be reduced by adoption of specific hygiene guidelines. In less severely ill patients, the need of a central line for PN administration may be a direct cause of bloodstream infections, but in most critically ill patients, a central line is necessary for medical management even if no PN is initiated. Hyperglycemia, a common complication of PN, may at least partially explain the excess infections provoked by PN in older studies [59]. Indeed, avoiding hyperglycemia has been shown to be very effective in preventing new infections in the ICU [60–62]. However, in the recent feeding studies, excessive hyperglycemia was prevented, especially in the EPaNIC trial where all patients had tight glucose control [19].

Another potential contributing factor to the increased infection rate with early PN may be the lipid administration and/or lipid content. Intravenous lipids, particularly soybean derived lipids, may directly affect immune cells, reduce chemotactic migration and provoke lymphocyte and neutrophil apoptosis [63–65]. Also the reticuloendothelial system, when overwhelmed by excessive/rapid lipid infusion, may be hampered in its phagocytic capacities in a dose- and substrate-dependent way [66–68]. Clinically, however, administration of olive oil rather than soybean oil did not affect infectious or any other complication in critical illness [16]. Randomized controlled trials evaluating lipid-free versus lipid-containing PN are rare. Lipid-containing PN did, in a small study of trauma patients, indeed increase infectious complications and prolong duration of mechanical ventilation, ICU length of stay and hospital length of stay as compared to lipid-free PN [69]. In this trial, however, it is not possible to distinguish the role of the lipids alone versus the additional energy burden. In one meta-analysis of PN versus standard therapy in critical illness, interventions based on fat-free PN were more likely to induce clinical benefit than lipid-containing PN [70]. However, similar results were found for older versus more recent studies, and for low quality versus higher methodological quality trials [70].

Why Early PN has Failed to Attenuate Muscle Wasting and Functional Decline

Functional outcome data generated by early supplemental PN in the recent RCTs was also disappointing. There was no clear benefit of the intervention in the Early PN trial [21]. There was an increased incidence and hampered recovery of ICU acquired muscle weakness in the EPaNIC trial [31]. The EPaNIC long-term functional evaluation after 1–5 years is ongoing [71]. No assessment of muscle strength or function was reported for the SPN trial [17]. Strikingly, even enhanced *enteral* nutrition did not provoke any functional improvement as compared to enteral trickle feeding in ARDS patients in the EDEN trial. Up to target feeding indeed did not improve muscle strength 6 and 12 months after randomization as compared to trickle feeding, in spite of prevention of a substantial energy deficit [35, 72, 73].

The EPaNIC study protocol included a detailed analysis of macroscopic [74], microscopic and molecular changes within the muscle in patients randomized to early versus late PN [31]. In addition, analysis of the cumulative nitrogen balances allowed to gain more insight in the metabolic fate of infused amino acids. These analyses contribute to our understanding of the apparent failure of early PN to improve functional outcome.

Repetitive quantitative CT scanning at the mid-femoral and low abdominal level in an EPaNIC subgroup of neurosurgical patients provided insight in muscle and fat changes during the first week in ICU. Based on their specific X-ray attenuation, 3D units (voxels) of muscle and fat were automatically recognized. After manual delineation of the muscle compartment, intramuscular and subcutaneous fat volumes were separated. Within the muscle compartment, the muscle quality was further quantified based on the attenuation, whereby a shift towards lower attenuation reflected increased fat or water content within the muscle [75]. These analyses revealed a pronounced reduction in femoral muscle mass. Regardless of the randomization group, about 7 % of the femoral muscle mass was lost [74]. Early PN was not only unable to attenuate muscle wasting, it also induced lipogenesis reflected by increased intramuscular fat areas and loss of muscle attenuation. Unfortunately, the central neurologic lesions in this patient subgroup prevented correlation of morphological changes with muscle strength. Failure of early enhanced feeding to prevent muscle wasting while inducing lipogenesis has been reported long ago in non-randomized intervention studies [76].

Microscopic examination of quadriceps femoris muscle samples obtained after 1 week in 122 well-matched early and late PN patients confirmed an important decrease in myofiber diameters of both type I and type II myofibers, regardless of randomization [31]. On the molecular level, the ubiquitin–proteasome pathway, responsible among many other things for myofibrillar breakdown, was activated in both randomization groups. There was no suppressive effect of early PN on the ubiquitin–proteasome pathway. Muscle protein synthesis was suppressed to a very low and comparable level in both late and early PN patients as compared with healthy controls. In contrast to the catabolic ubiquitin–proteasome pathway, early PN did suppress the catabolic autophagy pathway. In the late PN group, in contrast, autophagy was activated in muscle biopsies. Similar observations were made in a critically ill animal model, in which early PN-induced suppression of autophagy was accompanied by signs of muscle degeneration [77].

As is the case for vital organs (see above), intact autophagy is crucial for maintaining cellular homeostasis in the muscle and for muscle integrity. Indeed, animals with a muscle-specific knockout, even when induced in adult life, develop severe muscle wasting and weakness, with severe structural and ultrastructural abnormalities [48]. Hence, the reduced "muscle quality" invoked by early PN, as observed on the sequential CT examinations, as well as the higher incidence of muscle weakness and hampered recovery from muscle weakness, may be explained by a negative impact of feeding on autophagy. The functional relevance of the autophagy suppression by early PN in the EPaNIC study was further supported by multivariable logistic regression analysis, in which the degree of autophagy activation/suppression, as expressed by the molecular LC3-II/LC3-I ratio was an independent determinant of muscle weakness.

The inability of early nutrient administration to attenuate muscle wasting also raises the question of the fate of the supplementary administered amino acids. An in depth analysis of the nitrogen intake and excretion during and beyond the time window of the randomized intervention of the EPaNIC trial provided some answers to this question [28]. It showed that the ability to retain nitrogen or to effectively suppress net catabolism is very limited in acute critical illness. Indeed, despite the relatively low amino acid content of the commercial PN preparations used in EPaNIC, Early PN resulted in a substantially increased ureagenesis with increased urinary nitrogen losses and only a small and temporary improvement of nitrogen balances. This suggests that a substantial fraction of the extra administered amino acids by early PN were, in effect, wasted. Over the first 2 weeks in ICU, approximately two thirds of the extra supplied amino acids appeared as urea (Fig. 6.3). The increased ureagenesis may have contributed to the prolonged duration of renal replacement therapy in early PN patients. These findings were recently confirmed by an Australian RCT, the Nephroprotective trial, in which parenteral protein administration up to recommended levels did not provide any clinical benefit, but increased duration of renal replacement therapy by increased ureagenesis) [78]. These observations also question the critique on the EPaNIC trial that the protein intake would have been too low. As the capacity of the body to retain nitrogen was already exceeded with the administered amount of amino acids, it seems unlikely that a higher amount of nitrogen intake, with possibly even more

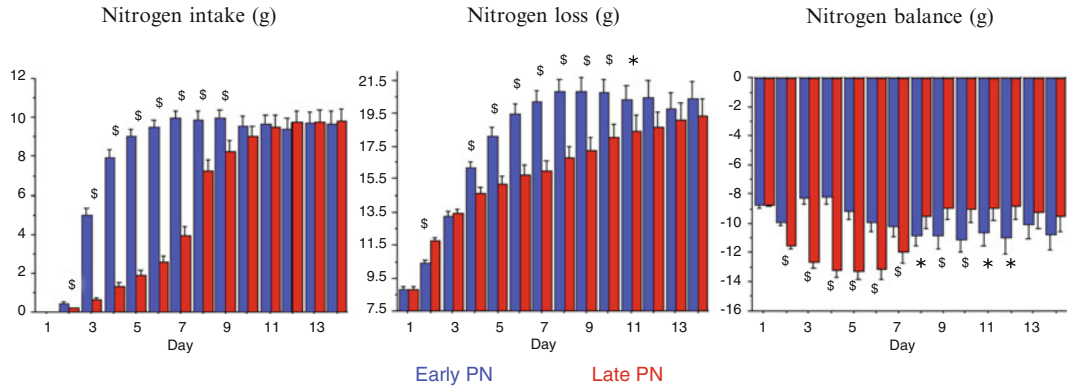


Fig. 6.3 Fate of infused protein in EPaNIC. Time profile of nitrogen intake, loss, and balance. Nitrogen intake, nitrogen loss, and nitrogen balance from day 1 until day 14 for the whole study population in the EPaNIC study. *Bar graphs* represent mean and 95 % confidence interval. *P* values lower than 0.01 are shown. *asterisk* and $ represent $0.0001 \leq p < 0.01$, respectively, $p < 0.0001$ between randomization groups. Adapted from Gunst J, Vanhorebeek I, Casaer MP, Hermans G, Wouters PJ, Dubois J, et al. Impact of early parenteral nutrition on metabolism and kidney injury. J Am Soc Nephrol 2013 May;24(6):995-1005

ureagenesis, would have led to beneficial effects. The potential mechanisms behind the profound resistance of critical illness-associated catabolism to feeding have been studied in detail by Yves Boirie and coinvestigators in the context of obesity and inflammation [79]. Future research should focus on how to overcome the profound feeding-resistant catabolism in critical illness, without invoking negative impact on housekeeping processes as autophagy.

Pragmatic Approach to the Timing and Indication of PN Initiation and Conclusion

In adult (non-pregnant) critically ill patients with a BMI above 17, there is no evidence for improved clinical outcome with supplemental PN initiated before day 8. Indeed, early administration of PN in these patients did not reduce morbidity, did not improve survival nor functional outcome and may even be harmful [43]. Therefore, supplemental PN, a costly intervention, should be abandoned in the acute phase of critical illness in these patients, even when EN is contraindicated (Fig. 6.4).

If EN is judged insufficient during the first week in ICU, there are several therapeutic options. Measurement of gastric residual volume can be omitted or higher volumes can be accepted [80, 81]. Gastroprokinetics and postbulbar feeding, albeit not without risk, may improve enteral intake [82]. Finally, lower energy and macronutrient intake could be accepted. However, a minimum amount of glucose (enteral and/or parenteral) could be administered and deficiencies in micronutrients should be prevented as they may lead to muscle weakness, lactic acidosis, and arrhythmias [26, 83].

If after 1 week in ICU, EN remains unsuccessful despite the interventions suggested above, it is reasonable to initiate parenteral nutrition.

No recommendations can be made for the use of supplemental PN in critically ill children, critically ill pregnant patients, critically ill patients with a BMI below 17, as well as in patients readmitted to the ICU, as these patients were mostly excluded from the large RCTs. The optimal timing of parenteral nutrition in children is currently being studied (NCT 01536275).

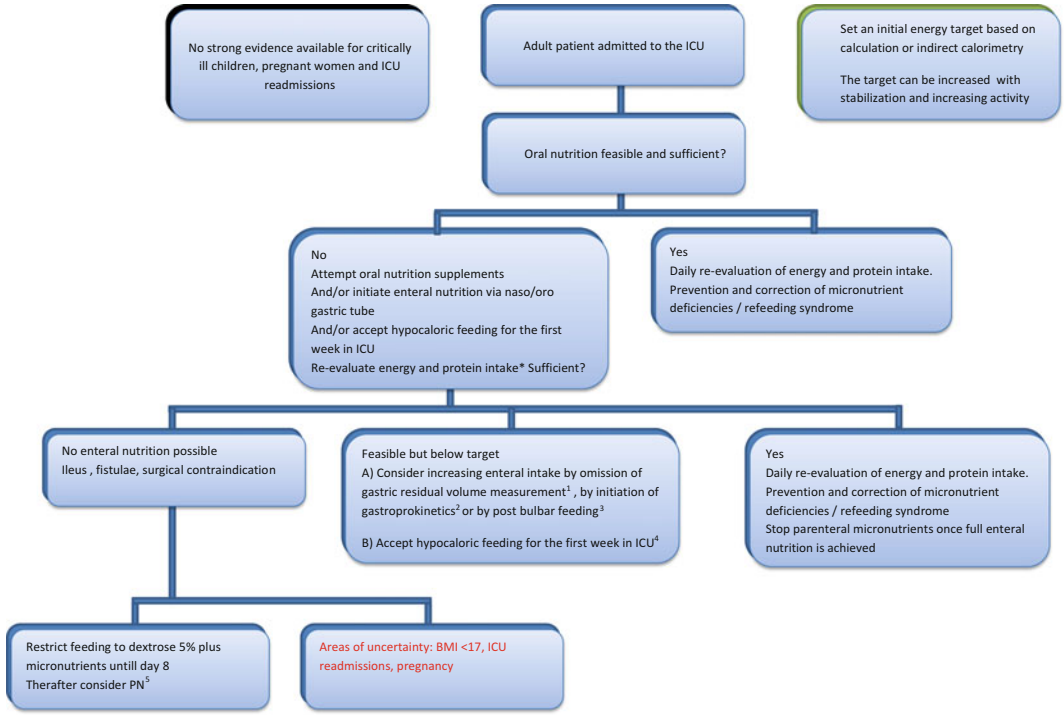


Fig. 6.4 Pragmatic decision tree: When to start PN in adult critically ill patients?

Future research should be aimed at identifying a reliable measure to recognize the optimal time point for enhanced feeding in individual patients rather than starting on a fixed day. Also a better understanding of the mechanisms behind the failure and burden of enhanced feeding may allow to circumvent these problems when feeding is initiated.

Conclusion

Parenteral nutrition was developed 40 years ago primarily for patients without a functional gastrointestinal tract. Its use has expanded to many other indications, which has probably led to overconsumption and has exposed patients to a treatment proven to lack benefit and which may potentially induce harm. Today PN comes home from this decades-long journey and finds its way back to the patients it was originally developed for, those suffering from a prolonged failure of the gastrointestinal tract.

References

1. Dudrick SJ. Early developments and clinical applications of total parenteral nutrition. JPEN J Parenter Enteral Nutr. 2003;27(4):291–9.
2. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Can intravenous feeding as the sole means of nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. Ann Surg. 1969;169(6):974–84.
3. Ikeda S, Kudsk KA, Fukatsu K, Johnson CD, Le T, Reese S, et al. Enteral feeding preserves mucosal immunity despite in vivo MAdCAM-1 blockade of lymphocyte homing. Ann Surg. 2003;237(5):677–85.

4. 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.
5. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25(2):210–23.
6. 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.
7. Elke G, Kuhnt E, Ragaller M, Schadler D, Frerichs I, Brunkhorst FM, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis. A secondary analysis of the VISEP trial. Med Klin Intensivmed Notfmed. 2013;108(3):223–33.
8. 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.
9. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009;35(10):1728–37.
10. Gershengorn HB, Kahn JM, Wunsch H. Temporal trends in the use of parenteral nutrition in critically ill patients. Chest. 2013;145(3):508–17.
11. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNM, Delarue J, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24(4):502–9.
12. Schetz M, Casaer MP, Van den Berghe G. Does artificial nutrition improve outcome of critical illness? Crit Care. 2013;17(1):302.
13. 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.
14. Peduzzi P, Henderson W, Hartigan P, Lavori P. Analysis of randomized controlled trials. Epidemiol Rev. 2002;24(1):26–38.
15. Hansen LM, Hardie BS, Hidalgo J. Fat emulsion for intravenous administration: clinical experience with intralipid 10%. Ann Surg. 1976;184(1):80–8.
16. 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(6):1792–8.
17. Heidegger CP, Berger 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.
18. Doig GS, 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.
19. 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.
20. Sheean PM, Peterson SJ, Gomez PS, Troy KL, Patel A, Sclamberg JS, et al. The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment. JPEN J Parenter Enteral Nutr. 2014;38(7):873–9.
21. Doig GS, Simpson F. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a full economic analysis of a multicenter randomized controlled trial based on US costs. Clinicoecon Outcomes Res. 2013;5:369–79.
22. Drummond M, Sculpher M. Common methodological flaws in economic evaluations. Med Care. 2005;43(7 Suppl):5–14.
23. Casaer MP, Wilmer A, Van den Berghe G. Supplemental parenteral nutrition in critically ill patients. Lancet. 2013;381(9879):1715.
24. Temple R, Pledger GW. The FDA's critique of the anturane reinfarction trial. N Engl J Med. 1980;303(25):1488–92.
25. Heidegger CP, Berger MM, Thibault R, Zingg W, Pichard C. Supplemental parenteral nutrition in critically ill patients – authors' reply. Lancet. 2013;381(9879):1716–7.
26. Byrnes MC, Stangenes J. Refeeding in the ICU: an adult and pediatric problem. Curr Opin Clin Nutr Metab Care. 2011;14(2):186–92.
27. Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1(8):621–9.

28. Gunst J, Vanhorebeek I, Casaer MP, Hermans G, Wouters PJ, Dubois J, et al. Impact of early parenteral nutrition on metabolism and kidney injury. J Am Soc Nephrol. 2013;24(6):995–1005.
29. Vanwijngaerden YM, Langouche L, Brunner R, Debaveye Y, Gielen M, Casaer M, et al. Withholding parenteral nutrition during critical illness increases plasma bilirubin but lowers the incidence of biliary sludge. Hepatology. 2014;60(1):202–10.
30. Vanderheyden S, Casaer MP, Kesteloot K, Simoens S, De RT, Peers G, et al. Early versus late parenteral nutrition in ICU patients: cost analysis of the EPaNIC trial. Crit Care. 2012;16(3):R96.
31. Hermans G, Casaer MP, Clerckx B, Güiza FG, Vanhullebusch T, Derde S, et al. Impact of tolerating macronutrient deficit on the development of intensive care unit-acquired weakness. Lancet Respir Med. 2013;1(8):621–9.
32. Berger MM, Mustafa I. Metabolic and nutritional support in acute cardiac failure. Curr Opin Clin Nutr Metab Care. 2003;6(2):195–201.
33. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med. 2013;187(3):247–55.
34. 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.
35. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, et al. Physical and cognitive performance of acute lung injury patients one year after initial trophic vs full enteral feeding: EDEN trial follow-up. Am J Respir Crit Care Med. 2013;188(5):567–76.
36. Frankenfield DC, Ashcraft CM. Estimating energy needs in nutrition support patients. JPEN J Parenter Enteral Nutr. 2011;35(5):563–70.
37. Tappy L, Berger M, Schwarz JM, McCamish M, Revelly JP, Schneiter P, et al. Hepatic and peripheral glucose metabolism in intensive care patients receiving continuous high- or low-carbohydrate enteral nutrition. JPEN J Parenter Enteral Nutr. 1999;23(5):260–7.
38. Schwarz JM, Chiolero R, Revelly JP, Cayeux C, Schneiter P, Jequier E, et al. Effects of enteral carbohydrates on de novo lipogenesis in critically ill patients. Am J Clin Nutr. 2000;72(4):940–5.
39. Tappy L, Schwarz JM, Schneiter P, Cayeux C, Revelly JP, Fagerquist CK, et al. Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis, and respiratory gas exchanges in critically ill patients. Crit Care Med. 1998;26(5):860–7.
40. da Rocha EE, Alves VG, da Fonseca RB. Indirect calorimetry: methodology, instruments and clinical application. Curr Opin Clin Nutr Metab Care. 2006;9(3):247–56.
41. Sundstrom M, Tjader I, Rooyackers O, Wernerman J. Indirect calorimetry in mechanically ventilated patients. A systematic comparison of three instruments. Clin Nutr. 2013;32(1):118–21.
42. Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med. 2011;37(4):601–9.
43. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014;370(25):2449–50.
44. 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.
45. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371(18):1673–84.
46. Kroemer G, Marino G, Levine B. Autophagy and the integrated stress response. Mol Cell. 2010;40(2):280–93.
47. Komatsu M, Waguri S, Ueno T, Iwata J, Murata S, Tanida I, et al. Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. J Cell Biol. 2005;169(3):425–34.
48. Masiero E, Agatea L, Mammucari C, Blaauw B, Loro E, Komatsu M, et al. Autophagy is required to maintain muscle mass. Cell Metab. 2009;10(6):507–15.
49. Nakai A, Yamaguchi O, Takeda T, Higuchi Y, Hikoso S, Taniike M, et al. The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress. Nat Med. 2007;13(5):619–24.
50. 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):177–89.
51. Carchman EH, Rao J, Loughran PA, Rosengart MR, Zuckerbraun BS. Heme oxygenase-1-mediated autophagy protects against hepatocyte cell death and hepatic injury from infection/sepsis in mice. Hepatology. 2011;53(6):2053–62.
52. Hsieh CH, Pai PY, Hsueh HW, Yuan SS, Hsieh YC. Complete induction of autophagy is essential for cardioprotection in sepsis. Ann Surg. 2011;253(6):1190–200.
53. Lo S, Yuan SS, Hsu C, Cheng YJ, Chang YF, Hsueh HW, et al. Lc3 over-expression improves survival and attenuates lung injury through increasing autophagosomal clearance in septic mice. Ann Surg. 2013;257(2):352–63.

54. Yuk JM, Yoshimori T, Jo EK. Autophagy and bacterial infectious diseases. Exp Mol Med. 2012;44(2):99–108.
55. Shahnazari S, Brumell JH. Mechanisms and consequences of bacterial targeting by the autophagy pathway. Curr Opin Microbiol. 2011;14(1):68–75.
56. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature. 2011;469(7330):323–35.
57. Kuwahara T, Shimono K, Kaneda S, Tamura T, Ichihara M, Nakashima Y. Growth of microorganisms in total parenteral nutrition solutions containing lipid. Int J Med Sci. 2010;7(3):101–9.
58. Kuwahara T, Kaneda S, Shimono K, Inoue Y. Growth of microorganisms in total parenteral nutrition solutions without lipid. Int J Med Sci. 2010;7(1):43–7.
59. 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.
60. Van den Heuvel I, 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(19):1359–67.
61. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–61.
62. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I., et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009;373(9663): 547–56.
63. Cury-Boaventura MF, Torrinhas RS, de Godoy AB, Curi R, Waitzberg DL. Human leukocyte death after a preoperative infusion of medium/long-chain triglyceride and fish oil parenteral emulsions: a randomized study in gastrointestinal cancer patients. JPEN J Parenter Enteral Nutr. 2012;36(6):677–84.
64. Cury-Boaventura MF, Gorjao R, de Lima TM, Fiamoncini J, Torres RP, Mancini-Filho J, et al. Effect of olive oil-based emulsion on human lymphocyte and neutrophil death. JPEN J Parenter Enteral Nutr. 2008;32(1):81–7.
65. Nordenstrom J, Jarstrand C, Wiernik A. Decreased chemotactic and random migration of leukocytes during Intralipid infusion. Am J Clin Nutr. 1979;32(12):2416–22.
66. Seidner DL, Mascioli EA, Istfan NW, Porter KA, Selleck K, Blackburn GL, et al. Effects of long-chain triglyceride emulsions on reticuloendothelial system function in humans. JPEN J Parenter Enteral Nutr. 1989;13(6):614–9.
67. Jensen GL, Mascioli EA, Seidner DL, Istfan NW, Domnitch AM, Selleck K, et al. Parenteral infusion of long- and medium-chain triglycerides and reticuloendothelial system function in man. JPEN J Parenter Enteral Nutr. 1990;14(5):467–71.
68. Olivecrona G, Olivecrona T. Clearance of artificial triacylglycerol particles. Curr Opin Clin Nutr Metab Care. 1998;1(2):143–51.
69. Battistella FD, Widergren JT, Anderson JT, Siepler JK, Weber JC, MacColl K. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. J Trauma. 1997;43(1):52–8.
70. 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.
71. Casaer MP, Hermans G, Wilmer A, Van den Berghe G. Impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients (EPaNIC trial): a study protocol and statistical analysis plan for a randomized controlled trial. Trials. 2011;12:21.
72. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med. 2010;38(5):1276–83.
73. 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.
74. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De DB, Guiza FG, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med. 2013;41(10):2298–309.
75. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol. 2000;89(1):104–10.
76. 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.
77. Derde S, Vanhorebeek I, Guiza F, Derese I, Gunst J, Fahrenkrog B, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology. 2012;153(5):2267–76.
78. Doig GS, Simpson F, Sweetman EA, Heighes P. The Nephro-Protective Trial, oral presentation at ESPEN 2013. 3-9-2013. 2-7-2013. Personal communication.
79. Guillet C, Delcourt I, Rance M, Giraudet C, Walrand S, Bedu M, et al. Changes in basal and insulin and amino acid response of whole body and skeletal muscle proteins in obese men. J Clin Endocrinol Metab. 2009;94(8):3044–50.

80. Reignier J, Mercier E, Le GA, Boulain T, Desachy A, Bellec F, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309(3):249–56.
81. Montejo JC, Minambres E, Bordeje L, Mesejo A, Acosta J, Heras A, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. Intensive Care Med. 2010;36(8):1386–93.
82. Ridley EJ, Davies AR. Practicalities of nutrition support in the intensive care unit: the usefulness of gastric residual volume and prokinetic agents with enteral nutrition. Nutrition. 2011;27(5):509–12.
83. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg. 1996;131(10):1043–7.

Chapter 7
Access and Complications of Parenteral Nutrition

Dustin R. Neel

Keywords Parenteral nutrition • Venous anatomy • Peripheral venous catheter • Midline catheter • Central venous catheter • Peripherally inserted central catheter (PICC) • Tunneled central venous catheter • Implantable central venous port • Thrombophlebitis • Catheter-related infections • Blood stream infections • Pneumothorax • Air embolism • Catheter malposition • Pinch-off syndrome • Catheter occlusion • Catheter thrombosis • Hyperglycemia • Hypoglycemia • Hyperlipidemia • Essential fatty acid deficiency • Hepatic steatosis • Nephromegaly • Metabolic bone disease • Refeeding syndrome

Key Points

- Peripheral venous access is indicated for short-term parenteral nutrition in those with adequate veins and those whom can tolerate high volumes of low osmolality solutions but cannot tolerate short-term starvation. Peripheral parenteral nutrition is rarely necessary. The major complication of peripheral venous access is thrombophlebitis.
- Non-tunneled central venous catheters are placed via the Seldinger technique. The majority of complications including pneumothorax, air embolism, and bleeding, occur during initial placement. These catheters may be used for short-term parenteral nutrition therapy.
- Peripherally inserted central catheters (PICCs) are indicated for intermediate-term access. Compared to central venous catheters, they have a lower infection risk but a higher incidence of thrombophlebitis, but dislodgement and difficulty with daily activities remain the major disadvantages.
- Tunneled central venous catheters are the preferred route of administration of parenteral nutrition in those patients that require it for an extended period of time. Occlusion and thrombosis results from a fibrin sheath formation which is a long-term complication of all access lines.
- Infection is the number one complication in central venous catheters, with a wide range of presentations. Sepsis is associated with significant morbidity and mortality. The most commonly isolated

D.R. Neel, MD (✉)
Surgical Intensive Care Unit, Department of Surgery,
Truman Medical Center, Kansas City, MO, USA
e-mail: dustin.neel@tmcmed.org

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_7,

organism is *Staphylococcus epidermidis*. Tunneled, cuffed central venous lines placed in the subclavian vein carry the lowest infection risk.
- Hyperglycemia, hyperlipidemia, and refeeding syndrome are complications of parenteral nutrition associated with its internal composition.

Introduction

Nutrition support has been a crucial component of medical practice for decades. While voluntary oral nutrition is the best route of nourishment delivery for most patients, and enteral nutrition is considered the best alternative, some patients ultimately require parenteral nutrition (PN) [1]. Since the first laboratory demonstration of its efficacy by Dudrick and Wilmore in 1968, PN has been used successfully to support patients with intestinal failure [1–3].

The first patient received PN at home in 1968 [4, 5]. Home PN is used largely for short-bowel syndrome, high-output enterocutaneous fistulae, or severe chronic gastrointestinal dysfunction, and is used to treat both electrolyte abnormalities and to provide all required nutrients [6]. Over 40,000 patients require PN at home annually, and there are many others who require PN temporarily during a medical or surgical crisis [1, 4, 7, 8]. Despite 45 years of successful clinical use, PN has been called poison and condemned as being inferior to enteral nutrition [9–12]. However, when making comparisons of PN to enteral nutrition it is important to remember that PN should not be considered a replacement for enteral nutrition; rather, it is intended to treat patients who cannot sustain oral or enteral feeding [5, 12]. In fact, all humans start their life on parenteral nutrition and adapt to enteral nutrition after exiting the womb and entering the world [10]. In the words of Sir David Cuthbertson, a prominent biochemist and nutritionist, "Lest we forget, I would remind you that we all owe our fetal life till parturition to the passage of the nutrients we require from the blood vessels of our mothers into blood vessels as they transverse the chorionic villi in close relation" [13, 14].

Parenteral Access and Complications

In 1656, Sir Christopher Wren first experimented with PN. He administered wine, ale and morphine to a dog via a goose quill attached to a pig's bladder [5, 11]. Three hundred years later, Dudrick and Wilmore used vinyl catheters in six beagle puppies to show that PN could support growth and development [10]. Today, PN is widely used, and we have a bewildering variety of catheters available [15]. Over 50% of hospitalized patients have either a peripheral or central catheter, and over five million central venous catheters are inserted yearly [16, 17]. But despite all of the advances, vascular access still remains one of the most important and challenging components of PN.

Vascular Anatomy and Physiology

Venous return is the most important characteristic in choosing which access to use in the delivery of PN to the patient. An understanding of the basic anatomy and physiology of the vasculature is helpful in determining best access locations and safe practices.

Veins have three layers: the tunica intima, tunica media, and tunica adventitia. The innermost layer is the tunica intima which is in direct contact with the venous flow via a nonthrombogenic smooth low-friction surface. The middle layer is the tunica media which contains connective tissue with

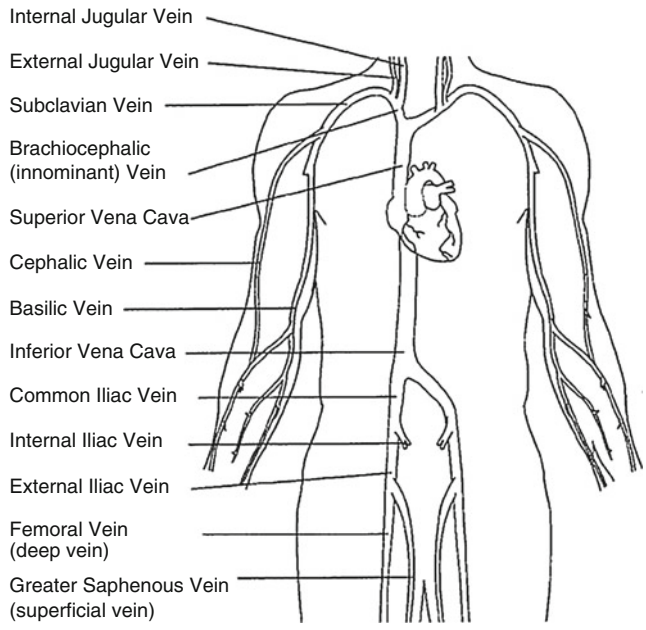


Fig. 7.1 Upper and lower extremity venous anatomy [21]. Reprinted by permission of SAGE Publications. Vanek VW, Nutrition in Clinical Practice, 17(2), pp. 85–98, copyright © 2002 by SAGE Publications

elastic fibers. This allows the veins to stretch in order to tolerate changes in pressure. The outermost layer is the tunica adventitia which contains the nutrient-supplying blood vessels to the walls of the larger veins. These are known as the vasa vasorum [18–20]. The major veins are diagrammed in Fig. 7.1.

The superficial veinsof the upper extremity include the cephalic, the basilic, and the median antebrachial veins. The basilic vein becomes the axillary vein at the lateral chest wall (teres minor). The cephalic vein drains directly into the axillary vein. The average diameters of the basilic, cephalic, and axillary are 8, 6, and 16 mm, respectively [18, 19, 21]. The axillary vein becomes the subclavian vein as it crosses the first rib. The neck has two major veins: the internal jugular and the external jugular. The external jugular vein drains the face and scalp, and it ultimately empties into the subclavian vein. The average diameter of the subclavian vein is approximately 19 mm. The internal jugular vein drains the head and brain and combines with the subclavian vein to create the brachiocephalic, also referred to as the innominate vein. The left brachiocephalic crosses the chest to join the vertically oriented right brachiocephalic to create the superior vena cava (SVC). The SVC measures approximately 20–30 mm, and is approximately 7 cm in length. The last centimeter of SVC is inside the pericardium, where it joins the right atrium [18–22].

The veins in the lower extremity include both a superficial and a deep venous system. The deep venous system has a rich collateral network and ultimately drains into the popliteal vein. The common femoral vein is the continuation of the popliteal vein above the adductor (Hunter's) canal. The superficial system drains into the greater saphenous vein and ultimately into the common femoral vein. The profunda femoral vein also drains into the common femoral vein. The common femoral vein courses superiorly and becomes the external iliac vein at the inferior border of the inguinal ligament. The internal iliac vein joins the external iliac vein to become the common iliac vein. The right and the left common iliac veins join to become the inferior vena cava (IVC) at approximately L5. The IVC then drains into the right atrium [19, 21, 22].

Venous return to the heart is aided by many physiologic principles. Muscle contraction aids the return of blood to central circulation via compression of the superficial veins of the lower extremities. Paired valves within these veins prevent retrograde blood flow and the muscle contractions propel blood towards the heart. Blood flow within central veins is not dependent on valves; instead the negative intrathoracic pressure of inspiration accelerates blood into the central circulation [18]. The SVC and the IVC have large diameters to accommodate high blood flow. This makes the central veins the preferred vessels for PN as it rapidly dilutes the hyperosmotic solution. The flow through the SVC is estimated at 2000 mL per minute versus 150–250 mL/min in forearm veins [18, 21].

Peripheral Vein Access Versus Central Access

The position of the distal catheter tip, not the location of the entry site, determines whether or not the vascular access is peripheral or central. Central access catheters have distal tips that terminate in the SVC or the IVC [21], although it should be noted that the preferred terminus for catheters used for central parenteral nutrition is at the vena caval entry into the atrium.

Peripheral Venous Access

Peripheral vein access should only be used for a short-term therapy, and because of the increasing ease and safety of PICCs peripheral parenteral nutrition (PPN) is rarely necessary.

Peripheral venous access is simply placing an intravenous cannula into a peripheral vein. It remains the safest, easiest and fastest ways to gain vascular access, in general, but is fraught with difficulties when used for PPN. Examples of peripheral venous access include: needles, short peripheral catheters, and midline catheters. While midline catheters resemble PICCs, they are not central lines. They are placed peripherally and terminate in larger veins usually in the upper arm. The main limitation of peripheral access for patients requiring PN remains the high tonicity of the PN, which is often 1200 mOsm/L or more in centrally infused formulas [23]. Peripheral intravenous cannulas should not be utilized for solutions greater than 900 mOsm/L as "burning" of the vein will occur [2, 21, 24, 25]. This is why peripheral parenteral nutrition requires such a larger volume and why standard PN cannot be infused peripherally, including via midline catheter.

PPN solutions can only be given through peripheral catheters for short periods; usually a few days. This type of access is not approved for patients with inadequate veins, those requiring longer than 5 days of therapy, and those who cannot handle large volumes of fluid, as in patients with congestive heart failure. PPN solutions should contain no more than a final concentration of 3 % amino acids and no more than 10% dextrose [21]. The primary advantages of peripheral venous access are fewer infections, and easy access if adequate veins are present [21, 23, 24].

The primary complication of peripheral venous access is thrombophlebitis of the peripheral vein. Infusion thrombophlebitis is the inflammation of a cannulated vein resulting in pain and discomfort and occurs in a large percentage of patients with peripheral access [21, 22, 24, 26]. The inflammation results in venous thrombosis and possible occlusion, and leads to skin changes and edema, erythema, pain, and often a palpable venous cord. The main risk factors for peripheral thrombophlebitis are the type and concentration of infusate, the location of the catheter, and the duration. Infusates including dextrose, amino acids, lipids, and irritant drugs including antibiotics, chemotherapeutic drugs, acidic solutions, and vasoactive agents also increase the risk of thrombophlebitis [21, 26]. Blood, medications, electrolytes, and other infusates not included in the PN should be given via separated peripheral access sites [24].

There is a marked increase in the incidence of thrombophlebitis after 48 h of infusion, which has led to recommendations to change the site of the every 24–72 hours to decrease this risk [2, 23, 24, 26–28]. The lowest rate of thrombophlebitis occurs at solution osmolarity below 450 mOsm/L [21, 24]. For reference, the osmolality of normal saline is approximately 285 mOsm/l. Recent infusion guidelines allow peripheral access to remain for 72 hours as long as the sites are free from visible complications [27]. Access should be changed sooner if the patient develops pain, erythema, or other signs of vascular site compromise, or a break in sterile technique occurs. If thrombophlebitis develops, rapid removal of the cannula should occur, and replacement should be distant from the original site, preferably in an alternative limb [28]. Various techniques have been attempted to decrease the risk of thrombophlebitis associated with PN, including topical anti-inflammatory agents, buffering solutions, and heparin, but none has resulted in significant reductions [21, 23, 24]. Other complications include cellulitis and sepsis, discussed later in the chapter.

Midline Cathethers

Midline catheters are also considered peripheral access, and are not recommended for infusion of standard PN or any other caustic or highly concentrated solution. It is preferable to place a PICC for central PN since the insertion techniques are similar, and the PICC has fewer downsides. Midline catheters are usually approximately 8 in. long, and are inserted into the basilic vein with the distal tip in the proximal basilic or axillary vein, but not into the subclavian vein. Due to the size of the vein, there is a decreased risk of thrombophlebitis compared with standard peripheral lines when infusing low osmolality solutions, but venous stenosis is a potential longer-term sequela. Midline catheters function for a median of 7 days, but may be used in general for up to several weeks. Advantages of midline catheters are the ease of placement by a specially trained nurse, longer dwell time, and minimal post-placement care. In addition, midline catheters have lower rates of thrombosis in the deep brachial veins compared to PICCs. Disadvantages include the need to change the catheter every 14 days, increased cost compared with peripheral cannulas, and the lack of central access and the attendant issues related to PPN [21, 24].

Central Venous Access

As mentioned above, the determination of central versus peripheral is the location of the distal tip, not the access location. Central venous catheters (CVC) have distal tips located in the central circulation, specifically the SVC, the IVC, or the right atrium [2, 22]. A PICC, as noted above, is inserted in a peripheral vein, usually the cephalic or basilic, and terminates in the SVC. Even though the tip of PICCs is central, because the insertion technique and useful lives of PICCs and temporary central catheters are significantly different, they are addressed in separate sections. For the sake of clarity, the term CVC refers to temporary, non-tunneled central catheters other than PICCs, and are distinguished from tunneled central venous catheters, discussed below. Common places for CVC puncture sites include the subclavian, internal jugular, and femoral veins. CVCs have multiple uses including the administration of solutions, including PN, that may cause phlebitis or sclerosis if infused peripherally. These uses include PN, laboratory draws, as well as central venous pressure monitoring. Multiple types of central catheters exist, each with their pros and cons [15].

Temporary non-tunneled CVCs are placed via the Seldinger technique. This involves the use of a needle to pierce the vein, followed by the cannulation of the vein with a wire. One or more dilators

are used to dilate the tract, and the catheter is subsequently placed over the wire. With the exception of PICCs, non-tunneled CVCs are most commonly placed in the internal jugular or subclavian, and advanced to the SVC. Femoral access to the IVC may be performed in an emergency, but is not recommended for routine use, particularly for PN, because the risk of infection and venous thrombosis are both higher [29].

CVCs have a high success rate of placement, providing immediate access for those needing central access. Advantages include the availability of multiple lumens within the catheter for patients requiring multiple infusions, the ability to monitor central venous pressure, and the ability to draw frequent labs without venipuncture. The complication rate associated with CVCs is approximately 10%, with over half associated with the initial placement. Early complications include pneumothorax, great vessel injury, hemothorax, bleeding, air embolism, arrhythmia, cardiac tamponade, nerve injury, and misplacement of the catheter [18, 19, 21, 22, 24, 30–32]. Pneumothorax is less common in internal jugular access compared with subclavian access, and is a non-issue in femoral access. The increased usage of ultrasound for placement has reduced but not eliminated complications [18, 27, 30, 33]. Because the risk of infection and thrombosis is higher in femoral access, the Center for Disease Control (CDC) and most other authorities recommend using the subclavian or jugular access [2, 29, 30, 34].

Immediate Complications of Central Venous Access

As with any invasive procedure, central line insertion is associated with complications. Those specific to PICC line insertions will be addressed in a separate section below. Pneumothorax occurs when the pleura is nicked or punctured by the needle, introducer, or dilator. The incidence ranges widely, and is probably most dependent on the experience of the operator. These are very rare with PICCs. The size of the pneumothorax determines management [21, 31, 33]. If it is less than 10–15%, and the patient is asymptomatic, it may be monitored simply with repeated chest radiographs. However, if the pneumothorax is larger, the patient is symptomatic, or the patient is ventilated with positive pressure, a tube thoracostomy may be needed to re-expand the lung. Bleeding may result from the venous puncture or from accidental laceration of the vein or artery, especially if coagulation is impaired. At the extremes bleeding may result in a simple hematoma, responsive to gentle pressure, or may create a life-threatening exsanguination. Bleeding into the pleural space may result in a hemothorax. Unrecognized misplacement of a CVC into the pleural space and infusion of fluids will result in hydrothorax. The position of the tip of every CVC must be confirmed by X-ray or other proven methods, so this should be an extremely rare event. A chylothorax is also possible if the thoracic duct is lacerated during CVC placement, most commonly occurring via the placement into the left subclavian vein. While minor pleural complications may be simply observed with serial radiographs, more serious complications may require tube thoracostomy, video-assisted thoracotomy, or even a thoracotomy to repair the complication [21, 33].

Injury to nearby arteries, particularly the internal carotid artery, the subclavian artery, and femoral artery may occur. Direct pressure is effective for puncture injuries of internal jugular or femoral arteries, but the subclavian artery cannot be easily be compressed. Any of these may on occasion, require intervention with an intravascular stent or even an open surgical repair. Arterial bleeding can cause airway compression, or even arteriovenous fistula, retrograde aortic dissection, or cerebrovascular events in extreme cases [31, 33]. Nerve injury of the phrenic, brachial plexus, vagus, recurrent laryngeal, and cervical sympathetic chain may cause pain, numbness, paralysis, or autonomic dysfunction [21, 33].

Air embolism is a life-threatening complication from any central catheter insertion. Care must be taken to prevent the catheter hub from being open during patient inspiration. Negative intrathoracic

pressure can suck air in through the catheter. Except for confirming blood flow from the catheter, the hub should always be occluded. When air is pulled through the catheter, a froth of air bubbles and blood develops within the right atrium. If nothing is done, the air bubbles can pass into the right ventricle, and these may block perfusion. The patient should be placed on his or her left side immediately, leaving the catheter in place. The expectation is that air will rise to the right atrium and cava, thus allowing aspiration via the recently placed catheter. Further, as long as the air remains in the atrium, it will slowly be absorbed. Elevating the legs (decubitus Trendelenburg position) may also aid in keeping the air bubbles from passing into the heart [32, 33, 35].

Cardiac arrhythmias often result from the guidewire "tickling the heart." The wire is passed through the central veins into the right atrium and right ventricle. The wire can irritate the ventricular endocardium, resulting in premature ventricular beats or even runs of ventricular tachycardia. The endocardium around the tricuspid valve is especially sensitive. Generally, the ectopic rhythm is corrected by simply pulling the wire out of the heart. Perforation of the atrium or ventricle by a guide wire or dilator may be catastrophic, but is very rare. This results in blood accumulating in the pericardium, cardiac tamponade, cardiogenic obstructive shock, and ultimately cardiac arrest. Temporary life-saving treatment for cardiac tamponade is pericardiocentesis, but median sternotomy or thoracotomy may ultimately be required to repair this complication [19, 32, 33].

Malposition of CVCs occurs in 4–10% of central access insertions [21, 33]. To avoid the intrapericardial portion of the vena cava, the best location is 1–2 cm above the junction of the SVC and the right atrium. But many authorities feel that placing it at the junction or in the atrium for 1–2 cm decreases the risk of later occlusion by keeping the catheter tip in motion [21, 36]. The ideal location of the distal tip is still a matter for disagreement. Common incorrect positions of the distal tip include: the contralateral subclavian vein, the ipsilateral internal jugular vein, the right atrium, the right ventricle, and IVC. As stated, a chest radiograph is required for confirmation of placement prior to use to both detect and avoid this complication [2, 19, 21, 22, 32, 33].

Late Complications of Central Venous Access Catheters

Late complications occur beyond those events related to initial placement and are directly related to the length of time the catheter is in place. Catheter dislodgement can be both a devastating and costly complication. Multiple techniques have been developed to secure the catheter in place, including: suturing, commercial devices that adhere to the skin, and a combination of the two. Catheters still become dislodged despite these methods. This results in the need for replacement, exposing the patient to the risks mentioned above that are associated with initial placement. In addition, secondary delayed catheter migration and malposition have been reported [22].

Catheter occlusion and thrombosis are additional late complications that restrict the use of the central catheters. Occlusion is the second most common complication behind infection, and the incidence increases as catheter life span increases [8, 35]. Incidence varies from 7–40% per catheter-year [37]. Catheter thrombosis should be suspected if it is difficult to draw blood from the catheter or resistance is experienced during infusion. Occlusion is usually caused by the formation of a fibrin sheath around the catheter tip. The central catheter injures and disrupts the venous intima, resulting in the formation of a fibrous sheath around the catheter. The result is blockage or a plug at the catheter tip [4, 8, 15, 21, 36, 38–40]. Venous thrombosis may develop as well. Patients at highest risk for thrombosis include those with hypercoagulable states, such as malignancy, renal failure, and sepsis [4, 8, 40].

Thrombosis associated with central catheters occurs due to Virchow's triad: intimal damage due to the catheter tip, altered flow, and stasis [33, 36, 41]. Thrombosis of the central veins is related to the elevated osmolality, change in pH and viscosity. Because of the rich collateral venous network

associated with the thorax, central vein thrombosis rarely results in skin changes [21, 40]. Central vein stenosis and thrombosis occurs at a rate of 0.25 episodes per 1000 catheter access days [21]. The subclavian vein and upper extremity veins can develop catheter-related venous thrombosis. These can propagate and embolize [8, 35, 40], but pulmonary embolism (PE) rarely occurs in the presence of upper extremity and chest thrombosis [4]. Another rare complication (incidence 0.03%) of venous thrombosis is superior and inferior cava syndromes [4, 8, 42]. Intracardial thrombosis has also been reported in those catheters with the tip in the right atrium [4]. The actual catheter-related venous thrombosis rate is not entirely known because many patients may be asymptomatic [40, 43].

Thromboses and hematomas may become infected and result in septicemia [24, 36, 38, 40]. In fact, thrombosis and infection are frequently found together [24, 40]. Infection will be discussed in further detail with the long-term tunneled central venous catheters.

Peripherally Inserted Central Catheter (PICC)

As the name implies, PICCs are generally inserted into the superficial veins, usually the cephalic or basilic veins of the arm, and advanced into the central veins. In 1957, Ross used peripherally inserted central venous catheters to infuse hyperosmotic solutions [44]. In 1975, Hoshal described the first long-term use of a PICC for intravenous nutrition [45, 46]. PICCs are longer than other CVCs so they can be inserted in the antecubital fossa, or preferably under ultrasound guidance into the basilic vein between the biceps and triceps medially, and subsequently advanced through the axillary vein into the SVC [18, 21, 22, 44, 45]. Negotiating the acute angle of the cephalic-axillary vein confluence makes the cephalic vein less appealing than the basilic vein.

PICCs are indicated for intermediate and long-term access, usually for an anticipated duration of 6 days or longer [15, 20, 30, 47]. They are used to provide PN, intravenous antibiotics, and intravenous medications [30, 44, 45]. PICCs function for an average of 10–73 days, but have been kept in place as long as 307–421 days [30, 44, 47]. Contraindications to PICC placement include thrombophlebitis of the antecubital veins, active inflammation, cellulitis or burns, thrombosis, arteriovenous fistula, history of axillary dissection or active lymphedema. As the law of Laplace states, liquid flow velocity is inversely related to diameter and length of the tube. Due to their length and small lumens, most PICCs are not recommended for high volume, rapid boluses or pressurized injections [20, 44, 46]. There are, however, newer versions of PICC catheters designed to both withstand rapid and higher pressure infusions. These allow for both pressure monitoring and bolus infusions of substances such as intravenous dyes for procedures such as CT scans.

Complications of PICC insertion include malposition, catheter occlusion, infection, thrombosis and thrombophlebitis [15, 20, 22, 44–46]. As with other central catheters, the ideal location for the distal tip is still in question; either above, at, or below the cavo-atrial junction, as described above. Those not in one of these locations are by definition, malpositioned. They can be over inserted (located too far in the right atrium or in the IVC), under inserted (located in the ipsilateral axillary vein and subclavian vein), or they can be aberrantly located (ipsilateral internal jugular or contralateral subclavian vein) [19, 45, 46, 48]. Again, confirmatory radiographs are required to confirm location.

Thrombophlebitis occurs at a rate of 9.2%, while thrombosis has been reported at rates of between 0 and 7%. These rates are higher than those reported with CVCs [44, 45, 48]. If thrombophlebitis occurs, removal of the PICC is indicated [30]. Thrombosis risk is increased when the catheter is malpositioned [44, 46]. Occlusion of PICC catheters occurs between 2 and 18 %. This is more frequently in those catheters used intermittently, such as for periodic antibiotics or chemotherapy, as compared with those used daily, as with PN or daily antibiotics [44]. Occlusion occurs as a result of fibrin sheath formation as discussed above. The catheter tip can develop a blood clot at the tip or inside the catheter, ultimately

resulting in occlusion. Frequent use, daily flushing, and flushing after each use all reduce occlusion rates [15, 20, 38, 44].

Infection rates in PICCs are less than non-tunneled temporary CVCs [15, 44, 47, 48]. It is theorized that the reduced infection rate may result from decreased colonization due to the location of the PICC. The antecubital fossa is cooler, resulting in less moisture, which results in less colonization of the antecubital fossa versus the chest and neck [44, 47]. Secretions from the nares, mouth, tracheostomy, and endotracheal tube also likely related to the increase in contamination of subclavian and internal jugular CVCs due to the proximity of these catheters to the secretion source. Maximum barrier precautions are recommended to aid in the reduction of infectious complications [30, 36]. Catheter-related infections are further discussed later in the chapter.

Complications associated with PICC placement include median nerve injury and accidental puncture of the brachial artery, resulting in arterial bleeding, hematoma, arteriovenous fistula, and ischemia to the distal hand [2, 11, 44]. Uncommon complications include vein perforation, chest wall abscess, venous extravasation, cardiac arrhythmia, cardiac tamponade and perforation, and distal embolism due to shearing of the PICC tip [19, 20, 31, 32, 45, 46].

A study from the Mayo Clinic reporting noninfectious PICC complications during placement and usage concluded that dislodgment was the most frequent complication, occurring in 8.9%. Other complications included: malposition (5.8%), catheter clotting and thrombophlebitis (3.8% each), catheter infection (3.8% confirmed, additional 3.6% suspected), and bleeding (0.5%) [32, 44, 47, 48]. Advantages of PICC include the ability to place at the bedside, possibility for specialized nursing teams to perform the placement, easy removal, option of single or multiple lumens, lack of additional skin punctures for access or blood drawing, lower cost of insertion than tunneled central venous catheter, and lack of risk of central complications including pneumothorax and bleeding from major arteries [47]. Disadvantages include isolation of one arm from daily activities, difficulty in caring for the catheter with one hand, self-image issues, dislodgment and malposition risk, need for occlusive dressing at all times, and requirement of adequate veins [15, 46].

Long-Term Tunneled Central Venous Catheters

Broviac et al. first described the use of tunneled catheters for long-term access in 22 patients in 1973 [46, 49]. The silicone catheter was 90 cm long with a Dacron felt cuff midway between the insertion site and the tunneled exit site approximately 15 cm away. The Dacron cuff supports tissue ingrowth, which both anchors the catheter to prevent inadvertent dislodgement and prevents bacterial migration along the catheter from the skin exit site [19, 24, 49, 50]. These catheters are primarily inserted into the subclavian vein, internal jugular vein, or via cephalic vein cut down in the deltopectoral groove. The catheter enters the skin usually over the pectoralis on the anterior chest, and is tunneled subcutaneously to where it enters the vein. This subcutaneous tunnel, often 10 or more centimeters long, creates a longer indirect route for bacteria to enter the bloodstream—from the exit skin site to the vein—and thus decreases the likelihood of contamination [4, 24]. Hickman used a larger diameter but similar catheter in 1979 [23, 50]. The terms "Broviac" and "Hickmann" are used interchangeably to describe central catheters that are both cuffed and tunneled, but the more generic name of "tunneled central venous catheter" is preferable [46]. Tunneled catheters are primarily used for daily intravenous therapies administered for an extended period of time, especially home PN [2, 6].

Tunneled catheters are placed in similar locations as the non-tunneled-CVCs via the Seldinger technique, as previously described. Likewise, the distal tip position should be confirmed by post-procedure chest radiograph [2, 19]. Complications in placement of tunneled central catheters are

similar to the non-tunneled variety as discussed in detail previously, and include: pneumothorax, hemothorax, air embolism, cardiac arrhythmias, cardiac perforation with pericardial tamponade, arterial perforation with bleeding, and catheter misplacement [15, 32, 41]. Malposition may either be immediate or due to delayed migration. However, the incidence of immediate malposition is reduced with the assistance of fluoroscopy during placement. Delayed secondary migrations should be corrected as soon as possible, especially when irritating drugs or hypertonic agents such as PN are given [33, 51]. The incidence of occlusion and thrombosis are directly related to the duration of the catheter insertion; therefore, they are more common in tunneled catheters due to the long-term nature of the catheters. Thrombus formation occurs more frequently with secondary migration of the catheter tip to an inappropriate location [19, 41, 51]. However, thrombus formation is uncommon (2%) despite the more common fibrin sheath (85%). The fibrin sheath may create a ball-valve occlusion, leading to the inability to aspirate despite the ability to flush and infuse through the catheter [38, 39]. However, this can eventually lead to either catheter occlusion or venous occlusion, deep vein thrombosis, or a combination of both. Occluded catheters can often be salvaged with thrombotic therapy, usually tissue plasminogen activator (t-PA) or Urokinase [3, 4, 8, 20, 24, 37, 51], and treatment is recommended twice prior to declaring the catheter unusable and removing it [24].

Originally thought to be of no clinical significance, upper extremity deep venous thrombosis (DVT) has become more frequently diagnosed and determined to be consequential [40, 41, 43, 52]. Upper extremity DVTs can lead to both chronic venous insufficiency and pulmonary embolus (PE). Upper extremity DVTs are responsible for 7–9% of symptomatic PEs [43]. Treatment of upper extremity DVTs should be equivalent to lower extremity DVTs and should involve aggressive anticoagulation or thrombolytic therapy. A close parallel to DVTs is SVC occlusion which can lead to both shock and death if it occurs acutely. The incidence of SVC occlusion associated with PN ranges from 8–14% [37]. Standard treatment for DVTs and SVC occlusion include both thrombolytic therapy and systemic anticoagulation with heparin followed by coumadin. Treatment of SVC occlusion may progress to involve balloon angioplasty and expandable metal stents in refractory cases [37].

"Pinch-off syndrome" was first described in 1984 by Atiken and Minton [32, 53]. The catheter becomes obstructed due to compression as it transverses between the sternoclavicular joint and the first costosternal articulation. The compression creates narrowing, pinching, and ultimately obstruction, which may be intermittent and positional [53]. Eventually, the catheter may fracture, with a mean time of 6.5 months from insertion to fracture. Fracture of the catheter can be quite dangerous, and even fatal if the distal portion embolizes to the right ventricle or pulmonary arteries. Other complications include extravasation of fluids at the fracture site as well as arrhythmias. Treatment may require angiographic retrieval or open operative intervention [32, 36]. Extravasation is associated with an intense tissue inflammatory reaction which can lead to tissue necrosis or amputation in extreme cases [25]. If pinch-off is discovered early, removal of the catheter is recommended prior to fracture [15, 32, 44].

Line damage may also occur, directly dependent on the catheter life span and individual line care [35]. Shearing of the distal tip of the catheter can lead to both catheter embolism, as in pinch-off syndrome, and air embolism [33, 35]. Line damage mandates removal and replacement to avoid these potentially fatal complications from catheter embolism; approximately 39.5% [35]. Dislodgement is a constant risk, decreased by both the Dacron patch in tunneled lines and by catheter stabilization devices [3, 19, 27].

Advantages of tunneled central catheters include: multiple lumen varieties, higher insertion success rate, reduced dislodgement and decreased bacterial migration due to the Dacron cuff. In addition, there is no additional skin puncture following catheter placement as with accessing ports, described below, and it is easier for the patient to conceal as compared to PICCs, as described above. The patient can also use both hands to care for the catheter because it is located in a very accessible place on the chest. It is even possible to repair the external portion of the catheter if broken without removing and

replacing the catheter. Disadvantages include: physician time for placement and removal, operating room time for placement, and the presence of a catheter emerging from the chest [19, 30].

Central Venous Catheter Infections

Infections are the most common complication associated with tunneled and non-tunneled CVCs [7]. While improved since, in 2004 it was estimated that over 200,000 catheter-related blood stream infections occurred yearly in ICUs patients [34]. A rate of approximately one systemic infection, with a mortality of 25%, for every 20 CVCs was reported in a similar time period [17]. Infectious complications for tunneled and non-tunneled-CVCs include exit site infections, catheter colonization, tunnel infections, and catheter related or central line associated blood stream infections (CLABSI).

Infections of central lines result from either transition or deposition of microorganisms during insertion, migration along the catheter from the insertion site, contamination from injectable infusions or access hubs/sites, or from distance source seeding [4, 15, 30, 36, 51, 54]. Maximal barrier precautions during insertion, prepping with proper antiseptic, and vigilant care and surveillance of central access sites aid in the reduction of central line infections [30, 51]. Care of the hub, which can serve as an access point for infection, is often overlooked. The hub/access port should be cleaned carefully with an antiseptic agent prior to each use [6, 44, 54]. Removal of the central access catheter as soon as it is no longer needed will obviously decrease the opportunity for the development of CLABSIs [34]. The CDC does not recommend routine central line changes unless clinically warranted [30]. Cuffed tunneled central catheters have a lower rate of CLABSI compared to non-cuffed catheters; thus, these are recommended for long-term access catheters. Subclavian access is also associated with decreased infection rates as compared with other sites [31].

Skin insertion site and catheter tip infections are most commonly associated with bacteremia and sepsis. Parenteral solution contamination is uncommon, particularly when compounding occurs following best practices in experienced pharmacies. When it does occur, the organism is generally an unusual pathogen [4, 8, 30].

Insertion site infection is defined as the presence of pus, a quantitative culture of the subcutaneous tunnel or catheter tip with 10^3 colony forming units, or a semi qualitative culture of >15 colonies [3, 8, 35]. These infections can result from the line itself becoming infected or being seeded from a secondary source. The diagnosis of CLABSI require a positive blood culture from both the central catheter and the peripheral blood, without another obvious source of contamination [8, 30, 36]. Central line-associated infections can also seed other locations, specifically endocarditis and mycotic aneurysms [35]. The incidence of line sepsis ranges from 2–33% and carries significant morbidity and mortality [33, 35, 55]. Line infections are increased in those catheters with multiple lumens and those that are non-tunneled [4, 8, 15, 30]. Lines placed in the upper extremity have the least infective complications, followed by those placed in the subclavian, cervical, and femoral veins, in that order [8, 29].

Skin insertion site infections are local infections at the site where the catheter exits the patient's skin, manifesting as tenderness, erythema, induration, and purulent drainage. These infections account for 17–45% of all central venous access infections. Treatment varies from local wound care with warm compresses and central line dressing care to complete removal and replacement of the catheter in a new location [21, 30, 54]. The subcutaneous tunnel is longer in the tunneled central venous group and so-called "tunnel infections" are an additional infectious complication in these catheters. Tunnel infections generally require removal of the catheter and replacement in a separate uninvolved location [44].

CLABSIs occur at a rate of 1.4–2.3 episodes per 1000 catheter days. Treatment usually includes removal of the catheter in addition to intravenous antibiotics. Occasionally, intravenous antibiotics

without removal of the catheter are used to attempt to salvage the catheter in patients in whom it is difficult to obtain access [44]. Recent estimates suggest each CLABSI adds on average $45,000 to the cost of hospitalization. Death from CLABSI is approximated at 28,000 annually [56]. Infections of tunneled central catheters result from similar pathogenesis as non-tunneled CVCs. These infections result from either transition or deposition of microorganisms during insertion, migration along the catheter from the insertion site, contamination from injectable infusions or access hubs/sites, or seeding from distant sources [21, 30, 51, 54]. The act of tunneling the catheter is thought to decrease the migration of organisms along the catheter. The cuff associated with the tunneled catheter also aids in decreasing infection rates compared to non-tunneled catheters. Additional techniques to decrease and prevent catheter-related infections include antibiotic-impregnated cuffs and antibiotic locks [30, 51]. While interesting, these techniques have not been proven to be more effective than simply maintaining meticulous care of the catheter and the exit site.

Colonization of a central catheter is distinguished from CLABSI by persistence of microorganism growth despite central access catheter exchange over a wire and a lack of systemic signs of sepsis [36, 54]. CLABSIs are the most severe infection associated with central catheters, and are often associated with fever, tachycardia, hypotension, leukocytosis, and other systemic signs of sepsis [30, 51], with historical rates in the critically ill two to five times that of the general hospital population [21, 54]. As mentioned previously, the diagnosis of CLABSI is made by drawing blood cultures from both the catheter and a peripheral source.

After CLABSI is diagnosed, there are two schools of thought as to the continued management of the catheter. One recommends the removal of all catheters involved in CLABSI and replacement at an alternate location. Others promote the practice of removal and replacement of the catheter over a guidewire [15, 21, 54, 57]. The risk of insertion complications is less with guidewire exchange than a de novo insertion. However, this is balanced against the risk of infecting the new catheter via contamination by bacteria left in the insertion tract or on the guide wire as the infected catheter is removed. Most authors recommend that the catheter be removed and replaced with initiation of appropriate antibiotic therapy [21, 44, 54].

Patient- and disease-related factors, catheter-specific factors, and the intrinsic virulence of the organism play integrated roles in increasing the risk of developing CLABSIs [35]. Extremes in age, both under 1 and over 60, immunosuppression, and severity of underlying illness are patient related factors that will both increase the risk of development and effect the outcome of CLABSIs. Insertion site location, catheter type, previous experience of the physician, and the development of thrombus around the distal tip are all catheter-specific risks for the development of CLABSIs [33]. Subclavian vein access is associated with a decreased risk of CLABSI compared to internal jugular access [21]. Thrombus formation around the distal tip of the catheter is associated with up to a 2.6-fold increased risk of CLABSI. Coagulase-negative staphylococcus, *Staphylococcus epidermidis*, is the most common organism, accounting for 33.5% of CLABSIs. Staphylococci produce a biofilm slime coat that both protects and allows adherence to the catheter [3, 4, 8, 16, 17, 24, 36, 54, 57]. In one study, other organisms causing CLABSI included: *Staphylococcus aureus*, Enterococccus sp, *Candida albicans*, and Enterobacter, with frequencies of 13.4, 12.8, 5.8, 5.2%, respectively [54]. Gram negative rods (*Klebsiella pneumoniae*, *Escherichia coli*, Pseudomonas species, *Serratia marcescens*, and *Enterobacter cloacae*) and fungi (Candida) have also been isolated [3, 4, 8, 17, 24, 30, 35, 38, 57, 58]. Bacterial resistance has become more prevalent and problematic, especially with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Candida related CLABSI remains associated with a high mortality (30–60%) [54, 59].

Line removal and broad spectrum intravenous antibiotics with later narrowing, based upon culture data, are now the standard of care for patients experiencing sepsis associated with CLABSIs [3, 4, 8, 35]. Novel methods have been proposed to avoid the need to remove catheters. These include antibiotic locks and high concentration antibiotics with elevated minimum inhibitory concentrations for 14 days. These may be tried in those patients with difficult access, alleviating the risks associated with

catheter placement and allowing access site preservation. However, frank pus or clinical deterioration mandate catheter removal and replacement [4, 8, 15, 17]. The presence of gram negative rods or candidemia also require line removal and replacement as the rate of cure without removal is even lower with these organisms. It is recommended that in patients with CLABSI a new catheter not be replaced until repeat blood cultures are negative. It is also recommended to withhold TPN for 24 hours following line removal. Length of treatment varies from 7 days to 4 weeks depending upon the isolated organism [3, 4].

Prevention of line sepsis is at least as important, if not more, than treating it. Maintaining sterile technique during insertion, appropriate line care, and strict aseptic technique of solution preparation and administration all aid in preventing line sepsis [30, 35, 36, 58]. The catheter used for PN infusion should be used solely for that purpose.

Implantable Central Venous Port

The first implantable central venous port was described in 1982 [60]. While there are several commonly used trade names, the generic but descriptive "implantable central venous port" is the preferred descriptor [16, 44]. Implantable central venous ports have distal tips above or at the cavo-atrial junction, as with other central lines. Access to the venous system is usually via the subclavian or internal jugular vein, although the femoral or even the external iliac or IVC can be accessed in extreme circumstances [15, 16, 44]. Fluoroscopy is generally used to ensure proper placement. The catheter is tunneled subcutaneously from the implantable port, placed in a subcutaneous pocket, to the access vessel [15, 16, 24]. Final location of catheter tip should be confirmed post-procedure with a sitting or upright chest radiograph [2]. The port access site is covered by a self-sealing silicone rubber septum and is accessed via a special Huber needle (Fig. 7.2). Ports should never be accessed with a standard coring needle. Standard needles do not allow the silicone septum to reseal itself and fluid and blood can leak out, resulting in complications. The Huber needle, has its bevel parallel to the axis of the needle, rather than across the axis, and will not carve a core out of the septum. Using the Huber needle maintains the integrity of the septum and allows for 1500–2000 punctures. Monthly heparinized saline flushes are required to maintain patency if the port is unused [15, 44].

Complications of implantable central venous port placement are similar to the complications associated with other central lines. Malposition of the distal tip of the port can occur during placement or later, due to delayed secondary catheter migration and malposition as mentioned previously. Intracranial infusion of PN fluids, which can be catastrophic, is a rare occurrence [24]. Fluoroscopy during placement helps reduce malposition errors, but the distal tip of the catheter can change postoperatively after the patient sits up (incidence 2–18%) [44]. Postoperative chest radiograph is required to confirm the location of the distal tip and to evaluate for pneumothorax [2, 15, 30, 60]. As with other long-term venous access, catheter occlusion increases as device life increases [24]. Occlusion can either be partial, allowing infusion but not aspiration, or complete, allowing neither. In addition to the formation of a fibrin sheath or blood clot at the tip of the catheter, partial occlusion of implantable central venous ports can occur if the distal tip becomes compressed against the vein wall [36, 39, 51]. Partial occlusion from fibrin sheath formation and blood clots at the distal tip can be treated with fibrinolytics such as tPA, urokinase, or streptokinase [36]. As mentioned above, treatment is recommended twice prior to the removal of the port [24]. Complete occlusion can occur from catheter thrombosis, medication precipitation, or solution precipitation. Pinch-off syndrome and catheter fracture have a similar incidence in implantable central venous ports as compared to tunneled central catheters, although placement through the jugular vein can eliminate this problem. Separation of the catheter and port due to the slippage of the locking device also can also occur resulting in catheter embolism [15, 32].

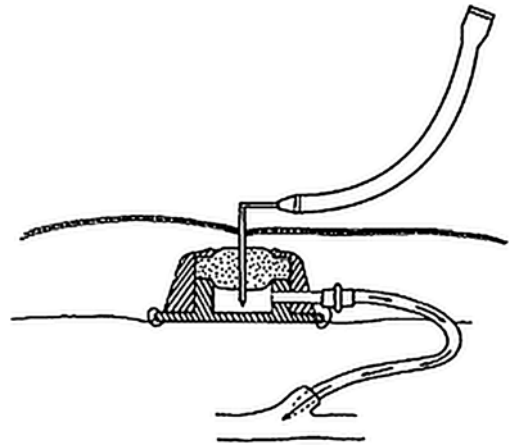


Fig. 7.2 Image of implantable central venous port [44]. Vanek VW, Nutrition in Clinical Practice, 17(3), pp. 142-155, copyright © 2002 by SAGE Publications. Reprinted by permission of SAGE Publications

As with other long-term access, the most common complication of implantable central venous ports is infection. Infectious complications in ports are of similar types to other tunneled central venous catheters, including catheter colonization, tunnel infections, and CLABSIs. In addition, ports have a subcutaneous pocket that houses the port. This potential space is vulnerable to so-called "pocket infections" [54]. Repeated daily puncture for access to ports increases the chance that any particular access will introduce infection. An indwelling needle for access to a port provides a ready entrance for bacteria through the relatively short needle tract. For these reasons, most clinicians avoid using ports for home PN [44, 54].

Treatment of infected ports is similar to tunneled central venous catheters with the mainstay being removal and replacement. However, a trial of intravenous antibiotics may be reasonable should the patient have poor or difficult vascular access and the patient is not hemodynamically compromised or have other signs of septic shock. Compared to tunneled central catheters, implantable central venous ports have a significantly lower rate of CLABSIs overall and a trend towards lower site infections. However, it is important to remember that implantable central venous ports are used primarily for intermittent therapy such as chemotherapy, blood draws or infusion, while tunneled central catheters are used primarily for daily therapies including intravenous antibiotics and PN [2, 44].

Ports are advantageous, as they are entirely beneath the skin when not accessed and no external tubing is visible to interfere with daily activities. Ports also come in single and double lumens and require less maintenance; a monthly flush when not in use. However, ports do require repeated skin puncture for access to the port, and require a physician and an operating room for insertion and removal [19]. The monthly flush must be done with full sterile precautions and may not be easily done at home. Ports may also interfere with MRI and CT scans due to scattering of radiation beams [44].

Each vascular access device type has a different useful life-expectancy, and the average duration of insertion is 23 days for PICC, 125 days for tunneled central venous catheter, and 221 days for implanted ports [24, 44, 46].

Other Vascular Access

There are other, less common vascular access options for those patients requiring PN whom have exhausted the traditional access locations. The use of arteriovenous fistulaehas been used as dual

access for hemodialysis and PN in patients with end-stage renal disease, a lack of alternative venous access, and intestinal failure with success in three patients [24, 57]. The use of AV fistulas was less successful, however, in those without chronic renal disease [24]. There is even a case report of accessing the intercostal vein for patients who have exhausted normal vascular access sites [61]. In the setting of SVC occlusion, the azygous vein can be used [19]. Finally, direct placement of a catheter into the IVC via trans-lumbar approach, trans-hepatic approach or directly into the right atrial appendage via thoracotomy, an extremely invasive and "last-ditch" maneuver, have been reported [8, 15, 19, 61].

Recommendations

Ideal vascular accessis specific to the patient, the disease-state, the use, and the projected duration. Should the patient have an adequate basilic vein between the biceps and triceps or in the antecubital fossa, and the need for access estimated to be weeks to months, a PICC may be a favorable selection. However, should the patient need a longer duration of PN, months to years, or the patient does not have adequate superficial veins, a tunneled central catheter should be used. Implantable ports may be used, but are less favored for PN. If the therapy is intermittent, such as chemotherapy, an implantable port is likely to be favored because of improved cosmetic appearance and decreased maintenance. If the therapy is daily and long term, as with PN, a tunneled catheter should be used [2].

Complications of Parenteral Nutrition

Parenteral nutrition is an extremely complex mixture of often more than 70 distinct components, including dextrose, fat emulsions, water, electrolytes, amino acids, trace elements, and vitamins [2]. Serious harm can occur with an inappropriate mixture [6]. Mirtallo et al. noted the deaths of two individuals from microvascular pulmonary emboli as a result of calcium phosphate precipitation [2]. Care must be exquisite for the creation of a safe product, as further discussed in Chapter 13. The major complications can be divided into catheter complications and metabolic complications.

Catheter Complications

Specific catheter complications and infections have been discussed in detail above. Complications associated with central lines occur at a rate of 1–4% [33, 35, 55]. Generally, complications associated with line placement are easily treated, but surgical intervention may be required if serious sequelae develop. It is important to remember that the patient's disease state, the experience of the physician placing the catheter, and the specific type of line itself all impact complication rate in catheters [35].

Catheter Occlusion

Patients on PN are specifically vulnerable to catheter occlusion resulting from precipitation of medications or solutions [4, 8, 35]. Mineral solutions, intravenous lipids and medications can precipitate and lead to catheter occlusion. Complete occlusion from precipitated medications, lipids, or calcium phosphate can be treated by the instillation of bicarbonate, ethanol, or 0.1 M hydrochloric acid

solutions, respectively [3, 4, 8, 33, 35, 36, 51]. Ethanol (70%) solution can help dissolve triglyceride deposits [4, 8]. Line occlusion requires removal and replacement if the precipitate does not dissolve with treatment [4, 35].

Metabolic Complications of Parenteral Nutrition

Glycemic Control

Hyperglycemia is common with patients using PN due to the glucose loads, and the increased blood sugar levels associated with PN calories relative to enteral nutrition, likely due to the loss of the first-pass effect of the liver [6]. Patient factors such as pre-existing diabetes mellitus, systemic inflammation, postoperative changes, and disease-induced insulin resistance can make glucose control challenging [35]. Maintaining appropriate glucose control can reduce morbidity and mortality in critically ill patients. Along the same line, providing the appropriate amount of glucose is necessary to prevent both overfeeding and underfeeding. Overfeeding results in excess carbon dioxide production and may even lead to respiratory compromise. Underfeeding results in starvation [9, 35]. Hyperglycemia may lead to increased glycation of certain proteins resulting in their dysfunction. It is also associated with increased infection rates and decreased wound healing [9]. Hyperglycemia associated with excessive dextrose administration may also predispose to PN associated hepatic steatosis [8, 9].

Hypoglycemia is less common but can be more devastating. Certain patient populations, including infants, patients in renal and liver failure, patients with adrenal insufficiency, patients with diabetes at baseline, septic and severely malnourished patients, and any patient with impaired insulin clearance are more prone to hypoglycemia due to imparied gluconeogenesis. Stopping the infusion of PN abruptly has historically been reported to result in occasional precipitous hypoglycemia. This is thought to be due to the continued circulation of insulin due to more rapid clearance of glucose than insulin, and lack of substrate [6, 35]. Fear of post-cessation hypoglycemia still drives protocols replacing suddenly halted PN with 10 or 20% dextrose solution infusions. However, in the current era, in which calorie prescriptions are far more conservative than in the earlier days of PN, hypoglycemia associated with PN cessation is an unusual occurrence, and with frequent point-of-care glucose determinations this practice is unnecessary and may lead to complications such as hypokalemia and hypophosphatemia. Tapered cessation of PN is often practiced, and should help prevent hypoglycemia in this setting, but is not always feasible in the ICU. For example, in patients with septic shock due to presumed line-related sepsis, immediate removal of the offending foreign body, the central line, may be lifesaving. Comparative trials of tapered versus abrupt cessation have indeed shown no difference in hypoglycemia incidence [2, 35, 62]. Tapered stopping of PN may no longer be necessary, and automatic replacement with dextrose infusions is certainly made obsolete, in the era of conservative calories and frequent point-of-care glucose determinations in the ICU. Close monitoring of glucose levels during PN administration and cessation remains an important component of PN management.

Lipid Metabolism

Hyperlipidemia can be induced by the lipid and calorie content of the PN. Disease states such as critical illness, diabetes, sepsis, renal and liver failure, and familial hyperlipidemia can lead to decreased lipid clearance and increased hyperlipidemia. Interestingly, underfeeding leads to ketogenesis, and may also ultimately result in hypertriglyceridemia [35, 63]. PN-related hyperlipidemia is generally benign and self-limited when lipid infusion is stopped. However, severe elevations, in the range of

1000 mg/dl, may be associated with pancreatitis [35]. Elevated lipid infusion rates, greater than 1 g/kg/day, may lead to cholestasis, resulting in hepatic dysfunction [8].

Essential fatty acid deficiency develops if an insufficient amount of linoleic acid and/or linolenic acid is provided in the PN [11, 63]. Fatty acid deficiencies can lead to impaired lipoprotein synthesis resulting in triglyceride accumulation in the liver and causing hepatic steatosis [4]. Clinical signs of essential fatty acid deficiency include neuropathy, hepatosplenomegaly, dry skin with a flaky rash, poor wound healing and thrombocytopenia [2, 4, 63]. A minimum of 4–8% of calories should be provided from lipid emulsion, 50% of which should be linoleic acid, to prevent essential fatty acid deficiency in patients completely dependent on PN [35]. Essential fatty acid deficiency is rare today as long as fat supplementation is not withheld for more than 2 weeks [4]. Diagnosis is made by fatty acid level analysis and specifically the triene–tetraene ratio.

Hepatobiliary Complications

The first description of TPN-associated liver disease was in 1971 [4, 64]. Hepatic dysfunction is quite common, seen in approximately 47% of home PN patients, and has a broad spectrum of presentation and severity [35, 65]. In children and neonates, hepatic complications occur in 50% of those on chronic PN, while 15–30% of adults have hepatic complications [4, 8]. Shortened bowel length, specifically less than 100 cm, is associated with increased liver dysfunction.

Elevations of bilirubin and liver function tests (LFTs) greater than 1.5 times the upper limit of normal are the mildest form of hepatic dysfunction, and usually develop 1–2 weeks after PN initiation [4, 8, 65]. A hepatocellular pattern is commonly seen in adult patients demonstrating steatosis, while a cholestatic pattern is often seen in children [4, 8, 35]. These abnormalities are consistent with periportal steatosis. A prolonged elevation of LFTs for over 6 months is associated with patients on prolonged PN, generally from prolonged intestinal failure [35]. The prevalence in an earlier study was 26% at 2 years and 50% at 6 years. There was a 22% mortality associated with liver disease as a cause of death of those patients on home PN [66]. Again, in this study, shorter bowel length, less than 50 cm, played a significant role in the formation of liver disease in home PN. Other factors for hepatobiliary complications included chronic cholestasis, excess protein administration and elevated lipid intake of 1 g/kg/d or more [4, 8, 35, 65, 66]. Lecithin and choline administered parenterally may help decrease hepatic steatosis in patients on PN. In previous generations of additives, aluminum was also known to increase hepatic cholestasis. As mentioned above, hyperglycemia and hyperlipidemia can also lead to hepatic dysfunction and steatosis [8, 35, 65].

In addition, cholestasis is thought to develop from lack enteral stimulation and cholecystokinin stimulation, resulting in biliary stasis and sludge formation. Data on the incidence of this complication requires updating, as a large part of the incidence seen in the early days of PN therapy was due to overfeeding resulting in steatohepatitis. Historically, elevation of bilirubin and alkaline phosphatase, suggestive of stasis, have been found to occur in as little as 4 weeks for 50% of patients, and in 100% by 6 weeks [4, 8, 66]. Gallstones or acalculous cholecystitis from biliary stasis and sludge [3, 4, 8, 35] led to recommendations that considered prophylactic cholecystectomy reasonable in the early era of PN [3], but this is no longer appropriate. Lack of enteral stimulation can also allow for bacterial overgrowth and the production of lithocholate, which is a hepatotoxic bile acid [35, 65, 66]. Daily oral intake, even if the patient requires PN to meet caloric needs, may help decrease the risk of biliary stasis and cholecystitis [4, 65, 66]. Liver injury associated with PN varies from reversible injury, including cholestasis and steatosis, to more permanent steatohepatitis and cirrhosis [35, 65]. Early cycling was proposed to help limit or prevent the progression of liver disease and complications, but this is unproven. PN-dependent patients with intestinal failure and permanent hepatobiliary

complications should be listed early for combination liver-small bowel transplants. Historically, the death rate is higher for liver failure associated with PN than for other liver diseases, with essentially no survival at 5 years [4, 35, 67].

Gastrointestinal Complications

Obviously, when the patient is fully dependent on PN, the "gut" is not used. The lack of intestinal stimulation has consequences. Mucosal atrophy has been demonstrated in patients that do not receive enteral feeding, although the significance is not quite understood. The mucosal atrophy of jejunal villi is quite profound in animal models, but is less pronounced in humans. Cellular permeability is also altered in profound intestinal isolation. Cellular edema and decreased intraluminal mucosal lining contribute to increased permeability, but is not associated with bacterial translocation. Marked pancreas atrophy due to lack of trophic substances also develops in patients without enteral stimulation. Exocrine function decreases in those dependent on PN long-term. The incidence of delayed gastric emptying also increases over time with chronic PN [4, 8].

Bone Disease

Shike et al. and Klein et al. first described PN-associated bone disease in 1980 [4, 68, 69]. This syndrome was originally characterized by transient hypercalcemia, normal or low serum parathyroid hormone, high normal plasma 25-OH vitamin D3, hypercalciuria, and a negative calcium balance with normal phosphorus levels and decreased mineralization and increased osteoid on bone biopsy [4, 69, 70]. Patients on home PN have an increased risk of bone disease manifesting as osteoporosis (41%), osteopenia (81%), bone pain (35%), and fractures (10%) [3, 35, 68, 71]. Most will be asymptomatic [70]. The cause of bone disease in PN patients is not completely understood, but preexisting disease including intestinal failure contributes. Obesity, inactivity, hypogonadism, timing of intestinal failure, smoking, alcohol abuse, and prolonged steroid therapy are all pre-existing disease states that contribute to bone disease in long-term home PN patients [35, 70, 71]. PN-specific factors predisposing to bone disease include deficiency of phosphorus, calcium, or magnesium, vitamin D excess or deficiency, and aluminum toxicity. Hypercalciuria in PN denotes an increase in bone loss [8, 68]. Aluminum toxicity can lead to decreased parathyroid hormone secretion due to inhibition [4, 8, 35]. Despite the efforts to remove aluminum from solution additives, patients on PN still receive a significant amount [8, 70, 71]. Vitamin D excess can decrease PTH secretion and stimulate bone resorption. Bone mineral density loss and PN-associated bone diseases are treated with bisphosphonates, calcium supplementation, and calcitonin [35, 70].

Kidney Injury

Nephromegaly develops in chronic PN, perhaps due to glomerular hyperfiltration associated with an elevated creatinine clearance, although the exact mechanism is unknown and may be due to repeated metabolic insults [4, 8]. It is not associated with amino acid content, but creatinine clearance decreases by an average of 3.5% per year while on PN [72]. Glomerular necrosis can develop with long-term PN, resulting in decreased renal function [8, 72]. Increasing age, use of nephrotoxic

drugs, and episodes of bacteremia/fungemia all contribute to the development of renal dysfunction and nephromegaly. However, it is unclear to what degree each participates.

Hyperoxaluria results from abnormalities in bile absorption. Oxalate is normally absorbed in the colon after binding to bile salts and fatty acids. However, in PN patients in whom bacterial overgrowth occurs, increased glycolate formation creates increased oxalate formation and absorption [35]. Hyperoxaluria is especially common in those patients with ileal resection and can result in a nonreversible oxalate nephropathy.

Refeeding Syndrome

Patients who are extremely malnourished, particularly if they have electrolyte losses due to high output enterocutaneous fistulae, recurrent vomiting, etc., are at increased risk for refeeding syndrome if they are initially fed too aggressively. The syndrome results in severe electrolyte abnormalities and Wernicke syndrome [1, 73]. Refeeding is not isolated to PN alone but can also occur in those patients who are malnourished receiving oral or enteral nutrition, or even intravenous hydration containing 5% dextrose. Refeeding syndrome is characterized by hypokalemia, hypophosphatemia, and hypomagnesemia, and is likely mediated by a sudden rise in insulin as the patient shifts from starvation to a postprandial state. Early symptoms may be vague and include weakness, myalgia, and shortness of breath. Patients that experience refeeding syndrome have an increased morbidity and mortality from cardiac arrhythmias and respiratory failure [35, 73]. Being astute to the correction of electrolyte abnormalities and supplementation of thiamine before and during nutritional support, including measuring and supplementing electrolytes repeatedly during a single day in high-risk patients, as well as starting PN with a reduction in dextrose, or all components, to approximately 50% of goal, are of the utmost importance in preventing complications from this syndrome [73].

Conclusion

PN has come a long way since Dudrick et al first showed positive nitrogen balance and growth in beagle puppies using solely intravenous alimentation (5,12). However, with great advances come unintended complications. Fortunately most of these complications are treatable (4). Mean expected survival rate is 90% at one year and 60% at five years on chronic PN (71). In fact, PN is life-saving in many instances! Patients with intestinal failure can survive on PN and live a relatively normal life (5,7,65). In the correct patient population, the benefits of patient survival outweighs the significant risks of complications. Careful choice of catheter placement, proper monitoring of patients and the prevention and treatment of complications will result in better outcomes.

References

1. Spencer CT, Compher CW. Total parenteral nutrition, an ally in the management of patients with intestinal failure and malnutrition: a long-term view. JPEN J Parenter Enteral Nutr. 2003;27(5):374–81. PubMed.
2. 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. Erratum in: JPEN J Parenter Enteral Nutr. 2006;30(2):177. PubMed.
3. Steiger E. Home parenteral nutrition. Components, application, and complications. Postgrad Med. 1984;75(6):95–102.

4. Buchman AL. Complications of long-term home total parenteral nutrition their identification, prevention and treatment. Dig Dis Sci. 2001;46:1–18.
5. Dudrick SJ, Palesty JA. Historical highlights of the development of total parenteral nutrition. Surg Clin North Am. 2011;91(3):693–717.
6. Kumpf VJ, Tillman EM. Home parenteral nutrition: safe transition from hospital to home. Nutr Clin Pract. 2012;27(6):749–57. doi:10.1177/0884533612464888. Epub 2012 Oct 22. Review. PubMed.
7. 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.
8. Montalvo-Jave EE, Zarraga JL, Sarr MG. Specific topics and complications of parenteral nutrition. Arch Surg. 2007;392:119–26.
9. Schloerb PR. TPN or intravenous food poisoning? Nutrition. 2001;17(7–8):680–1.
10. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery. 1968;64(1):134–42. PubMed.
11. Macht SD. Three hundred years of parenteral nutrition: the history of intravenous nutritional therapy. Conn Med. 1980;44(1):27–30. PubMed.
12. Dudrick SJ, Pimiento JM. Parenteral nutrition and nutritional support of surgical patients: reflections, controversies and challenges. Surg Clin North Am. 2011;91(3):675–92.
13. Dudrick SJ. A three and one-half decade nutritional and metabolic iliad. J Am Coll Surg. 2007;205:S59–64.
14. Cuthbertson D. Historical background to parenteral nutrition. Acta Chir Scand. 1980;498(Suppl):20–5.
15. Asch MR. Venous access: options, approaches, and issues. Can Assoc Radiol J. 2001;52:153–64.
16. Segarra-Newnham M, Martin-Cooper EM. Antibiotic lock technique: a review of the literature. Ann Pharmacother. 2005;39(2):311–8. Epub 2004 Dec 28. Review. PubMed.
17. Bestul MB, Vandenbussche HL. Antibiotic lock technique: review of the literature. Pharmacotherapy. 2005;25(2):211–27. Review. PubMed.
18. Sansivero GE. Venous anatomy and physiology. Considerations for vascular access device placement and function. J Intraven Nurs. 1998;21(5 Suppl):S107–14. Review. PubMed.
19. Sansivero GE. Features and selection of vascular access devices. Semin Oncol Nurs. 2010;26(2):88–101. doi:10.1016/j.soncn.2010.02.006. Review. PubMed.
20. Pettit J. Assessment of infants with peripherally inserted central catheters: part 1. Detecting the most frequently occurring complications. Adv Neonatal Care. 2002;2(6):304–15. PubMed PMID: 12881943 Review.
21. Vanek VW. The ins and outs of venous access: part I. Nutr Clin Pract. 2002;17(2):85–98. PubMed.
22. Lum PS, Soski M. Management of malpositioned central venous catheters. J Intraven Nurs. 1989;12(6):356–65. PubMed.
23. Moran BJ. Access methods in nutritional support. Proc Nutr Soc. 1994;53(3):465–71.
24. Meguid MM, Eldar S, Wahba A. The delivery of nutritional support. A potpourri of new devices and methods. Cancer. 1985;55(1 Suppl):279–89. Review. PubMed.
25. Gil ME, Mateu J. Treatment of extravasation from parenteral nutrition solution. Ann Pharmacother. 1998;32(1):51–5. PubMed.
26. Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters. A randomized controlled trial. Ann Intern Med. 1991;114(10):845–54. PubMed.
27. Rosenthal K. Are you up-to-date with the infusion nursing standards? Nursing. 2007;37(7):15. PubMed.
28. Boyd S, Aggarwal I, Davey P, Logan M, Nathwani D. Peripheral intravenous catheters: the road to quality improvement and safer patient care. J Hosp Infect. 2011;77(1):37–41. doi:10.1016/j.jhin.2010.09.011. Epub 2010 Dec 3. PubMed.
29. Harden JL, Kemp L, Mirtallo J. Femoral catheters increase risk of infection in total parenteral nutrition patients. Nutr Clin Pract. 1995;10(2):60–6. Review. PubMed.
30. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control. 2011;39(4 Suppl 1):S1–34. doi:10.1016/j.ajic.2011.01.003. PubMed.
31. Timsit JF. What is the best site for central venous catheter insertion in critically ill patients? Crit Care. 2003;7(6):397–9. Epub 2003 Mar 28.
32. Ingle RJ. Rare complications of vascular access devices. Semin Oncol Nurs. 1995;11:184–93.
33. Grant J. Recognition, prevention, and treatment of home total parenteral nutrition central venous access complications. JPEN. 2002;26(Suppl):21–8.
34. Timsit JF, L'Hériteau F, Lepape A, Francais A, Ruckly S, Venier AG, et al. A multicentre analysis of catheter-related infection based on a hierarchical model. Intensive Care Med. 2012;38(10):1662–72. Epub 2012 Jul 14. PubMed.
35. Ghabril MS, Aranda-Michel J, Scolapio JS. Metabolic and catheter complications of parenteral nutrition. Curr Gastroenterol Rep. 2004;6:327–34.

36. Nakazawa N. Infectious and thrombotic complications of central venous catheters. Semin Oncol Nurs. 2010;26(2):121–31. doi:10.1016/j.soncn.2010.02.007. Review. PubMed.
37. Hemphill DJ, Sniderman KW, Allard JP. Management of total parenteral nutrition-related superior vena cava obstruction with expandable metal stents. JPEN J Parenter Enteral Nutr. 1996;20(3):222–7. PubMed.
38. Raad II, Luna M, Khalil SA, Costerton JW, Lam C, Bodey GP. The relationship between the thrombotic and infectious complications of central venous catheters. JAMA. 1994;271(13):1014–6. PubMed.
39. Sandstedt S, Heselvik F, Marklund T, Stenport G. Percutaneous, tunneled silicone elastomer central venous catheters for TPN: low sepsis and thrombosis rate. A prospective study of 325 catheters. Nutrition. 1989;5:23–6.
40. Timsit JF, Farkas JC, Boyer JM, Martin JB, Misset B, Renaud B, et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. Chest. 1998;114(1):207–13. PubMed.
41. Eastridge BJ, Lefor AT. Complications of indwelling venous access devices in cancer patients. J Clin Oncol. 1995;13:233–8.
42. Buchman AL, Misra S, Moukarzel A, Ament ME. Catheter thrombosis and superior/inferior vena cava syndrome are rare complications of long term parenteral nutrition. Clin Nutr. 1994;13:356–60.
43. Mustafa S, Stein PD, Patel KC, Otten TR, Holmes R, Silbergleit A. Upper extremity deep venous thrombosis. Chest. 2003;123:1953–6.
44. Vanek VW. The ins and outs of venous access: part II. Nutr Clin Pract. 2002;17(3):142–55. PubMed.
45. Hoshal Jr VL. Total intravenous nutrition with peripherally inserted silicone elastomer central venous catheters. Arch Surg. 1975;110(5):644–6. PubMed.
46. Smith JR, Friedell ML, Cheatham ML, Martin SP, Cohen MJ, Horowitz JD. Peripherally inserted central catheters revisited. Am J Surg. 1998;176:208–11.
47. Ng PK, Ault MJ, Maldonado LS. Peripherally inserted central catheters in general medicine. Mayo Clin Proc. 1997;72:225–33.
48. Duerksen DR, Papineau N, Siemens J, Yaffe C. Peripherally inserted central catheters for parenteral nutrition: a comparison with centrally inserted catheters. JPEN. 1999;23:85–9.
49. Broviac JW, Cole JJ, Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. Surg Gynecol Obstet. 1973;136:602–6.
50. Hickmann RO, Buckner CD, Clift RA, Sanders JE, Stewart P, Thomas ED. A modified right atrial catheter for access to the venous system in marrow transplant recipients. Surg Gynecol Obstet. 1979;148:871–5.
51. Rumsey KA, Richardson DK. Management of infection and occlusion associated with vascular access devices. Semin Oncol Nurs. 1995;11:17483.
52. Prandoni P, Polistena P, Bernandi E, Cogo A, Casara D, Verlato F, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med. 1997;157:57–62.
53. Atiken DR, Minton JP. The "pinch-off sign": a warning of impending problems with permanent subclavian catheters. Am Surg. 1984;148:633–6.
54. Krzywda EA, Andris DA, Edmiston CE. Catheter infections: diagnosis, etiology, treatment and prevention. NCP. 1999;14(4):178–90.
55. Cowl CT, Weinstock JV, Al-Jurf A, Ephgrave K, Murray JA, Dillon K. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally-inserted central catheters. Clin Nutr. 2000;19:237–43.
56. Pronovost PJ, Goeschel CA, Colantuoni E, Watson S, Lubomski LH, Berenholtz SM, et al. Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. BMJ. 2010;340:c309. doi:10.1136/bmj.c309. PubMed PMID: 20133365; PubMed Central PMCID: PMC2816728.
57. Ytang VC, Morsey MA, Chemla ES. Using arteriovascular fistulae as a dual access for hemodialysis and total parenteral nutrition administration is feasible with a good outcome: a case series. J Vasc Access. 2007;8:305–8.
58. Madeo M, Lowry L. Infection rates associated with total parenteral nutrition. J Hosp Infect. 2011;79(4):373–4. doi:10.1016/j.jhin.2011.08.012. Epub 2011 Sep 29. PubMed.
59. Stratov I, Gottlieb T, Bradbury R, O'Kane GM. Candidaemia in an Australian teaching hospital: relationship to central line and TPN use. J Infect. 1998;36(2):203–7. PubMed.
60. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery. 1982;92:706–12.
61. Lammermeier D, Steiger E, Cosgrove D, Zelch M. Use of an intercostal vein for central venous access in home parenteral nutrition: a case report. JPEN. 1986;10:659–61.
62. Nirula R, Yamada K, Waxman K. The effect of abrupt cessation of total parenteral nutrition on serum glucose: a randomized trial. Am Surg. 2000;66:866–9.
63. Crook MA. Lipid clearance and total parenteral nutrition: the importance of monitoring plasma lipids. Nutrition. 2000;16:774–5.

64. Peden VH, Witzleben CL, Skelton MA. Total parenteral nutrition. J Pediatr. 1971;78(1):180–1.
65. Luman W, Shaffer H. Prevalence, outcome, and associated factors of deranged liver function tests in patients on home parenteral nutrition. Clin Nutr. 2002;21:337–43.
66. Cavichi 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.
67. Fryer J, Pellar S, Ormond D, et al. Mortality in candidates waiting for combined liver-intestine transplants exceeds that for other candidates waiting for liver transplants. Liver Transpl. 2003;9:748–53.
68. Klein GL, Targoff CM, Ament ME, Sherrard DJ, Bluestone R, Young JH, et al. Bone disease associated with total parenteral nutrition. Lancet. 1980;2:1041–4.
69. Shike M, Harrison JE, Sturtridge WC, Tam CS, Bobechko PE, Jones G, et al. Metabolic bone disease in patients receiving long-term total parenteral nutrition. Ann Intern Med. 1980;92(3):343–50.
70. Seidner DL. Parenteral nutrition-associated metabolic bone disease. JPEN J Parenter Enteral Nutr. 2002;26(5 Suppl):S37–42. Review. PubMed.
71. Pironi I, Labate AM, Pertkiewicz M, Przedlacki J, Tjellesen L, Staun M, et al. Prevalence of bone disease in patients on home parenteral nutrition. Clin Nutr. 2002;49:497–500.
72. 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. 1993;17:438–44.
73. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001;17:632–7.

Chapter 8
Surgical Intensive Care Considerations

Charles W. Van Way III

Keywords Stress response • Hypermetabolism • Trauma • Operation • Head injury • Gastrointestinal tract injury • Liver injury • Burn injury • Intestinal obstruction • Pancreatitis • Short bowel syndrome • Enterocutaneous fistula

Key Points

- Surgical patients are characterized by response to an acute event, either surgery or injury.
- The stress response is a coordinated neuroendocrine, circulatory, inflammatory, and metabolic response.
- Injured patients should receive enteral or parenteral nutrition support relatively early, usually within 1–2 days post-injury.
- Enteral nutrition is best, if the gastrointestinal tract can be used.
- Patients with gastrointestinal injuries may require parenteral nutrition, but most centers start it after 2–4 days, because of the added risk involved.
- Head injured patients should be fed early, using enteral nutrition.
- Burn injured patients are often dependent on enteral nutrition for up to several weeks.
- Postoperative patients may tolerate several days without adequate nutrition, but should be supported with enteral nutrition by 5–7 days.
- Use of parenteral nutrition in the postoperative patient should be reserved for patients who cannot tolerate enteral nutrition.
- Prolonged ileus following gastrointestinal surgery often requires the use of parenteral nutrition after 5–7 days.
- Glutamine, arginine, and other "immunotherapy" nutrients are often used in surgical patients, but the evidence in favor of their use is equivocal at best.
- Management of intestinal obstruction may require parenteral nutrition if the obstruction does not resolve.
- Pancreatitis is best managed using either oral intake or enteral nutrition, contrary to earlier practice using parenteral nutrition and "bowel rest."
- Patients with short bowel syndrome, including patients with enterocutaneous fistula, often require parenteral nutrition, and frequently must be treated with home parenteral nutrition.

C.W. Van Way III, MD, FACS, FCCP, FCCM, FASPEN (✉)
Department of Surgery, Truman Medical Center, School of Medicine,
University of Missouri–Kansas City, 2301 Holmes Street, Kansas City, MO 64108, USA
e-mail: cvanway@kc.rr.com

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_8,

Introduction

What is surgical intensive care, and why are we giving it special consideration? Is not one critically ill patient much like another? In fact, no. Some patients are commonly regarded as "surgical," and for good reasons. They have a number of characteristics in common, and are different from the so-called "medical" patients. To generalize, "medical" patients are in the ICU because of exacerbations of chronic diseases—most commonly respiratory, cardiac, or renal, often in combination, and frequently with diabetes as well. "Surgical" patients need intensive care because they have had a major acute event, usually either an injury or an operation. To be sure, there is much overlap. Surgical patients may also have major chronic diseases. They may develop organ failure syndromes. But that being said, "surgical" patients have a set of problems that are different from those seen in "medical" patients. Caring for them requires a somewhat different mindset than dealing with chronic disease.

The prototype of the surgical intensive care patient is the injured patient. A patient is suddenly injured, perhaps massively, and often requires one or more operations. Oral nutrition is cut off abruptly. Now, healthy people can tolerate a day or two without food easily, and several days without apparent ill effects. At some point, starvation begins to interfere with healing, and to impair the patient's recovery. There may be delayed wound healing, wound infection, or dehiscence. Prolonged lack of nutrition may also predispose to other infections such as urinary tract infections and pneumonia, and to decubitus ulcers.

Postoperative patients are not unlike injured patients. The metabolic response to operation is similar to that of injury. Here again, healthy people can go without food for several days. Most surgical procedures interrupt eating for only a day or two. Even in gastrointestinal surgery, keeping patients "*nil per os*" for as long as 5–7 days while the GI tract recovers has long been surgical practice. But in the postoperative patient, like the injured patient, there comes a time after which the patient simply must be fed.

In most hospital settings, care of the "surgical" critical care patient is carried out by surgeons. Traditionally, attending surgeons care for their own patients in the ICU. More recently, this is commonly done by Surgical Critical Care (SCC) specialists. SCC requires an extra year or two of training. SCC specialists usually practice surgery as well, often trauma or acute care surgery. While any surgical specialist can become trained and qualified in SCC, most who do so are general or cardiothoracic surgeons. Anesthesiologists and emergency medicine specialists can also be trained in and practice SCC.

It is the purpose of this chapter to outline the particular requirements of nutrition support in the surgical patient, emphasizing largely the injured and/or postoperative patient. To begin this discussion, it is best to start with the metabolic characteristics that are seen in the surgical patient, and can be said to define this group of patients.

Metabolic Characteristics of the Surgical Patient

The acute response to any type of stress is characterized by endocrine events, inflammatory response, and metabolic response. In brief, the body undergoes a number of changes that collectively prepares it for the challenge of surviving injury. The basics of this have been known since the pioneering work of Cuthbertson during the 1930s [1]. Many others have elaborated on it since [2–4]. Indeed, the response to injury and to operation are similar, as both are modifications of the stress response. This response may be somewhat arbitrarily divided into neuroendocrine, inflammatory, and metabolic.

Neuroendocrine response begins with activation of the hypothalamus. This stimulates the pituitary to release ACTH, which in turn stimulates the adrenal cortex to produce cortisol. Cortisol in turn raises the blood sugar and mobilizes fatty acids by lipolysis of fat stores. It also depresses the immune system.

At the same time, the sympathetic nervous system is activated. This stimulates the adrenal medulla to produce catecholamines, largely epinephrine, whose secretion may increase 20-fold. These changes produce increases in blood pressure, heart rate, and cardiac output. The metabolic rate increases. These changes produce increases in blood pressure, heart rate, and cardiac output. Temperature increases modestly. There is increased blood flow to muscles, skin, heart, and viscera. There is increased blood flow to muscles, skin, and heart, with constriction elsewhere in the body, such as the viscera. Gastrointestinal activity is depressed by sympathetic nervous stimulation. All of this—mobilization of energy stores, redistribution of blood flow, tachycardia, and increased cardiac output—prepares the organism to respond to stress [1–4].

There are increases in secretion of both glucagon and insulin from pancreatic islet cells. At the same time, there is decreased responsiveness to insulin [5]. This insulin resistance characterizes not only injured patients, but postoperative patients as well [6]. As further discussed, it is actually deleterious to recovery.

Hemorrhagic shock exaggerates the "normal" stress response. Such patients show all of the above changes. Resuscitation with crystalloid and blood products may restore the blood pressure and appear to restore perfusion to normal. It may take up to 3 days to completely resuscitate patients from hemorrhagic shock. Current practice is to limit the time of initial operation to an hour, the so-called "damage control" procedure. The intent is to control hemorrhage and prevent further blood loss, removing devitalized tissue (including bowel), but making little effort to reconstruct the injuries. Then the patient is taken to the ICU for continued resuscitation. Second and third operations follow at intervals of 12–24 h, until the wounds are completely debrided, reconstruction of bowel and/or vascular continuity carried out, and the patient is completely resuscitated. Current thinking on resuscitation emphasizes the simultaneous administration of packed red cells, platelets, and clotting factors (fresh frozen plasma) in a 1:1:1 ratio [7, 8].

A number of metabolic changes are produced, many in response to the neuroendocrine changes already outlined [9]. Hypermetabolism is a part of the stress reaction. Lipolysis releases ketone bodies and fatty acids into the circulation, to be metabolized for energy by skeletal muscles, heart, and most viscera. Stored glycogen is broken down for glucose, to provide energy to those systems that require glucose—the central nervous system, the hematopoietic system, and healing tissues. With many parts of the body being inadequately perfused, anaerobic glucose metabolism occurs, releasing lactate into the circulation. Indeed, lactate levels are often used as an index of the degree to which a patient has been adequately resuscitated.

After the stress response begins, the body runs out of stored glycogen in 4–6 h. Proteolysis begins, producing amino acids, notably alanine and glutamine. Alanine is the main substrate for gluconeogenesis by the liver, which provides glucose after glycogen runs out in about 24 h. Glutamine can be used directly for energy by the gut. The protein breakdown of stress can be modulated by providing at least modest amounts of glucose; in an adult, 400–500 cal, or 100–125 g, is sufficient. For this reason, 5 % dextrose in water is commonly used, usually with added sodium and potassium to meet maintenance requirements [4]. Unfortunately, many physicians use normal saline or lactated Ringer's solution for routine maintenance. These overload patients with sodium and chloride, and provide little or no potassium. Worse, these fluids contain no calories, and their use fails to attenuate protein breakdown.

The systemic inflammatory response is the final element of the response to injury [3, 4, 10]. It is mediated in part by the hormonal changes discussed above. But the greatest part of systemic inflammation is mediated through a number of mediators, most of which are still being actively investigated. Pro-inflammatory cytokines are prominent. These include TNF-α, IL-1β, IL-6, and IL-8. Besides TNF and the interleukins, cytokines include chemokines, lymphokines, and interferons. All of these are small proteins, 5–10 kDa in size, produced by cells, and generally act on other cells through cell-surface receptors. Cytokines may be pro- or anti-inflammatory cytokines [10].

Hormones based on long-chain fatty acids are also involved in the stress response [11]. These include thromboxanes, leukotrienes, and prostaglandins. Remarkably, the series of hormones derived from omega-3 fatty acids (arachidonic acid) form a pro-inflammatory group, while those derived from omega-6 fatty acids (fish oil, linoleic acid) are anti-inflammatory. Finally, there are a number of other factors that are upregulated in the inflammatory response, including oxidizing agents, hepatic acute phase proteins, adhesion molecules, and others. The protein resistin and the adhesion molecule ICAM-1 are prominent in the systemic inflammatory response. Inflammation research is a major field of investigation today, and new factors are being actively discovered. Detailed discussion is well beyond the scope of this chapter.

Nutrition Care of the Injured Patient

The central problem with feeding the injured patient is that we know the patient is going to be hypermetabolic, but we have only an approximate idea of how much and how long [3, 4]. The duration of hypermetabolism following injury is somewhat dependent on the extent of injury, modified by such factors as the presence of infection, amount of tissue damage, operations necessary to repair the injury, any complications which may develop, and the patient's baseline medical condition. While many patients return to normal in a few days, some patients remain hypermetabolic for 3–4 weeks. The duration of hypermetabolism depends a great deal on the individual patient's response, and cannot be predicted accurately from the extent of injury. This makes it very difficult to answer two very basic questions. First, how much should such patients be fed? Second, how soon after injury is it necessary to begin feeding? Complicating this further is that some patients may be just fine with oral nutrition, others will not be able to eat enough, for a variety of reasons, and still others will require enteral or parenteral nutrition. At one extreme, a major burn injury will require multiple debridement and skin grafting, and may have a doubled metabolic rate for 1–2 months following injury [12]. Enteral nutrition will be required, possibly with additional parenteral nutrition, for many weeks [13]. At the other, a stab wound of the chest may be adequately treated with a simple chest tube, and will respond well to an oral diet.

Despite the many similarities between postoperative patients and the injured patients, the injured patient is at higher risk for complications and adverse outcomes. The practice of most trauma surgeons is to feed the patient as soon as feasible following injury, and to wait no more than 3 days following injury before initiating a feeding regimen. Even then, a patient may have an energy deficit of 5000–8000 kcal before feeding is initiated. Enteral nutrition is very clearly the method of choice (see Chap. 4). Injuries to the gastrointestinal tract may mandate parenteral nutrition in some cases.

The concept of caloric balance was introduced 30 years ago, by Robert Bartlett [14]. Using indirect calorimetry, he studied 57 patients with multiple organ failure. He calculated their cumulative caloric balance, calories in minus calories expended, during the hospitalization. He found that there was a break point at around 10,000 kcal. A negative caloric balance above that level was associated with a 20 % survival, while a positive balance was associated with a 90 % survival. While a number of studies have been done since then, the level of 10,000 kcal remains a useful clinical guide. One goal of feeding the injured patient, then, should be to avoid a large energy deficit. But it should be noted that there is considerable uncertainty about how best to achieve this goal [15].

During the resuscitation phase, nutrition is only a distant consideration. The patient is usually receiving saline or lactated Ringer's, blood, and blood products. Current therapy of trauma calls for less crystalloid and more aggressive replacement of red blood cells, fresh frozen plasma, platelets, and often cryoprecipitate. Once resuscitation is complete, on the basis of serum lactate, vital signs, and clinical parameters, it is best to discontinue the use of high-sodium solutions. If used excessively,

which is to say for several days, these solutions will produce fluid overload, peripheral edema, and possibly adult respiratory distress syndrome, as well as hyperchloremic acidosis from the use of normal saline. The protein breakdown of stress can be modulated by providing at least modest amounts of glucose; in an adult, 400–500 cal, or 100–125 g, is sufficient [4]. For this reason, 5 % dextrose in half-strength or quarter strength saline with added potassium is recommended for routine maintenance fluid administration.

Hemodynamic stabilization can usually be achieved relatively quickly, but completion of resuscitation may take 24–48 h, or even more. Current major trauma surgery will frequently utilize an initial "damage control" laparotomy, to be followed the next day with a more definitive procedure after resuscitation is complete. Once resuscitation has been accomplished, the patient should be fed. Feeding patients with an open abdomen can be carried out successfully [16]. While the oral route is obviously best, it is often insufficient. If so, enteral feeding is to be preferred. Gastric intubation is adequate for most situations. Although trans-pyloric tube placement into the jejunum has the advantage of bypassing the stomach, and avoids the problem of delayed gastric emptying, most patients whose injuries do not involve the gastrointestinal tract have no difficulty with gastric feedings.

The literature is decidedly mixed on the subject of gastric versus post-pyloric feedings [17]. Most studies, it should be noted, have been done on mixed medical and surgical patient populations. Heyland et al. carried out a prospective study in 33 patients, finding that aspiration was highest in gastric feedings, lower in duodenal, and lowest in post-duodenal [18]. This conclusion was supported by a retrospective study by Metheney et al. [19] and by a meta-analysis carried out by Heyland's group [20]. The latter concluded that the incidence of pneumonia was significantly lower in patients fed using post-pyloric placement of tubes. But two other meta-analyses have concluded that tube placement, whatever effect it may have upon rate of aspiration, did not influence the incidence of pneumonia, nor other measures of outcome [21, 22] (This issue is discussed more comprehensively in Chap. 5).

Since many severely injured patients require multiple operations, there is always a temptation to wait until these are complete before beginning enteral nutrition. But this may unduly prolong the duration of starvation. Consider burn injuries, in which debridement and skin grafting may continue for weeks. There is no particular reason why patients cannot be fed despite going to the OR every day or two. Coordination with the anesthesia service is of course essential, to avoid taking the patient to the OR with a full stomach.

How much should be given? In general, injured patients should be given relatively high amounts of calories, and extra protein. This means 30–35 kcal/kg/day, and 1.5 g/kg/day of protein. The enteral regimen should be chosen with this in mind, using a calorie to non-protein nitrogen ratio somewhat lower than would be given to a less-stressed patient Any one of several formulas may be employed: calories per kilogram, Harris-Benedict, Penn State, etc. But all formulas, including calories per kilogram, should be regarded as imprecise. Estimates may be off by as much as plus or minus 50 %. If indirect calorimetry is available, measurement will allow considerably more precision in providing calories. Particularly in obese patients, it may be extremely difficult to determine the proper amount to give without being able to use indirect calorimetry (see Chap. 12 for a discussion of feeding the obese patient).

Finally, most of us assume that the trauma patient is usually young, healthy, and well-nourished. This assumption is incorrect. In military medical practice, patients are very often nutritionally depleted. Most soldiers lose weight during extended periods of combat, even if they are fit to begin with. Civilian casualties in a war zone are even more likely to be malnourished. On the home front, the same is often true for urban warriors, depleted by poor diets, drug and alcohol use, and general stress. Just as many surgical patients are nutritionally depleted before their operation, many injured patients are poorly nourished before their injury.

Management of Specific Injuries

Abdominal and Bowel Injuries

Management of patients with gastrointestinal (GI) tract injuries frequently requires the patient to be placed on parenteral nutrition (PN). Lack of GI function makes it difficult to adhere to the recommended practice of initiating enteral feedings within 2–3 days of injury and/or operation. But most surgeons begin PN in postoperative patients only after 5–7 days, if the patient is still unable to eat. So, is it justified to delay the onset of PN in injured patients? There is relatively little evidence on this point. There is a general consensus that it is best to begin enteral nutrition within 24–48 h of injury, as advocated by Moore and colleagues [23–25]. Early enteral nutrition has been shown to be superior to early parenteral nutrition in critically ill patients in general [21, 22] (see Chap. 4 for a more detailed discussion).

There is less evidence concerning when, if enteral nutrition cannot be used, parenteral nutrition should be started in the seriously injured patient. Indeed, there is considerable uncertainty in the critically ill patient, in general [15]. The major pitfall in caring for such patients is "one more day," otherwise known as unwarranted optimism. The surgical team may be convinced that the patient will begin to eat in a day or two, while the patient quietly starves in bed. While consensus is difficult to obtain, most trauma centers begin parenteral nutrition after 2–4 days in patients who cannot take enteral nutrition. At most, this is only a day or 2 after the time that enteral nutrition would have been started if the patient were able to accept it. Injured patients, especially those with major GI injuries, usually have a lot of tissue damage, and large incisions to heal. But this is an area in which research cannot yet provide the answer.

Patients with GI tract injuries may end up, after one to three operations, with ileostomies or colostomies. Management of the ostomy in an injured patient may introduce further nutritional issues. For one thing, the ostomy may not function for up to 2 weeks. True, this may occur after any GI injury or bowel surgery. But there is a tendency to see the ostomy as something of a short cut. Because of postoperative adhesions, pain medicines, or trauma-induced dysfunction, it is common for a week or more to pass before the GI tract begins to function, and the ostomy begin to have output. Such patients should be on parenteral nutrition, if not from the very start, certainly as soon as becomes evident that there will be a delay in restoration of GI function.

At the opposite extreme, the ostomy may put out more than expected. One may see losses of 2, 3 or 4 L per day, until the patient's GI tract accommodates itself to the new realities. There is no predicting this. The same patient may delay opening up for 2 weeks, and then a week later have a high-output ileostomy. The problem is more likely to happen with an ileostomy than a colostomy, but can happen with either. Once the ostomy output exceeds 1 L a day, it is usually best to adjust fluid volumes with extra intravenous fluids, rather than by adjusting PN. Half strength saline with added potassium is the optimal choice.

As noted earlier, one of the by-products to the current technique of damage control surgery for trauma is the increasing number of patients with open abdominal incisions. While most such patients are re-explored and closed within a day or two, some cannot be closed. And too, there are patients who simply dehisce their abdominal closures. These patients represent a unique problem. They are usually managed with some sort of wound suction system. With continuous suction, they may lose anywhere from a few hundred milliliters to several liters per day of fluid from the wound. Wound fluid is basically an exudate, with high sodium and low potassium, and contains significant amounts of protein. Nutritional management must be closely coordinated with fluid and electrolyte management. Some patients with open abdomens will require parenteral nutrition, but many, if not most, can be fed enterally, or by oral nutrition [16].

Nutrition support appears especially important in severely injured patients. Although randomized studies are not feasible in this group of complex patients, retrospective studies have been done.

Collier et al. studied 78 patients in one trauma center. Patients requiring PN were excluded. Of the 78, 55 % had early enteral nutrition, which was found to be associated with earlier fascial closure, fewer fistulae, and considerably lower cost, as compared with those having later enteral nutrition. There was no reduction in pulmonary infections [16]. Dissanaike, Moore et al. secondarily reviewed 100 open abdomen patients from a large multicenter study. Patients with bowel injuries were excluded. Early enteral nutrition was used in 32 %; the rest were started after 4 days. Many of the "late" group received parenteral nutrition before they received enteral nutrition. Early enteral nutrition was associated with a large reduction in pulmonary infections, but no effect on mortality, hospital stay, or other morbidity. Time to fascial closure was shorter in the early group, but not significantly so [26]. The major importance of these studies is in the demonstration that early enteral nutrition can be both feasible and effective. Neither study provided data on just how many open abdomen patients can be fed enterally. In a study on this point by Byrnes et al. 52 % of 23 patients could be fed enterally before fascial closure [27]. Nonetheless, the presence of major bowel repairs, prolonged ileus, intestinal fistula, or intra-abdominal infection may prevent enteral nutrition and require parenteral nutrition.

Management of patients with major liver injuries has changed considerably over the last two decades. While it was once mandatory to explore possible liver trauma, superior radiologic techniques have now allowed identification and classification of liver injuries. There is a current tendency to manage patients with Class I and II injuries nonoperatively, and even to consider nonoperative management in Class III injuries. The net result is a decrease in open operation for smaller injuries to both liver and spleen. Just incidentally, this has produced a substantial decrease in the cost of caring for liver injuries [28]. This has also simplified nutritional support, as most patients managed nonoperatively may be started on oral nutrition within a day or two of the injury.

For severe abdominal injuries, nutrition support remains a major challenge. Damage control laparotomy for liver injuries usually involves leaving the abdomen open for up to several days, with one or more reoperations [29]. Thus, many patients with liver injuries will be in the "open abdomen" category noted above. Prichayudh et al. reviewing 218 cases in their institution, found that 45 patients were treated with damage control laparotomy [30]. Clemente et al. from Italy, found a similar proportion in 308 patients with liver injuries treated over 10 years [31]. Feeding these patients is, as already discussed, problematic. Many patients with Class IV and V liver injuries will also have injuries to other abdominal organs, particularly the bowel. Enteral nutrition remains the first choice, but parenteral nutrition may be required.

Head Injuries

Patients with head injuries, and with central nervous system injuries in general, can be highly deceptive. The brain consumes approximately 25 % of the normal resting energy budget of the body. After brain injury, energy expenditure rises markedly, up to 150 % of normal resting values, and may maintain this level for 4 weeks or longer. Therefore, the apparently quiet, comatose patient on a ventilator may have a metabolic rate half again baseline. It is important to begin feeding the comatose patient as soon as resuscitation is complete [32–34]. Nearly always, enteral nutrition can be used. But amounts should be 25–50 % above normal.

The value of nutrition support in head-injured patients was recognized by Young et al. as long as 25 years ago [35]. Current neurosurgical guidelines emphasize the role of nutrition in the management of such patients [36]. There is a strong recommendation that such patients should be fed reasonably early, with all needs being met by no later than 7 days. Nutritional needs are definitely higher than baseline, as noted. Hyperglycemia is particularly to be avoided in head-injured patients. There remains considerable uncertainty about whether gastric, jejunal, or parenteral feedings are best, with published studies showing advantages of each over the others [34, 36].

Burn Injuries

Nutritional management of burn injuries is an extreme challenge. Everything said about the stress reaction to injury applies, but is magnified. A major burn injury will always cause a major increase in metabolic rate, even without infection. A number of studies have documented metabolic rates of 150–200 % of normal baseline [37, 38]. Even a 5 or 10 % burn may trigger a disproportionate response [12]. High protein intake is essential to support healing. Although all burn-injured patients lose weight over the course of their treatment, at least partly from disuse atrophy, excessive weight loss is associated with greater risk of death. Both caloric and protein intake must be considerably greater than in a "normal" injured patient. Estimation of caloric requirements may be especially inaccurate in the burned patient. Indirect calorimetry, while not universally used, is considered much more accurate than using one or another of the several formulas available [12, 13, 37, 38]. Patients respond to the burn injury in a highly individual manner, and the same size burn may produce different metabolic rates in different patients. If indirect calorimetry is not available, the Curreri formula has been advocated:

$$\text{Energy Expenditure(kcal/day)} = 25 \times \text{wt(kg)} + 40 \times \%\ \text{burn}\ [38]$$

This formula provides much larger values than the more traditional equations, but it was derived from observation of burned patients. It gives values which agree more or less with studies using indirect calorimetry [38].

The patient will need nutritional support throughout the period of treatment, which will certainly take weeks, and may take months. Repeated operations for debridement and for skin grafting will challenge the patient's ability to recover, and will interrupt nutritional therapy.

Burn therapy was one of the early indications for nutrition support. It was recognized in the 1980s that burn injuries produce prolonged hypermetabolism [39]. Parenteral nutrition was widely employed at first. But burned patients are usually colonized with a variety of bacteria, and the burn wound is a constant source of infection. The risk of central line infection is greater than in most patients. Studies going back 25 years have shown increased mortality with the use of parenteral nutrition, as compared with enteral nutrition [40]. There is a clear consensus that enteral nutrition is best, and that methods of ensuring consistency and adequacy of enteral nutrition are highly desirable [41, 42]. Parenteral nutrition may be "more beneficial than no nutrition…" [13], but should only be used when there is no other route available.

Nutritional management of burn injuries is difficult. The patient must be maintained on nutritional support throughout the period of treatment, which for a major burn will certainly take weeks, and may take months [43]. Repeated operations for debridement and for skin grafting will challenge the patient's ability to recover, and will interrupt nutritional therapy. Various strategies are used to maintain nutrition, including the use of supplemental perioperative enteral feeding in patients taking oral nutrition, naso-enteric tubes to allow bypassing the stomach, and even gastrostomy in selected patients. Supplemental use of parenteral nutrition to maintain optimal calorie and protein intake may be necessary. Whether this should be done is currently the subject of controversy within the critical care community.

Burn therapy evolves rapidly to accommodate new data and new practices. The American Burn Association Guidelines are more than 10 years old, although still widely cited [41]. Current practice is to start early, within 24–48 h, and to maintain a high protein diet which meets the high needs of the burned patient [42–44]. Currently, there is a consensus to follow the ASPEN/SCCM guidelines, and to use indirect calorimetry when available to determine energy needs [45]. Early excision and grafting has been found to produce better results than debridement and delayed grafting. This means that the patient will be operated upon quite frequently in the early post-burn period, which again will challenge nutritional therapy to maintain adequate nutritional intake.

Other Major Injuries

Thoracic and vascular injuries, unless there are associated abdominal injuries, are usually relatively straightforward to manage. Most patients can eat, or at least take fluids, the day after their injury. Even patients undergoing esophageal repairs are usually able to eat, although it is safer to give a liquid diet for a week or so. After all, the esophagus must pass 500–1000 ml of saliva each day; feeding is little greater burden. Most surgeons will put off feeding until after the patient has had a contrast study of the esophagus at 2 or 3 days.

The exception is patients with severe open or blunt chest and lung injuries. These often require intubation and ventilator support. Early use of enteral nutrition will usually be sufficient to meet the patient's needs. Calculation of needs in this situation should reflect the hypermetabolism seen with all major injuries. Concomitant abdominal injury may make it necessary to use parenteral nutrition, as discussed above.

Patients with major musculoskeletal injuries usually have hypermetabolism, which may often be prolonged. It appears that healing of a long bone fracture consumes a significant amount of energy. Combining long healing times with enforced inactivity often produces marked weight loss during the weeks following injury. Nutrition support is obviously important. A patient who is "tolerating a regular diet" is not necessarily taking enough nutrition to promote healing. Patients, especially elderly patients, often fail to eat well, especially once they are in the hospital. Besides regular physical activity to minimize disuse atrophy and rehabilitate the patient after injury, administration of nutritional supplements, including vitamins, will ensure that patients receive sufficient nutrition.

Nutrition Care of the Perioperative Patient

In many respects, reactions of patients to operations is similar to the stress response to trauma. The magnitude and duration of the hormonal, metabolic, and cytokine responses are smaller and shorter [1, 2, 6]. Most surgical procedures are limited to a small area of the body, and there is very little tissue damage remaining at the end of the procedure. Very large operations, such as hepatic resection, pancreatectomy, and pelvic exenteration, are obvious exceptions to this generalization. Emergency operations are generally associated with acute illness. Their stress response is similar to that of injured patients, rather than to elective surgical patients. But in most situations, the issue is less how to manage the stress of operation than how to manage the patient's preoperative preparation and postoperative nutrition.

Preoperative evaluation of the prospective surgical patient is generally fairly extensive, especially if there is major chronic disease present. Nutritional assessment should be an integral part of this. All patients should be evaluated with nutritional screening, and those with a history poor food intake, muscle wasting, or major weight loss should be considered for preoperative nutritional support. As noted in Chap. 3, nutritional assessment is multifaceted. Simple measurement of the albumin (or retinol-binding protein, or thyroxine-binding pre-albumin) may be used to aid this evaluation, but none of these proteins is sufficient to establish whether or not the patient is malnourished before undergoing an operation. There is fairly good evidence that in patients who are severely malnourished prior to operation, postoperative complications and death are more likely [17, 46].

Once a patient is known to be malnourished, perioperative nutrition is probably beneficial. This may be as simple as providing nutritional supplementation orally for a week or two preoperatively, or as complex as admitting a patient to hospital for preoperative parenteral nutrition. It is sufficient to feed for no more than a week or 10 days preoperatively, and may be sufficient to feed for only 3–4 days. However, the evidence on this point is not as clear as the evidence showing that preoperative

malnutrition is a predictor of poor outcome. Regaining the lost weight is not necessary. The object is to convert the patient's metabolism from net catabolism to net anabolism before operation.

One of the unrecognized problems in surgical nutrition is the identification and management of micronutrient deficiency syndromes. Deficiencies of vitamins and trace elements may be difficult to identify, yet may potentially interfere with healing. As an example, our medical center serves a disadvantaged urban population. A recent study showed that vitamin D deficiency (less than 30 ng/ml) was present in about 96 % of hospitalized patients in whom 25-hydroxy vitamin D levels were measured [47]. While this incidence is unusually high, the finding of vitamin D deficiency is quite common, both in the USA and worldwide [48]. Flynn et al. studied 66 adult surgical patients who were to undergo elective surgery [49]. Seventy-four percent had 25-hydroxy vitamin D levels less than 20 ng/ml. In these patients, hospital stay was longer, and infection rate higher in patients who were deficient. Laaksi et al. studied the incidence of respiratory infection in 800 army inductees. Only 24 (3.5 %) were deficient (less than 16 ng/l), but those few had rates of respiratory tract infections significantly higher than the rest [50]. Quraishi et al. studied retrospectively 770 patients undergoing gastric bypass surgery. Fifty-eight percent had 25-hydroxy vitamin D levels less than 30 ng/ml. Comparing the low and normal groups, the low group had a threefold increase in hospital acquired infections and a fourfold increase in surgical site infections [52]. Supplementation with vitamin D has been studied by Amrein, et al., who administered very large doses of vitamin D3 or placebo to 492 patients admitted to five intensive care units in Austria. The dose was 540,000 units, plus 90,000 per month for 5 months. They defined deficiency as 30 ng/ml, and severe deficiency as 12 ng/ml. The primary outcome of length of stay was not affected, but mortality was lower in the vitamin D3 group, as compared with controls, for patients with levels less than 20 and 12 ng/ml [51]. Significantly, the large doses appeared safe, and no related complications were observed.

The problem is, we do not know what this means. There is at least some evidence that vitamin D level correlates with high postoperative infection rates. But might it be that a low vitamin D level is an indication of multivitamin deficiency, or of more generalized poor nutrition? Is this an isolated finding relating only to vitamin D? Administration of multivitamins or dietary supplements containing multivitamins for a week or more preoperatively may be beneficial, but there is no evidence one way or the other. We cannot agree on a level that represents deficiency, as evidenced by the papers cited above. And we cannot agree on the appropriate dose of vitamin D, nor on the amount required to correct deficiency [53]. The dominant impression in the literature is that many medical scientists hope that the problem will go away by itself.

The situation regarding trace element deficiencies is even less certain. We do know that zinc deficiency can retard wound healing, but administration of supplemental zinc is futile unless deficiency can be proven. Zinc deficiency produces a characteristic skin rash, which is easily overlooked. Chromium deficiency is said to be relatively common in older Americans, but the overall effect of this is not clear. It may impair glucose tolerance, and may be suspected in an older patient with the onset of diabetes, but most elderly diabetics just have diabetes, and are not chromium deficient.

Nutritional deficiencies tend to be broad spectrum. That is, patients who have erratic or inadequate food intake or who have poor dietary habits may have deficiencies in many micronutrients and macronutrients. Alcoholic patients, for example, are commonly seen on our medical service. The incidence of thiamine deficiency in this group of patients is fairly high. It is standard to administer a "banana bottle" for 3 days. containing a B vitamin preparation, vitamin C, and extra thiamine. Does this prevent problems if the patients have to be operated upon? We do not know. After 3 days or so, patients are usually less confused. But that usually is because they have sobered, not because we have cured their beriberi. Use of the "banana bag" is not supported by any studies, and it is probably unnecessary. But it is commonly used.

The most common issue in surgical nutrition is when and how to feed the patient postoperatively. Obviously, a malnourished patient requiring enteral or parenteral nutrition preoperatively should be continued postoperatively. On the other hand, a well-nourished patient does not need supplemental nutrition for several days. Most patients are on a regular diet by that time.

Gastrointestinal Surgery

GI operations, including major hepatobiliary procedures, present a set of particular problems. Early oral feeding was once avoided, but has now become routine. Surgeons used to keep patients NPO until the GI tract was functioning ("Did you pass gas this morning? No? Well, no food for you!"). But why should the patient have bowel sounds if the intestines are empty? Considerable evidence has accumulated that early feeding does no harm, and may even speed up bowel recovery and rehabilitation [56, 57]. A review of early enteral nutrition in gastrointestinal surgery patients concluded that this strategy is beneficial, speeding recovery and lowering hospital stay [58]. The only adverse side effect appears to be an increase in the incidence of vomiting. Many surgeons feed patients the day after operation. Even without early oral feeding, most patients can eat within two or 3 days. But a subset of patients do not "open up" early, and may remain unable to eat for a week or longer. It is acceptable to wait several days before becoming concerned about the lack of nutritional intake. A brief period of postoperative starvation should not be harmful. However, the patient must be fed by 5–7 days postoperatively [54].

Prolonged starvation is a problem on three levels. Most obviously, the patient begins to feel the effects—weakness, lack of energy, and so on. Hunger is often absent, if the GI tract is not yet working. On another level, prolonged lack of intake predisposes the patient to infections, including pneumonia, urinary tract infections, decubitus ulcers, and surgical site infections. Wound healing may be impaired. On a third level, the patient and family may become concerned about prolonged starvation, and often begin to complain. Federal and state regulatory agencies are increasingly regarding this as a safety issue, and are taking such complaints very seriously.

When reviewing the charts of patients who were kept without nutritional intake for 2 weeks or longer, it has been notable that most of them had progress notes saying the patient was "ready to eat," would "eat tomorrow," or would have "clear liquids tomorrow." The hazard here is wishful thinking. The surgical team keeps hoping for a better day, and does not start aggressive support. Because parenteral nutrition is usually required in this situation, nutrition support requires a fairly major therapeutic intervention. There is an understandable reluctance to begin. Understandable, but wrong.

Current practice, as reflected in the ASPEN guidelines and elsewhere, emphasizes that, whatever the benefits of early oral feedings, postoperative patients without gastrointestinal function do not require parenteral feeding for several days [45, 54, 55]. Yet the guidelines emphasize that parenteral nutrition should be reserved for patients who are going to be on nutrition support for a week or more. We have known for the last decade or two that patients, especially with prolonged gastrointestinal failure, eventually run out of their energy stores and should be fed [59]. This can lead to an awkward dilemma. Patients that are fed parenterally at 5–7 days often go on to become able to take oral intake after only 3–5 days of nutrition support. So… is it wrong to feed patients who may only require a few days? Absent a clinically usable crystal ball, one must conclude that a short period of parenteral nutrition is usually not harmful, and is clearly beneficial if the patient does not "open up" for another week or more. Obviously, this question does not arise in patients who can take enteral nutrition. But if a GI surgery patient cannot take oral nutrition, he or she will not likely be able to take enteral feedings either.

Cardiothoracic and Vascular Surgery

In thoracic and vascular surgery patients, the GI tract is usually functional. Most patients can eat a day or two after cardiac or pulmonary surgery, and within 3–5 days after esophageal surgery. Nonetheless, patients undergoing cardiothoracic surgery have metabolic changes similar to those seen after other major operations [6]. However, especially in cardiac surgery, only a relatively few patients require more than a day or 2 of critical care. Those that do require prolonged critical care are usually on

ventilator support, and require intensive nutrition support. Even then, enteral nutrition is usually sufficient. As with other surgical patients, 3–5 days without nutrition will not have an effect on outcome. There is no evidence that early enteral nutrition is beneficial following thoracic surgery [60]. However, after 5–7 days, nutrition therapy should be started. If, on the other hand, the patient has had a major infection or is beginning to develop multiple organ failure, then nutrition should be started earlier.

Liver Resection and Transplantation

Patients undergoing liver surgery, and especially those having transplantation, are often malnourished. Preoperative nutritional supplementation is advocated, especially as patients may be waiting on the transplant list for up to several weeks. A number of studies have been carried out on various strategies for enteral and/or parenteral nutrition, but the optimal therapy for liver-transplanted patients has not yet been defined. Langer et al. writing for the Cochrane Collaboration, reviewed 13 trials, including trials of intravenous dextrose, branched chain amino acids, enteral nutrition, and parenteral nutrition [61]. They could reach no definitive conclusions. The studies were not sufficiently homogeneous to permit meta-analysis, most were small, and no one therapy predominated. Since then, Zhu et al. published a study on the effects of omega-3 lipid emulsion combined with parenteral nutrition in 98 transplant recipients [62]. They found the regimen effective as compared with either conventional PN or oral diet in reducing liver injury, decreasing the incidence of infections, and shortening the post-transplant hospital stay. In summary, there seems to be a consensus in the transplantation community that nutrition support is an important part of pre- and post-transplant care, but little agreement on just how that it should be carried out.

Nutrients Important in the Stressed Patient

Glutamine is a small amino acid characterized by an extra nitrogen group at the end of a short side chain. An important component of the normal diet, it comprises some 25 % of protein, and is synthesized in the body from glutamic acid. It serves as a nitrogen donor in a large number of synthetic reactions, such as purine and pyrimidine synthesis, leading to nucleotides. Based on work with isolated gut segments, it is preferred over glucose as an energy substrate for intestinal epithelial cells [63, 64].

Although glutamine can be made in the body, it appears to fall into a middle ground between essential and nonessential amino acids. In the stressed patient, synthesis appears to be inadequate to meet metabolic needs. The description “conditionally essential” has been used to describe this.

Glutamine cannot easily be given parenterally. While other amino acids are stable in solution, glutamine is not. When mixed with other amino acids, it degrades, releasing ammonia. The time frame is 30 days or so, but it makes glutamine impractical to mix with other amino acids as necessary to prepare parenteral nutrition. Amino acid solutions must be stable for 6–12 months, at least. For that reason, glutamine is not included in any parenteral nutrition solutions. Moreover, glutamine is less soluble than most amino acids. It is available in a 3 % saline solution, which is stable, and can be given intravenously. This concentration is too low to permit compounding with other amino acids, and glutamine will not dissolve in water or saline at greater concentrations. A reasonable dose of glutamine requires infusing an extra 1 or 2 L of saline, just to administer the amino acid. On the other hand, all enteral formulas provide glutamine. Enteral nutrition has fewer limitations, since much of protein is present as dipeptides and tripeptides.

Glutamine-containing dipeptides have been investigated to find a glutamine formulation sufficiently concentrated to allow parenteral use. The glutamine–alanine dipeptide, marketed in Europe as

Dipeptivin®, has been most commonly used. It is not currently approved for general use in the USA. Nearly all studies of parenteral "glutamine" administration have actually used the dipeptide. When given intravenously, peptidases in the plasma cleave the dipeptide to glutamine and alanine, thus effectively administering glutamine to the patient.

The dipeptide is effective in raising glutamine concentrations. But questions remain about its clinical effectiveness. There have been several large, well-designed, multicenter studies. They have not found a net clinical benefit, although the studies are not entirely in agreement. Even two recent meta-analyses by Bollhalder et al. and Chen et al. failed to agree [65, 66], Bollhalder's group looked only at parenteral administration, while Chen's group reviewed both parenteral and enteral trials. In Bollhalder's analysis, there was a net benefit in terms of mortality. Chen's group found otherwise, but noted variation among studies of different groups of patients. The subgroup of surgical studies appeared to show lower risk of mortality in the glutamine group, although the effect failed to reach statistical significance. benefit the most. Both meta-analyses showed that the use of glutamine lowered the incidence of nosocomial infections. This subject is discussed further in Chap. 4.

The ASPEN/SCCM guidelines [45] recommend using glutamine, but the recommendation is weak, and several studies have been completed since then. The current consensus is that the administration of glutamine–alanine dipeptide (i.e., glutamine) cannot be supported on the basis of evidence. That said, it remains widely used in Europe.

Arginine also appears to have actions beyond simple provision of nutrition [67]. Like glutamine, arginine has extra amino groups, and serves as a nitrogen donor in a number of synthetic reactions. It is also an intermediary in the urea cycle, splitting off part of its side chain with the amino groups to synthesize urea; it is then reconstituted from ornithine, by way of citrulline. The urea cycle removes ammonia from the cells, and convert it to urea to be excreted in the urine. Finally, arginine is the substrate for nitric oxide synthase. Nitric oxide is a molecular messenger, one of the very few gaseous messengers, and a free radical. It has a number of actions, and is a potent vasodilator, intimately involved in regulation of vascular tone and hence flow through local vascular beds. It stimulates NF-κB, a nuclear factor that in turn indices synthesis of a number of cytokines. Highly unstable, it has a half-life in body fluids of a few seconds, and is metabolized to nitrates. Nitric oxide is produced from arginine by one of several nitric oxide synthases (NOS), at least one of which (iNOS) is stimulated by NF-κB in a positive feedback cycle. Nitric oxide itself has been used as inhaled therapy in diseases benefitting from pulmonary vasodilatation, such as respiratory distress syndrome of newborns, pulmonary embolus, and paraquat poisoning.

All of this places arginine into the regulatory mechanisms for the immune system, and in particular the systemic inflammatory response [67, 68]. But is it harmful, or helpful? Based on studies in animal cells, it appears to enhance the recovery of macrophages and other immune cells following shock [68, 69]. Arginine is made in the body as part of the urea cycle, so it is not an essential amino acid. It is already present in parenteral amino acid solutions and in enteral preparations. The therapeutic question is, should it be given in larger amounts? Studies of its use have been somewhat equivocal. However, a systemic review of studies in perioperative patients by Drover et al. concluded that patients treated with arginine had fewer in-hospital infections, and shorter lengths of stay. Mortality was not affected [70]. In short, there appears to be a benefit for administering arginine in perioperative patients (see further discussion in Chap. 4). But many of these studies employed "immunonutrition" regimens, with other components than arginine.

In practice, the question of whether to use arginine comes down to the question of when to use "immunonutrition," which includes several different components. Usually, these are ribonucleic acid (RNA), Ω-3 polyunsaturated fatty acids, and "antioxidants." These last are substances thought to have antioxidant properties, and hence of value in suppressing the deleterious side effects of free radicals. They include selenium, ascorbic acid, and sometimes other compounds. Most commonly, immunonutrition encompasses enteral compounds with arginine, omega-3 fatty acids, and RNA, with or without selenium and/or ascorbic acid. In a meta-analysis of 21 published studies, Marik and Zaloga [71]

found a significantly lower odds ratio of acquiring a new infection in patients receiving immunonutrition, lowered wound infection rates, and shorter length of stay. This is consistent with the conclusions reached from analysis of data using arginine. There is considerable overlap between studies of immunonutrition and studies of arginine. While it is difficult to know whether to attribute these benefits to arginine alone, there does appear to be real benefit.

But if immunonutrition is good, when should it be used? We do not have a good answer. Most of the studies that have been carried out have been in subgroups of "high risk" surgical patients. But "high risk" has not been sufficiently well defined to be a guide. The therapeutic strategy employed at Truman Medical Center is to use an enteral formula with immunonutrition components in patients who exhibit signs and symptoms of the systemic inflammatory reaction. This, it should be noted, includes most surgical patients in the ICU. When should it be begun? Again, we do not really know. Marik and Zaloga recommended starting 5 days preoperatively in "high risk" patients, but they admit that there is little evidence to support this strategy [71].

Management of "Surgical Diseases"

Some diseases absolutely require surgical therapy. Patients with intestinal perforation need immediate operation, for example. But there is also a group of "surgical diseases" which may or may not require operative therapy. Dealing with this group of diseases is often challenging. It is not so much that they are difficult to manage, although some of them are, as that they involve difficult cross-specialty decision making.

Intestinal Obstruction

In many ways, this is the prototype "surgical disease." Usually, this is secondary to adhesions from an old operation. Patients presenting with obstruction have a generally good prognosis for recovery without further operation. Gastric decompression using a nasogastric tube will relieve much of the distension. By aspirating swallowed air, gastric suction will help to relieve intestinal dilatation. In a majority of patients, the obstruction will resolve in a few days. But a minority, perhaps 20–30 %, do not. If they become acutely worse, and develop peritoneal signs, they need immediate operation. More commonly, they simply fail to improve. Anywhere from a few days to 2 or 3 weeks may elapse before they have operative intervention. The rule here is similar to the postoperative patient. If the patient has been vomiting for a week or more, and is unable to eat, he or she is acutely malnourished. Nutrition support should be started immediately after admission. If the patient has been observed for several days, unable to eat, and is no better, then after 5 days or so, he or she should be fed. In both cases, feeding will require parenteral nutrition.

This is problematic from a practical standpoint. First, there is a general reluctance on the part of the care team to "admit defeat" and begin parenteral nutrition. Second, the decision to begin parenteral nutrition is, or should be, associated with a decision to continue nonoperative therapy for a week or more.

If the patient is then operated upon, what about postoperative nutrition? As was discussed in a previous section, a patient who has been NPO for a week or more will benefit from immediate postoperative nutrition. But this usually requires parenteral nutrition, which brings up the same problem as preoperative nutrition support. There is a tendency to believe that all patients will be immediately cured following operation for obstruction. Unhappily, this is simply not true. Patients with obstruction preoperatively very commonly have a prolonged postoperative recovery, and to be unable to eat for a week or more.

Pancreatitis

Pancreatitis is usually a fairly benign and self-limited disease. It was once thought that bowel rest was mandatory. Studies have shown over the last 10–20 years that enteral nutrition is not only safe in most cases, but is beneficial in helping to resolve the acute inflammatory process [72, 73]. Because gastric emptying may be delayed, secondary to inflammation in the pancreas immediately behind the stomach, post-pyloric feeding tube placement is often advocated. But in most patients, gastric feeding will be tolerated [74, 75]. The inflammatory process often takes a week or 10 days, or more, to resolve, and patients should be fed relatively early, certainly within the first 2 days.

A few patients, less than 5 %, will have a far more aggressive form of pancreatitis. This is usually called "hemorrhagic pancreatitis," or "necrotizing pancreatitis" [72, 76]. The difference between these is of interest only to the pathologist. To the clinician, either condition presents with severe illness, progressing to critical illness in 48–72 h. The intense systemic inflammatory reaction is indistinguishable from severe sepsis. Respiratory failure usually occurs, requiring intubation, and renal failure is common. The management of this severe variant of pancreatitis ranges from supportive care (ventilatory and circulatory support) to irrigation and drainage of the pancreatic bed by interventional techniques to open operation and pancreatic "necrosectomy," debriding the necrotic pancreas. Mortality is high no matter which alternative is employed.

Nutrition support in such patients must wait on stabilization of pulse and blood pressure, but should then be aggressive. The initial therapy is very comparable to treating a major burn, in that large volumes of resuscitation fluid, together with cardiovascular support, are required. Once past this phase, there is still some controversy concerning just how such patients should be treated. The role of the gut seems to be much more complicated than was initially thought. The beneficial effects of enteral nutrition may include maintaining the gut mucosal barrier to endotoxin, and perhaps even to cytokines which might otherwise be released into the lymphatic and portal circulations [73]. By this reasoning, the sicker the patient, the more important it is to feed enterally [74]. But a recent study from the Dutch Pancreatitis Study Group has challenged this assumption [77].

The role of early "immunonutrition" was investigated in a porcine model of severe pancreatitis by Zou et al. [78]. They compared standard enteral nutrition with enteral nutrition supplemented with arginine, glutamine, and probiotics. Intestinal permeability and plasma endotoxin were highest in parenteral nutrition-fed animals, and lowest in the "immunonutrition" fed animals, with conventional enteral nutrition in between. However, such findings have not yet been reproduced in clinical studies.

Like other patients with multiple organ failure syndromes, these patients are significantly hypermetabolic. The exact caloric requirements may be difficult to estimate. But daily calories should be given in the 30–35 kcal/kg/day range, and protein should be administered at 1.5–2.0 g/kg/day. Electrolyte replacement is required, even after resuscitation is achieved. There is third space fluid loss into the retroperitoneum and the peritoneal space, requiring continuing fluid and electrolyte replacement above that needed for maintenance.

Short Bowel Syndrome

This group of conditions, most commonly patients who have too little bowel, also includes enterocutaneous fistulae and high output ileostomy or colostomy. All of these are characterized by partial but inadequate absorption of nutrients and by large and variable losses of fluids and electrolytes. Almost all are postsurgical. Some patients with Crohn's disease may develop spontaneous enterocutaneous fistulae, and there are a few instances associated with other conditions. ESPEN has recently released an extensive review and set of recommendations for management [79].

Nutritional care of this group of patients is one of the most challenging aspects of surgical nutrition care [80, 81]. The combination of dysfunctional gastrointestinal tract and excess fluid and electrolyte losses makes enteral nutrition very difficult. A few patients can be fed successfully with enteral nutrition, but most will require central venous access and parenteral feeding. Some patients will be able to resolve their underlying problem, some will have successful reconstructive surgery, and some will require life-long parenteral nutrition.

In approaching a short bowel patient, the most critical piece of information is just how much of the gastrointestinal tract is left. Patients usually develop symptoms of short bowel syndrome after a resection which leaves 200 cm of small bowel or less [79]. There is considerable variation among patients [80]. Two patients with the same amount of bowel may behave very differently [81]. Often, for example, the surgical resection is emergent, as for mesenteric ischemia and bowel necrosis, and leaves an ileostomy rather than reanastomosing the small bowel to the remaining colon. But the prognosis for recovery is fairly good if more than 100 cm of small bowel remains. Recovery may take many months, and may require takedown of the ileostomy, however. In general, the shorter the amount of remaining small bowel, the worse the prognosis. Patients with less than 100 cm of small bowel may require parenteral nutrition for life. It is not always possible to determine which patients will require lifetime parenteral nutrition. Patients with as little as 70 or 80 cm of small bowel have recovered; patients with as much as 120 or 140 cm have required lifetime therapy.

Nutritional management of the parenteral nutrition is relatively straightforward. Initially, patients should be kept NPO, and fed with appropriate amounts of glucose and amino acids. In the immediate postoperative situation, or with complex situations such as open abdomen, the patient may be hypermetabolic. Even with no oral intake, there will be some amount of intestinal fluid and electrolyte losses. Initially, these should be replaced by fluids containing sodium, potassium, and chloride, in amounts sufficient to replace losses. In general, half normal saline with added potassium is adequate. Some patients may lose enough bicarbonate to develop acidosis, and sodium bicarbonate may be added as needed. Eventually, it is usually possible to incorporate the fluid and electrolyte replacement into the parenteral nutrition, requiring 3 L a day or more of fluid administration.

As the patient recovers from the initial operation, and moves into chronic short bowel syndrome, the emphasis changes. Dysfunction of the intestine and maintenance of NPO status has very deleterious psychologic effects. Nearly all patients go through a phase of depression. It is important to allow them to eat something, even if that increases stool or ostomy output. But this in turn may require additional fluid and electrolyte therapy.

Management of venous access is extremely important (see also Chap. 7). The patient may require lifetime therapy. Using a Hickman or other transcutaneous catheter with a Dacron felt cuff to prevent infection along the catheter tract is important. This must be combined with meticulous sterile care of the catheter and with cleaning regimens. With care, a Hickman catheter can last for years. Sending such a patient home with a PICC line, or using a venous access port, will predispose to early catheter infection.

The transition from hospital to home or facility care is critical. Ideally, patients should by this time be on cyclic feedings, which may be up to 16 h a day. This allows them some time free of the intravenous infusion. Also, by the time the patient goes home, there should be some oral intake. Coordination of care is essential, so that the feeding regimen will adjust to the changing (hopefully, improving) gastrointestinal losses, and to the increasing ability of the patient's intestine to absorb nutrients.

A significant number of patients will be treated with teduglutide (Gattrix®), a glucagon-like peptide 2 (GLP2) analog. It has been shown to facilitate recovery in short bowel patients [80, 82]. While effective, this therapy is extremely expensive, at $25,000/month. Patients are usually treated for up to several months. Treatment should not be started until the patient has stabilized, and is on home parenteral nutrition.

Surgical reconstruction in short bowel syndrome is usually done to take down the ileostomy and reestablish intestinal continuity. Trading a high output ostomy for chronic diarrhea may not be in the

patient's best interest at first, however, so that reconstruction is often delayed for several months. In infants and children, there has been initial success with more elaborate small bowel reconstruction. These techniques have been less widely applied in adults [82, 83]. Whether they will provide benefit to adult patients with short bowel remains to be investigated.

The patient with a high output ileostomy, even if there is adequate small bowel (i.e., >200 cm), is managed like any other patient with short bowel syndrome. It is not entirely clear why patients develop this complication. While it is by definition postsurgical, the operation may not be a major resection. It has been seen following very minor bowel resections, and after colon resections. The prognosis is considerably better, and most such patients will eventually recover, often within months.

Patients with enterocutaneous fistulae present as a very difficult problem in surgical management. Typically the product of either a surgical complication or of Crohn's disease, or both, they require both intensive acute management to control the fistula, chronic management to keep the patient nourished, and often major operative therapy to close a persistent fistula [84, 85]. A proper treatment of the surgical issues involved is beyond the scope of this book. Many patients have prolonged courses, often with multiple operations. From a nutrition standpoint, it is best to regard these as a particular form of short bowel. If the fistula is very distal, or if the distal end of a proximal fistula can be successfully cannulated, it may be possible to feed patients enterally. Most of the time, parenteral feeding will be required to support patients through their multiple surgical procedures. Very often, a trial of parenteral nutrition combined with octreotide will be used for up to several months, in an attempt to allow the fistula to heal while the bowel is at rest.

Conclusion

The so-called "surgical" patients are identifiable, and require a somewhat different nutritional approach than medical critical care patients. The effects of chronic disease are much less pronounced. Disease onset is frequently defined precisely, by injury, operation, or acute disease such as pancreatitis or intestinal perforation. Nutrition support has assumed an important role in the care of severely injured patients, in whom it is always a matter of clinical concern. Postoperative patients usually do not require any form of extraordinary support, with the major exception of gastrointestinal surgery.

The same principles, guide nutritional therapy in these patients as in other critically ill patients. The gut should be used whenever possible. Early enteral nutrition seems to be important in injured patients, those with pancreatitis, and postoperative patients. The place of parenteral nutrition is now, as it has been for the past 40 years, in patients who cannot take oral or enteral nutrition. While this has been and remains an important area of surgical practice, studies have not been done in many areas of interest. The literature is often less than helpful on questions such as timing of parenteral nutrition, adequacy of caloric and protein intake by whatever method, and the use of supplemental or specialized nutrient formulas.

References

1. Cuthbertson D. Post-shock metabolic response. Lancet. 1942;239:433–436.
2. Cairnie AB, Campbell RM, Pullar JD, Cuthbertson DP. The heat production consequent on injury. Br J Exp Pathol. 1957;38(5):504–11.
3. Monk DN, Plank LD, Franch-Arcas G, Fainn 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. 1996;223:395–405.
4. Blackburn GL. Metabolic considerations in management of surgical patients. Surg Clin North Am. 2011;91(3): 467–80.

5. Tsatsoulis A, Mantzaris MD, Bellou S, Andrikoula M. Insulin resistance: an adaptive mechanism becomes maladaptive in the current environment – an evolutionary perspective. Metabolism. 2013;62:622–33.
6. Jakob SM, Stanga Z. Perioperative metabolic changes in patients undergoing cardiac surgery. Nutrition. 2010; 26:349–53.
7. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg. 2008;248(3):447–58.
8. McSwain NE, Champion HR, Fabian TC, Hoyt DB, Wade CE, Eastridge BJ, et al. State of the art of fluid resuscitation 2010: prehospital and immediate transition to the hospital. J Trauma. 2011;70(5 Suppl):S2–10.
9. Atkinson M, Worthley LI. Nutrition in the critically ill patient: part I. Essential physiology and pathophysiology. Crit Care Resusc. 2003;5:109–20.
10. Jaffer U, Wade RG, Gourlay T. Cytokines in the systemic inflammatory response syndrome: a review. HSR Proc Intensive Care Cardiovasc Anesth. 2010;2:161–75.
11. Bulger EM, Maier RV. Lipid mediators in the pathophysiology of critical illness. Crit Care Med. 2000;28(4 Suppl):N27–36.
12. Mancusi-Ungaro Jr HR, Van Way III CW, McCool C. Caloric and nitrogen balance as predictors of nutritional outcome in burn injured patients. J Burn Care Rehabil. 1992;13:695–702.
13. Masters B, Wood F. Nutrition support in burns – is there consistency in practice? J Burn Care Res. 2008;29:561–71.
14. Bartlett RH, Dechert RE, Mault JR, Ferguson SK, Kaiser AM, Erlandson EE. Measurement of metabolism in multiple organ failure. Surgery. 1982;92(4):771–9.
15. Singer PI, Pichard C, Heidegger CP, Wernerman J. Considering energy deficit in the intensive care unit. Curr Opin Clin Nutr Metab Care. 2010;13(2):170–6.
16. Collier B, Guillamondegui O, Cotton B, Donahue R, Conrad A, Groh K, et al. Feeding the open abdomen. JPEN J Parenter Enteral Nutr. 2007;31:410–5.
17. Desai SV, McClave SA, Rice TW. Nutrition in the ICU. An evidence-based approach. Chest. 2014;145:1148–57.
18. Heyland DK, Drover JW, MacDonald S, Novak F, Lam M. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: results of a randomized controlled trial. Crit Care Med. 2001;29:1495–501.
19. Metheny NA, Stewart NA, McClave SA. Relationship between feeding tube site and respiratory outcomes. JPEN J Parenter Enteral Nutr. 2011;35:346–55.
20. 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 suppl 6:S51–5.
21. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. Crit Care. 2003;7:R46–51.
22. Ho KM, Dobb GJ, Webb SA. A comparison of early gastric and post-pyloric feeding in critically ill patients: a meta-analysis. Intensive Care Med. 2006;32:639–49.
23. Borlase BC, Moore EE, Moore FA. The abdominal trauma index: a critical reassessment and validation. J Trauma. 1990;30:1340–4.
24. Moore FA, Moore EE. The benefits of enteric feeding. Adv Surg. 1996;30:141–54.
25. Biffl WL, Moore EE, Haenel JB. Nutrition support of the trauma patient. Nutrition. 2002;19:960–5.
26. Dissanaike S, Pham T, Shalhub S, Warner K, Hennessy L, Moore EE, et al. Effect of immediate enteral feeding on trauma patients with an open abdomen: protection from nosocomial infections. J Am Coll Surg. 2008;207:690–7.
27. Byrnes MC, Reicks P, Irwin E. Early enteral nutrition can be successfully implemented in trauma patients with an "open abdomen.". Am J Surg. 2010;199:359–63.
28. Hafiz S, Desale S, Sava J. The impact of solid organ injury management on the US health care system. J Trauma Acute Care Surg. 2014;77(2):310–4.
29. Lin BC, Fang JF, Chen RJ, Wong YC, Hsu YP. Surgical management and outcome of blunt major liver injuries: experience of damage control laparotomy with perihepatic packing in one trauma centre. Injury. 2014;45:122–7.
30. Prichayudh S, Sirinawin C, Sriussadaporn S, Pak-art R, Kritayakirana K, Samorn P, et al. Management of liver injuries: predictors for the need of operation and damage control surgery. Injury. 2014;45:1373–7.
31. Clemente N, Di Saverio S, Giorgini E, Biscardi A, Villani S, Senatore G, et al. Management and outcome of 308 cases of liver trauma in Bologna Trauma Center in 10 years. Ann Ital Chir. 2011;82(5):351–9.
32. Borzotta AP, Pennings J, Papasadero B, Paxton J, Mardesic S, Borzotta R, et al. Enteral versus parenteral nutrition after severe closed head injury. J Trauma. 1994;37:459–68.
33. Krakau K, Omne-Pontén M, Karlsson T, Borg J. Metabolism and nutrition in patients with moderate and severe traumatic brain injury. A systematic review. Brain Inj. 2006;20(4):345–67.
34. Krakau K, Hansson A, Karlsson T, de Boussard CN, Tengvar C, Borg J. Nutritional treatment of patients with severe traumatic brain injury during the first six months after injury. Nutrition. 2007;23(4):308–17.
35. Young B, Ott L, Twyman D, Norton J, Rapp R, Tibbs P, et al. The effect of nutritional support on outcome from severe head injury. J Neurosurg. 1987;67:668–76.

36. Bullock MR, Povlishock JT. Guidelines for the management of severe traumatic brain injury. XII. Nutrition. J Neurotrauma. 2007;24(suppl1):S77–82.
37. Curreri PW, Richmond D, Marvin J, Baxter CR. Dietary requirements of patients with major burns. J Am Diet Assc. 1974;65:415–7.
38. Saffle JR, Medina E, Raymond J, Westenskow D, Kravitz M, Warden GD. Use of indirect calorimetry in the nutritional management of burned patients. J Trauma. 1985;25:32–9.
39. Long C. Energy expenditure of major burns. J Trauma. 1979;19:904–6.
40. Herndon DN, Barrow RE, Stein M, Linares H, Rutan TC, Rutan R, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. J Burn Care Rehabil. 1989;10:309–13.
41. Saffle JR. Practice guidelines for burn care. American Burn Association. Chapter 12: initial nutritional support of burn patients. J Burn Care Rehabil. 2001;21(Suppl):S59–66. http://www.ameriburn.org/PracticeGuidelines 2001.pdf.
42. Mosier MJ, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL, et al. Early enteral nutrition in burns: compliance with guidelines and associated outcomes in a multicenter study. J Burn Care Res. 2011;32(1):104–9.
43. Rodriguez NA, Jeschke MG, Herndon DN. Nutrition in burns: Galveston contributions. JPEN J Parenter Enteral Nutr. 2011;35:704–14.
44. Hold B, Graves C, Faraklas I, Cochran A. Compliance with nutrition support guidelines in acutely burned patients. Burns. 2012;38:645–9.
45. 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. JPEN J Parenter Enteral Nutr. 2009;33:277.
46. Ho JW, Wu AH, Lee MW, Lau SY, Lam PS, Lau WS, et al. Malnutrition risk predicts surgical outcomes in patients undergoing gastrointestinal operations: results of a prospective study. Clin Nutr. 2014. doi:10.1016/j.clnu.2014.07.012. Epub ahead of print.
47. Serrone R, Van Way III C, Geehan D, Loveless B, Frankel E. Persistence of vitamin D deficiency in patients admitted to a midwestern urban hospital. American Society for Parenteral and Enteral Nutrition, Clinical Nutrition Week, February, 11, 2013, Phoenix, AZ. Poster presentation.
48. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
49. Flynn L, Zimmerman LH, McNorton K, Dolman M, Tyburski J, Baylor A, et al. Effects of vitamin D deficiency in critically ill surgical patients. Am J Surg. 2012;203:379–82.
50. Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamäki H, et al. An association of serum vitamin D concentrations less than 40 nmol/L with acute respiratory tract infection in young Finnish men. Am J Clin Nutr. 2007;86:714–7.
51. Quraishi SA, Bittner EA, Blum EA, Hutter MM, Camargo Jr CA. Association between preoperative 25-hydroxyvitamin D level and hospital-acquired infections following Roux-en-Y gastric bypass surgery. JAMA Surg. 2014;149(2):112–8.
52. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA. 2014;312:1520–30.
53. Nestle M, Nesheim MC. To supplement or not to supplement: the U.S. Preventive Services Task Force recommendations on calcium and vitamin D. Ann Intern Med. 2013;158(9):701–2.
54. ASPEN Board of Directors and the Clinical Guidelines Task Force. 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.
55. Bragaa M, Ljungqvist O, Soeters P, Fearond K, Weimanne A, Bozzettif F. ESPEN guidelines on parenteral nutrition: surgery. Clin Nutr. 2009;28:378–86.
56. Lee TG, Kang SB, Kim DW, Hong S, Heo SC, Park KJ. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial. Dis Colon Rectum. 2011;54(1):21–8.
57. Klappenbach RF, Yazyi FJ, Alonso Quintas F, Horna ME, Alvarez Rodríguez J, Oría A. Early oral feeding versus traditional postoperative care after abdominal emergency surgery: a randomized controlled trial. World J Surg. 2013;37(10):2293–9.
58. Shrikhande SV, Shetty GS, Singh K, Ingle S. Is early feeding after major gastrointestinal surgery a fashion or an advance? Evidence-based review of literature. J Cancer Res Ther. 2009;5(4):232–9.
59. Atkinson M, Worthley LI. Nutrition in the critically ill patient: part II. Parenteral nutrition. Crit Care Resusc. 2003;5:121–36.
60. Wheble GA, Benson RA, Khan OA. Is routine postoperative enteral feeding after oesophagectomy worthwhile? Interact Cardiovasc Thorac Surg. 2012;15(4):709–12.
61. Langer G, Grossman K, Fleischer S, Berg A, Grothues D, Wienke A, Behrens J, Fink A. Nutritional interventions for liver-transplanted patients. Cochrane Database Syst Rev 2012;15:8. http://www.cochranelibrary.com.
62. Zhu X, Wu Y, Qiu Y, Jiang C, Ding Y. Effects of omega-3 fish oil lipid emulsion combined with parenteral nutrition on patients undergoing liver transplantation. JPEN. 2013;37:69–74.

63. Hanson PJ, Parsons DS. Metabolism and transport of glutamine and glucose in vascularly perfused small intestine of rat. Biochem J. 1977;166:509–19.
64. Beaulieu JF, Calvert R. Permissive effect of glutamine on differentiation of fetal mouse small intestine in organ culture. Differentiation. 1985;329:50–5.
65. Bollhalder L, Pfeil AM, Tomonaga Y, Schwenkglenks M. A systemic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. Clin Nutr. 2013;32:213–23.
66. Chen QH, Yang Y, He HL, Xie JF, Cai SX, Liu AR, et al. The effect of glutamine therapy on outcomes in critically ill patients: a meta-analysis of randomized clinical trials. Crit Care. 2014;18:R8–21.
67. Morris Jr SM. Arginine: master and commander in innate immune responses. Sci Signal. 2010;3(135), e27. www.SCIENCESIGNALING.org.
68. Angele M, Smail N, Ayala A, Cioffi W, Bland K, Chaudry I. L-arginine: a unique amino acid for restoring the depressed macrophage functions after trauma-hemorrhage. J Trauma. 1999;46:34–41.
69. Angele MK, Nitsch SM, Hatz RA, Angele P, Hernandex-Richter T, Wichmann MW, et al. L-arginine: a unique amino acid for improving depressed wound immune function following hemorrhage. Eur Surg Res. 2002;34:53–60.
70. Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PE, Ochoa JB, Heyland DK. Perioperative use of arginine supplemented diets: a systematic review of the evidence. J Am Coll Surg. 2011;212:385–99.
71. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. JPEN J Parenter Enteral Nutr. 2010;34:378–86.
72. Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. JAMA. 2004;291:2865–8.
73. Capurso G, Zerboni G, Signoretti M, Valente R, Stigliano S, Piciucchi M, et al. Role of the gut barrier in acute pancreatitis. J Clin Gastroenterol. 2012;46:S46–51.
74. McClave SA, Greene LM, Snider HL, Makk LJ, Cheadle WG, Owens NA, et al. Comparison of the safety of early enteral nutrition versus parenteral nutrition in mild acute pancreatitis. JPEN J Parenter Enteral Nutr. 1997;21:14–20.
75. McClave SA, Chang WK, Dhaliwal R, Heyland DR. Nutrition support in acute pancreatitis: a systematic review of the literature. JPEN J Parenter Enteral Nutr. 2006;30:143–56.
76. O'Keefe SJ, Broderick T, Turner M, Stevens S, O'Keefe JS. Nutrition in the management of necrotizing pancreatitis. Clin Gastroenterol Hepatol. 2003;1:315–21.
77. Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med. 2014;371:1983–93.
78. Zou XP, Chen M, Wei W, Cao J, Chen L, Tian M. Effects of enteral immunonutrition on the maintenance of gut barrier function and immune function in pigs with severe acute pancreatitis. JPEN J Parenter Enteral Nutr. 2010;34:554–66.
79. Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB, Cuerda C, et al. the Home Artificial Nutrition and Chronic Intestinal Failure and the Acute Intestinal Failure Special Interesst Groups of ESPEN. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171–80.
80. Storch KJ. Overview of short bowel syndrome: clinical features, pathophysiology, impact, and management. JPEN J Parenter Enteral Nutr. 2014;38(suppl):5S–7.
81. Tappenden KA. Pathophysiology of short bowel syndrome: considerations of resected and residual anatomy. JPEN J Parenter Enteral Nutr. 2014;38(suppl):14S–22.
82. Jeppesen PB. Pharmacologic options for intestinal rehabilitation in patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2014;38:45S–52.
83. Rege AS, Sudan DL. Autologous gastrointestinal reconstruction: review of the optimal nontransplant surgical options for adults and children with short bowel syndrome. Nutr Clin Pract. 2013;28:65–74.
84. Ren J, Yuan Y, Zhao Y, Gu G, Wang G, Chen J, et al. Open abdomen treatment for septic patients with gastrointestinal fistula: from fistula control to definitive closure. Am Surg. 2014;80:339–47.
85. Johnson EK, Tushoski PL. Abdominal wall reconstruction in patients with digestive tract fistulas. Clin Colon Rectal Surg. 2010;23:195–208.

Chapter 9
Major Infections and Sepsis

Eoin Slattery and David S. Seres

Keywords Parenteral nutrition • Enteral nutrition • Sepsis • Trophic feeding • Early PN • Supplemental PN • Lipids • Multi-chamber bags • Immunonutrition

Key Points

- Enteral feeding may have a positive (protective) impact upon the gut by promoting both structural and functional integrity and by doing so may have an important role in the immune-competence of patients.
- Meta-analyses of elective gastrointestinal surgery and surgical critical care patients undergoing a major operation have shown that early postoperative EN had a protective effect for development of secondary infections.
- Trophic feeding may be at least equivalent to full feeding with respect to critically ill patients as a whole, but the role trophic feeding has in the septic and critically ill patient remains open to debate.
- EN is associated with fewer complications than parenteral nutrition (PN) and is more cost-effective than PN to deliver nutrition to critically ill patients.
- There is unequivocal evidence that patients receiving parenteral nutrition are at increased risk of catheter-related blood stream infections (especially fungal).
- Timing of commencement of PN has been suggested to be a significant (and modifiable) risk factor for the development of sepsis related to PN use, such that early PN may in fact be harmful.
- Supplemental PN is not to be recommended. Studies have failed to demonstrate a clinical benefit.
- Questions surrounding safety and infectious sequelae relating to intravenous lipids remain unanswered (in particular, the potentially positive benefits of omega-3 fatty acids).
- Multi-chamber bags have been shown to decrease in infections in patients.
- Immunonutrition is a term used to describe enteral feeds that have been supplemented with some combination of amino acids, omega-3 oils, and antioxidants in the belief that these components may have a beneficial impact upon immune function. Unfortunately, the evidence to date is conflicting; despite over 30 trials and at least three meta-analyses.

E. Slattery, MD, MRCPI
Department of Preventive Medicine and Nutrition, Columbia University Medical Center-New York Presbyterian Hospital, New York, NY USA

D.S. Seres, MD, ScM, PNS (✉)
Department of Medicine, Columbia University Medical Center,
650 W 168th Street, P&S 9-501, New York, NY 10032, USA
e-mail: dseres@columbia.edu

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_9,

- While many questions remain unanswered there is abundant evidence to suggest that starvation is to be avoided, and where possible enteral nutrition should be the first strategy that is implemented.

Introduction

Each modality of nutrition support (from none through enteral to parenteral nutrition) has its own attendant benefits and risks, particularly with respect to sepsis. In this chapter we review some basic gut immunology as it pertains to sepsis and risk of developing infection in the starved patient, and more importantly the sequence of events in patients receiving supplemental artificial nutrition. Enteral and parenteral nutrition is discussed separately regarding risk of infection, including optimal management strategies in septic patients. Lastly, immune-nutrition and other nutritional interventions purported to have beneficial impact on outcomes of septic patients are discussed and analyzed. Much of what is contained within this chapter has been discussed elsewhere in the book. For example gut immunological physiology is described in detail in Chap. 2. But the information is synthesized here as it pertains to both prevention of complications and impact of nourishment in the presence of severe infections.

Gut Immunology

The gut, as a consequence of its extensive interaction with the external environment, plays an important role in host defense, thus making the gut one of the largest components of the immune system [1]. Indeed it has been suggested that mucosal-associated lymphoid tissue (MALT), residing as non-aggregated immune cells near the basement membrane or as aggregated lymphoid tissue (i.e., Peyer's patches) comprises 50 % of total body immunity and 70 % of total antibody production [2].

The single layer of epithelial cells that makes up the functional surface area of the gut lumen (approximately 400 m^2 in area) has a dual role. It provides a semipermeable membrane for absorption of nutrients and simultaneously serves as an impermeable barrier to undesirable elements in the intestinal milieu. It achieves this not only by forming a physical barrier but also by maintaining continuous controlled inflammation through a combination of innate and adaptive immunity [3–5]. The gut is the only place in the body where activated lymphocytes are present all the time.

The innate immune system may be divided into immunologic and non-immunologic. Non-immunologic processes protecting the intestinal mucosa include physicochemical (e.g., digestive enzymes, gastric acid), antimicrobial (e.g., secretory immunoglobulin A, lactoferrin, defensins) and mechanical (peristalsis, mastication, "tight junctions" between cells). Immunologic processes are based on cells, and are the first to contact invading microorganisms [6]. These immunologic components are a non-selective (but effective) method of defense. They include the complement system, phagocytes and recruitment of natural killer cells. This arm of the immune response recognizes bacteria mainly via pathogen associated molecular patterns (PAMPs)[7]. Such recognition allows immune cells to respond to a wide array of microorganisms using a limited number of receptors. A major family of PAMP receptors is toll-like receptors (TLRs), which bind to different bacterial products and mediate pro-inflammatory signals to the cells [7, 8].

Adaptive immunity is mediated through humoral immunity (B cells) and cellular immunity (T cells). Humoral immunity leads to appropriate production of antibodies, while cellular immunity protects against harmful intracellular events that are not amenable to the effects of antibodies. Following activation of the innate immune system, antigen presenting cells (APCs), which belong to the innate immune system, activate T cells that are part of the adaptive immune system [9]. T-cells may then differentiate into three types of so-called effector cells (Th1, Th2, and Th3) depending on

the antigen presented. Each subtype produces its own cytokine milieu, and may be involved in positive or negative feedback. Th1 cells release IFN-γ, TNF-α and IL-2, up-regulating the inflammatory response. Th2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13, which act to down-regulate the immune response [10, 11]. Th2 cells also activate B cells to differentiate into plasma cells. These are responsible for most of the total immunoglobulin production, in particular secretory IgA (sIgA). sIgA serves to prevent bacterial attachment to the mucosa and to inhibit immune system activation. The adaptive immune system can respond to specific antigens and is capable of immune memory.

Another important aspect of controlled intestinal inflammation in MALT/GALT is the migration of immune cells into the inflamed mucosa. Peyer's patches do not have lymphatic vessels, so alternative methods of recruitment are required. This process involves a sequence of rolling, activation, arrest and transmigration of the inflammatory cells. In the final steps of this process the cells are tightly linked to the tissue, mediated by cell-surface-expressed integrins (particularly L-selectin and α4β7-integrin) and tissue expressed adhesion molecules (particularly ICAM-1 and MAdCAM-1) [12–14]. Following antigenic exposure, activated lymphocytes (i.e., B and T cells) migrate to regional mesenteric lymph nodes. Once in the lymph nodes the cells undergo a process of maturation and proliferation. They then migrate out through the thoracic duct into the systemic circulation, and return to their tissue of origin.

Starvation may have a negative impact upon the gut by disturbing both structural and functional integrity. It is known for instance that starvation may induce villous atrophy. A decrease in mucosal mass of up to 15 % in humans has been observed. This decreases absorptive capacity and more importantly digestive (protective) brush border enzymes and antimicrobial secretions (pancreatic enzymes, proteases, etc.). Further, there is loss of tight junctions between enterocytes. There is diminished blood flow [15, 16], which leads to a reduction in the production and release of a variety of agents including cholecystokinin, gastrin, bombesin, and bile salts. All of these may have a trophic effect on the intestinal epithelium [17]. These changes further affect gut permeability and so predispose to significant bacterial translocation. Some studies have documented presence of microbial DNA from presumed trans-located bacteria, or components of bacteria, in septic patients who have negative blood cultures [18].

Not only can these changes impair the ability to respond to new infectious challenges, they may also lead to loss of established antiviral and antibacterial defenses and impair the ability to respond to new infectious challenges. For instance, in mice exclusively fed parenterally, as little as 5 days of gut disuse resulted in the loss of protection to a respiratory virus and a reduced clearance of that virus [19]. However, once the mice were refed enterally immunologic memory returned.

Similarly, absence of enteral nutrition (albeit while being parenterally fed) has been shown to decrease MAdCAM-1 expression in Peyer's patches in animal models within hours [20]. This leads to a 50–60 % reduction in cell counts, with subsequent alteration to CD4/CD8 counts (from a normal of 2:1–1:1) with associated reductions in IL-4 and IL-10 [21–23]. The consequences of these observed changes are activation of the adaptive immune system by inhibition of counter-regulation (i.e., a shift from Th2 to Th1 phenotype). Thus allowing primed or activated neutrophils to pass out of the gut and into the systemic circulation thereby (potentially) leading to a heightened and prolonged systemic inflammatory response and all of its negative consequences.

Enteral feeding may have a positive (protective) impact upon the gut by promoting both structural and functional integrity and by doing so may have an important role in the immune-competence of patients. This is discussed in more detail later.

Enteral Nutrition

Early enteral nutrition is recognized as an important adjunct in the management of the critically ill patient. Both the European Society of Parenteral and Enteral Nutrition (ESPEN) and the American Society of Parenteral Nutrition (A.S.P.E.N.) promote early enteral support (i.e., within 24–48 h) in these patients [24, 25]. Along with the putative nutritional benefits, early EN has been thought to support the immune and metabolic responses to stress and play a key role in maintaining gut integrity.

Experimental Animal Evidence

Kudsk and colleagues reported the first clinical and laboratory evidence to support the notion that enteral nutrition affects the metabolic response to sepsis and improves host defenses in an animal model [26]. Several authors subsequently demonstrated that disuse of the gut in animals that were supported by parenteral nutrition resulted in decreases in GALT lymphocyte cell number. Once enteral feed was reinstituted these changes reversed within days [21, 27, 28]. Similarly IgA levels were seen to drop with an associated decrease in B and T cells in the lamina propria in animals fed exclusively by the parenteral route [21, 27, 28]. Associated with atrophy of GALT lymphoid tissues, a quantitative decrease in adhesion molecules (especially MAdCAM-1) has been observed in animals not fed enterally [29]. Parenterally fed animals demonstrated decreases in IL-4 and IL-10 levels in the small intestine [22, 23]. In order to establish the functional impact of these changes on immunity, the same authors studied the effects of parenteral nutrition on established immunity [19, 30]. Kudsk and King were able to establish a loss in established respiratory mucosal immunity for *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and influenza.

These animal studies show that lack of enteral feeding has a profoundly negative effect on the overall immunological status. Whilst difficult to prove this hypothesis in humans, the circumstantial evidence in animals is highly suggestive. Inability or other failure to use the gut for nutrition appears to cause cytokine imbalances, in turn activating the innate immune system, and contributing thereafter to an overzealous stress response. At least in theory, this may ultimately lead to systemic inflammation and SIRS [31]. Early enteral feeding may attenuate this over-response and so lead to improved immune tolerance [32]. The recommendations of the professional societies, supporting the use of early enteral nutrition, lean heavily upon this supportive animal data.

Postoperative Infections

The positive results seen in animal studies have been reflected in the findings of a large meta-analysis of elective gastrointestinal surgery, and surgical critical care patients undergoing a major operation who were given early postoperative EN [33]. Patients receiving early EN demonstrated a significant reduction in infections (RR 0.72 CI 0.54–0.98) when compared to a "nil by mouth" approach. Decreases in hospital lengths of stay and anastomotic dehiscence were also seen. This beneficial effect is even more pronounced when EN is compared to PN. In all, six different meta-analyses have consistently shown the beneficial effect of EN over PN with respect to infectious sequelae [34–39].

Active Sepsis

These studies appear to confirm the benefit of EN in preventing sepsis as a complication (perhaps) of feeding route; but what of patients that are already septic and in septic shock?

A recent study from a German group has attempted to address this question [40]. They performed a secondary analysis of a prospective cohort of severely ill and septic ICU patients where the primary endpoint was response to intensive insulin therapy with the use of pentastarch resuscitation. In their secondary analysis, they found that mortality rates were substantially lower in patients fed using the EN as opposed to the use of EN and PN. (26.7 % vs. 41.3 %, $p=0.048$), with a protective effect observed in the EN group alone for development of secondary infections (HR1.89 95 % CI 1.27–2.81). This data should be interpreted with caution. Patients given PN may have been more severely

ill, given that the study was not randomized to PN vs EN. But even with this caveat, the study lends further support to the beneficial impact of EN in septic patients, and in improving overall outcomes from infectious complications.

Underfeeding

Recently underfeeding in the first week of critical illness has received much attention following the publication of three prospective trials designed to address this issue [41–43]. Based on these trials, the Surviving Sepsis Campaign guidelines suggested avoiding mandatory full caloric feeding in the first week of illness [44]. This recommendation was surprising, because none of the trials showed any difference in infectious outcomes, ventilator days or mortality. Arabi et al. did note a non-significant trend towards decreased mortality [41]. All three groups reported that patients fed less had less GI intolerance.

There were concerns expressed about the demographics of recruited patients in these studies. All patients were reasonably young, largely male, and incorporated both septic and non-septic patients. Elke and Heyland published a secondary analysis of their nutrition database to assess outcomes in a critically ill septic cohort [45]. Using a statistical model, they were able to demonstrate a beneficial effect of improved nutrition on mortality in long stay ICU patients. They hypothesize that individual patient characteristics may play an important role in how patients respond to various feeding strategies (e.g., older age, low or high BMI may fare worse). But there exists no data to support this theory. Moreover, in an observational analysis such as this, one can also conclude that sicker patients are harder to feed, and therefore improved nutrition is only a marker for wellness.

There remains the possibility that trophic feeding is at least equivalent to full feeding with respect to all critically ill patients, but the role of trophic feeding in the septic and critically ill patient remains open to debate.

EN Formulations

The formulation of EN has been suggested to play a role in the modulation of sepsis. Much work has been carried out on micronutrients and is discussed in detail later. The macronutrient composition of EN and in particular the lipid component of EN has been of interest to many.

Lipid-rich nutrition has been shown in animal models to attenuate inflammation and reduce organ damage [46–49]. In these studies, deHaan and colleagues were able to demonstrate amelioration in the initial hyper-inflammatory response by administration of a lipid-rich enteral formula. They used a custom made lipid-rich formula in which 50 % of administered calories were derived from fat. The lipids themselves were sourced from lecithin, with less than 5 % of fat derived from omega-3 or omega-6 fatty acids. By administering this formula, they were able to demonstrate stimulation of the autonomic nervous system via activation of cholecystokinin 1, leading to parasympathetic suppression of cytokine release. They showed a decrease in the early inflammatory response mediated by decreases in IL-6 and IL-10, leading to a subsequent increase in IL-12 and IFN-γ. Restoration of this IL-12/IL-10 balance has been shown elsewhere to improve defense against opportunistic pathogens [50].

This work has been expanded to preclinical studies, with similarly encouraging results [51]. Lubbers et al. from the same Dutch group demonstrated the potential benefit of a lipid-rich, protein-rich enteral formula in a human model of endotoxemia. Healthy human volunteers were administered *E. coli* lipopolysaccharide intravenously. Feeding with a lipid rich formula (analogous to that used in

the previously mentioned rodent studies) was shown to lead to a reduction in circulating levels of the pro-inflammatory cytokines, IL-6, TNF-α and IL-1 receptor antagonist.

Despite this intriguing research, evidence for a clinical role for enteral immunonutrition, especially lipid formulations, remains underwhelming and indeed divisive. Nevertheless, keen interest continues about the putative benefits of fish oils as a source of fat in enteral diets. Meta-analyses initially failed to observe any significant effect with the use of immunonutrients (including fish oils) despite recognizing a signal towards decreased infectious complications [52]. However, subsequent reviews (often from the same authors) initially suggested significant benefit and recommended the routine use of immune-nutrients (without differentiating between which ones) in critical care populations, only to rescind those recommendations with the exception of a benefit with fish oils in later reviews [53, 54].

Legitimate concerns have been raised about the heterogeneity of the studies reported and similarly the heterogeneity of interventions included. Put simply, a "well" postoperative patient receiving glutamine is not the same as a profoundly septic patient receiving omega-3 enriched enteral feeding formula.

Omega-3 fatty acids are predominantly derived from fish oils, but may also be obtained from some plant oils (walnut, chia, flaxseed etc.). Interest in their use in enteral nutrition has stemmed from the suggestive observation that omega-3 has anti-inflammatory effects. This effect was first observed in animal models and has led to several large clinical trials [55–57]. In these trials, omega-3 enriched diets appeared to be beneficial, leading to decreased time on ventilators, decreased length of stay and better outcomes in septic patients. However, concerns were subsequently raised about the validity of these findings. The concerns related to the use of enteral feeding formulas in the control groups that were high in omega-6, relative to the group that was given omega-3 enriched formulas. Omega-3 fats are felt to be pro-inflammatory and alterations in the omega-3/omega-6 ratio are potentially deleterious. As mentioned above, other elements of immune-nutrition have also been suggested to be beneficial. These are addressed separately.

At the present time, there remains insufficient evidence to promote one form of enteral nutrition (i.e., formula, amount, etc.) over another with respect to prevention of infectious complications.

Parenteral Nutrition

As described earlier, EN is associated with fewer complications than parenteral nutrition PN, and is more cost-effective to deliver nutrition to critically ill patients [58]. Consensus guidelines from A.S.P.E.N. have recommended that for adequately nourished patients who have contraindications to enteral nutrition, PN should be initiated only after 7 days of intensive care unit care [24]. On the other hand, for patients with clinical signs of protein–calorie malnutrition on admission to the ICU, A.S.P.E.N. guidelines recommend that it is appropriate to start PN as early as possible, once adequate fluid resuscitation has been completed. In contrast, ESPEN (European Society of Parenteral and Enteral Nutrition) have advocated commencing PN in patients within 2 days of ICU admission to meet 100 % of estimated calorie and protein needs not met by EN [25]. The disparity between the professional societies can largely be explained by differences of opinion both on the risk of PN and the benefits of full caloric and protein feeding.

Central Line Associated Infections

There is unequivocal evidence that patients receiving parenteral nutrition are at increased risk of catheter-related blood stream infections [59]. This risk is higher than patients who have central venous catheters but do not receive parenteral nutrition [60]. An observational study demonstrated that PN

administration can increase the risk of not only blood stream infection but also pneumonia, surgical site infection, and urinary tract infection [61]. Minimization or reduction of these complications can best be achieved by utilizing strategies to reduce the overall use of PN wherever possible. When PN is required, best practices to minimize catheter related blood stream infection should be strictly observed. Aseptic technique should be used for central catheter placement, and proper hand hygiene and maximal barrier precautions should also be used during the procedure. Introduction of care bundles has been shown to be effective in implementing these changes [62]. The site of central venous catheters has been shown to be an independent risk factor for development of blood stream infection (BSI). A large retrospective analysis of PN related BSI in a single Irish university hospital suggested that use of femoral lines increased the risk of BSI over the use of subclavian or internal jugular lines [63]. In general, single lumen catheters are preferred to multi lumen catheters, and the subclavian approach is a preferred location for central catheter placement. After central catheter placement, the single lumen of the catheter should be dedicated, and used solely, for parenteral nutrition [64].

Timing of PN

Timing of commencement of PN has been suggested to be a significant (and modifiable) risk factor for the development of sepsis related to PN use. A large randomized trial from Australia and New Zealand has attempted in part to address this issue [65]. They found no benefit to very early PN (<24 h) in patients with short term relative contraindications to EN, as compared to "standard of care", who received no nutrition. Of the patients in the "standard of care" group, only 51 % ever required PN. Interestingly, 40 % of the "standard of care" patients received no supplemental nutrition at all, either PN or EN, during their ICU stay (median 3.72 days). No adverse outcomes were observed. A post hoc analysis of a subgroup of patients from the EPaNIC study (discussed in more detail below) also examined the role of early vs. late initiation of PN in patients who had a contraindication to EN (i.e., where calories were derived from PN only, with no enteral component). This analysis found a statistically significant reduction in infection and a trend towards early discharge in the late initiation arm [66]. These results, while less reliable by their nature, seem to clarify that at least in the first 48 h of critical illness, there is no benefit to early provision of PN as far as infection is concerned. Indeed, the EPaNIC trial suggested that early PN may even be harmful.

Supplemental PN

Supplemental use of parenteral nutrition (in addition to EN) has been suggested as a solution to the perceived problem of delivery of inadequate calories, while simultaneously maintaining the benefit of EN with respect to impact on sepsis and other outcomes. A recent large multicenter prospective trial from Belgium (EPaNIC) investigated this approach [67]. In this study, early PN was used to reach 100 % of calories (within 48 hours) in patients unable to receive all their required calories enterally (for whatever reason). The control group did not receive PN until later in their ICU stay (i.e., 7 days). There was no associated effect on mortality. On the other hand, there was an observed increase in incidence of infection, prolonged mechanical ventilation and prolonged intensive care unit stay in the early PN cohort compared to the delayed PN cohort. But in the control group, a majority of patients never received PN at all. The data clearly supported the conclusion that if the patient doesn't need to receive PN, it is better not to give it early. A Canadian-led observational study using a similar approach documented an improvement in calorie provision but also failed to show any clinical benefit with the adoption of this strategy [67]. In the face of this data it would appear that supplemental PN is not to be recommended.

While it appears relatively clear that avoiding early PN in critically ill patients can reduce occurrence of infection, there are other questions that must be addressed. For instance, are there formulations and/or compounding methods of PN that may minimize infectious complications? Does type of central access device matter? These questions are further addressed in Chap. 7.

Role of Lipids

As with EN, the role of lipids in PN (with respect to sepsis) has been keenly debated. Joint guidelines from A.S.P.E.N. and Society for Critical Care Medicine (SCCM) recommended in their 2009 guidelines that soybean oil-based lipids should be omitted from PN in the first week of hospitalization in the ICU [24]. This recommendation was based on the results of a small study that suggested better outcomes in patients that did not receive lipids [68].

Early in vitro scientific studies demonstrated the ability of intravenous lipids to be used as a growth media for such organisms as *Staphylococcus aureus* and *Candida albicans* [69]. In contrast, PN formulations without added intravenous fat emulsion (IVFE) are quite hypertonic, and do not allow growth of microbial colonies (*Staphylococcus*, *Pseudomonas*, *E. coli*, and *Candida*) [70].

Several clinical studies have confirmed the association of intravenous lipids (in addition to dextrose/amino acids PN) with the occurrence of staphylococcal blood stream infections in pediatric cohorts. In the larger of the two, a case-control study demonstrated a 5.8-fold increase in staphylococcal bacteremia in pediatric neo-natal intensive care units (NICU) associated with lipid infusions [71]. This association was confirmed in a similar NICU-based study of very low birth weight infants [72]. This case-control study documented a ninefold increase in staphylococcal bloodstream infections in the cohort associated with the use of IVFE infusions.

In an analysis of a large database of patients (the Premier Perspective database, containing inpatient data from 45 million discharges from acute care facilities in the US) there was no increase in the risk of infectious morbidity when lipids were omitted from PN admixtures when adjusted for complexity and severity of illness [73]. The questions surrounding safety and infectious sequelae relating to intravenous lipids remain unanswered.

As with EN, alternative sources of lipid for PN has become of interest. In particular, the potentially positive benefits of omega-3 (and to a lesser extent omega-9) fatty acids relating to their anti-inflammatory properties has led to much work being done to assess their potential impact. It has also been suggested that omega-3 enriched PN may also slow or prevent progression of PN-related cholestasis and liver disease. Preclinical and small clinical studies have suggested the potential benefit of omega-3 fatty acids in reducing inflammatory burden in postsurgical patients [67, 74–76]. The results of these studies were summarized by Pradelli in a recently published meta-analysis of 23 studies [77]. While this analysis did not show any difference in mortality, they were able to demonstrate a reduction in infection rate (RR = 0.61, CI 0.59–1.33), with associated decreases in ICU and overall hospital length of stay. Omega-3 based lipids have been available in Europe for many years but as of yet remain unavailable in the US. This is likely to change pending the reporting of several trials to address the safety (and efficacy) of omega-3 lipids (Omegaven®, Fresenius Kabi, Hamburg, Germany) [78].

PN Compounding

PN compounding has been explored as a possible modifiable risk factor in decreasing the rate of blood-stream infections. Broadly speaking, PN may be compounded commercially, using multi-chamber bags, or locally, in a dedicated or hospital pharmacy. Turpin et al. were able to demonstrate

a decreased rate of blood stream infections with the use of multi-chamber bags compared to pharmacy compounded PN in a large retrospective database analysis [79]. This finding was further validated by the EPICOS study, a large, multicenter, prospective, open label trial [80]. In this study, a decrease in infections in patients was seen when the multi-chamber bags were used. The difference was small. It is likely that pharmacies that compound large amounts of PN solutions and adhere to appropriate safety measures will be able to minimize PN-related infections, similarly to manufactured multi-chambered PNs. Multi-chambered PNs are more likely to have benefit in settings where few PNs are prescribed. Moreover, the ease of prescribing a pre-manufactured bag may drive inappropriate use of PN upward. Further work is warranted with multi-chamber bags to assess their impact.

Infection Risk in the Community Setting

As discussed above, in the acute setting the type of line may have an important effect on BSI and overall risk of infection. What of patients in the home setting?

Buchman and colleagues have previously published their data on a large historical cohort of more than 500 patients infusing PN in the community [81]. They reported an overall infection rate of 0.37 per patient per year. Their study included patients over an 18-year period between 1973 and 1991. More recent data has suggested wide variations in incidence in BSI in home PN patients, ranging from 0.35 to 11 BSI per 1000 catheter-days [82–84]. Zhao and colleagues (who also reported a rate of BSI of 11/1000 catheter days) have suggested that the first 4 months of BSI are (not unsurprisingly) the time when most of these infections occur.

More recently Buchman et al. have reported on independent risk factors for developing BSI [85]. They identified use of subcutaneous ports (over tunneled catheters), multi-lumen catheters, increased frequency of lipid infusion, obtaining blood from the CVC and infusion of non-PN medications via the CVC as independent risk factors for BSI. Interestingly, increased PN frequency was associated with BSI in children but not with adults. All of this suggests that minimizing manipulation of the PN line is important in minimizing the risk of sepsis.

Central Access Devices

Historically, it was felt that tunneled catheters were the safest method to provide long-term PN [86]. This is particularly the case when compared to subcutaneous ports (as demonstrated by Buchman et al.) [85]. However, with the increasing use of peripherally inserted central catheters (PICC), this question needs to be readdressed. A recent uncontrolled and non-randomized but prospective French study compared occurrence of infections in home PN patients receiving their PN via Broviac catheter or PICC. The authors reported a significantly lower occurrence of infections in the PICC group when compared to the Broviac group (1.87 vs. 1.05 per 1000 catheter days, $p = 0.01$) [87]. Despite this, ESPEN still recommends that PICC be used for no longer than 3 months in the home setting for PN administration, acknowledging that the evidence base for this recommendation is weak [88]. A controlled and randomized study is required to address the issue of appropriate CVC in the home setting.

A multitude of other interventions have been suggested to reduce the risk of BSI [89–93]. They include (but are not limited to): different types of catheters impregnated with antibiotics, chlorhexidine, and a variety of catheter locks (heparin, vancomycin, citrate, ethanol and so on). Although questions remain over their efficacy, ethanol locks in particular show promise and are worthy of further investigation in an attempt to minimize BSI.

Immunonutrition

Immunonutrition is a term used to describe enteral feeds that have been supplemented with some combination of amino acids, omega-3 oils, and antioxidants in the belief that these components may have a beneficial impact upon immune function. Unfortunately, the evidence to date is conflicting; despite over 30 trials and at least three meta-analyses.

Omega-3 has been discussed in detail above with respect to both enteral and parenteral feeds. Here we concentrate on amino acids and antioxidants, both given enterally and parenterally.

Glutamine

Glutamine is the most abundant nonessential free amino acid in the human body. It plays an important role in nitrogen transport and provides the fuel for rapidly dividing cells (immune cells, enterocytes, hepatocytes, and others.). Low glutamine levels have been demonstrated in patients with critical illness [94, 95]. This observation led to the suggestion that replenishment of this amino acid may be beneficial in critical illness, and may ultimately lead to improved outcomes. A meta-analysis of six randomized trials published in 2002 which examined the role of glutamine in critical illness suggested a trend towards better outcomes [96]. While initially encouraging, some concerns were raised about the quality of this data.

Recently two large trials have refuted the suggestion that glutamine supplementation may be beneficial. The first study randomized patients in multiple Scottish centers to receive 20 g of Glutamine per day, with and without selenium [97]. They found no benefit with respect to mortality or infections. The second study, a large multicenter blinded prospective randomized controlled study recruited in excess of 1200 patients [98]. Patients were randomized in a 2×2 factorial design to receive glutamine (0.35 g/kg/day), a mixture of antioxidants (including selenium, zinc, beta-carotene, vitamin E and vitamin C), both glutamine and antioxidants, or placebo. Surprisingly, a statistically significant increase in mortality was seen at 6 months in the patients randomized to receive glutamine (with and without antioxidant supplementation).

Both A.S.P.E.N. and ESPEN recommend consideration of supplementary glutamine in their latest consensus guidelines, published prior to this study. However in the light of these new data, these recommendations are perhaps questionable. Research is ongoing.

Arginine

Arginine is a conditionally essential amino acid that has been demonstrated to have potential beneficial effects in improving nitrogen balance, and T-cell immune function [99]. As a consequence most of the commercially available immunonutrition feeds contain Arginine, although at widely ranging doses. One of the many meta-analyses performed suggested a dose-dependent benefit of supplemental arginine (i.e., >12 g/1000 kcal) [52]. Higher dose arginine led to a reduction in infections with no significant impact upon mortality. However, the widely different formulas and patient cohorts used to achieve this cumulative response means that this data should be interpreted with caution.

Selenium

Selenium is an endogenous antioxidant and an essential component of glutathione peroxidases, which can reduce free hydrogen peroxide and protect the organism from oxidative damage. Utilization of selenium is thought to increase in critically ill patients because critical illness is associated with generation

of oxygen free radicals and decreased selenium plasma concentrations. This has led some to postulate an increased requirement for selenium in critical illness. Patients from Europe and parts of Australasia are known to be prone to low pre-morbid levels of selenium due to low soil content. It has been suggested that this deficiency may predispose these patients to increased risk of oxidative damage and thus worsen clinical outcomes. This notion has (in part) been supported by animal models of sepsis and brain injury that worsen in the selenium deficient state [100]. Several investigators have tested the hypothesis that outcomes in sepsis could be improved with selenium supplementation with variable results.

Earlier smaller studies demonstrated that selenium supplementation may improve clinical outcomes by reducing illness severity, infectious complications, and decreasing mortality in critically ill patients [101–103]. However, a larger subsequent trial using high dose selenium (4000 μg on the first day, 1000 μg per day for the 9 following days) failed to show any improvement in clinical outcome [104]. Two more recent studies using lower doses of Selenium (500 μg/day) have shown some conflicting results. A Scottish multicenter prospective randomized control trial in which critically ill patients received selenium suggested a decrease in "new" infections if selenium was given for more than 5 days [97]. In contrast, an international multicenter trial found no benefit to administration of selenium [98]. Both trials were well designed, large multicenter trials using a 2×2 factorial design. However, the international trial recruited twice as many patients.

Unsurprisingly, questions remain about the appropriateness of provision of selenium supplementation. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommended initiating selenium supplements (350–1000 mcg/day) with an initial bolus followed by continuous infusion in critically ill conditions in their 2009 guidelines [105]. A.S.P.E.N., on the other hand, included no such recommendation in their subsequent guideline for nutrition support of the critically ill. Expert consensus remains divided [106, 107]. It has been suggested that supplementation of selenium in the deficient state is beneficial, but potentially harmful for patients with normal/adequate status [107]. In any event, further work is required to clarify the role of selenium supplementation.

Vitamin D

Vitamin D, and it's associated endocrine system (calcium, PTH), is known to have effects on innate and adaptive immunity as well as lung, muscle, endothelial and mucosal functions. Deficiency of vitamin D is recognized as one of the most common mild medical conditions worldwide. Recent reports have demonstrated that vitamin D levels are decreased in patients in the ICU [108]. It is unclear however if low vitamin D levels reflect a surrogate for disease activity or true functional depletion. Given the relative ease and low cost of repletion of vitamin D, supplementation has become of interest in the critical care setting. It appears that large doses (100,000 I.U.) are necessary to quickly return 1,25 vitamin D levels to normal. Data suggests that such dosing is safe, but little data exists at present as to the utility of such an approach. Additionally, decrements in critically ill patients may be due entirely to systemic inflammation-related decreases in vitamin D carrier proteins.

Antioxidants (Including Vitamin E and C)

Vitamins E and C serve as important endogenous antioxidants. Therefore, like other antioxidants, it has been proposed that daily requirement of vitamins E and C are increased in critically ill conditions due to increased rates of biological oxidation in critical illness. A prior randomized trial revealed that early administration of vitamins C and E reduces the incidence of organ failure and shortens ICU length of stay in the surgical intensive care unit (1000 U α-tocopherol given enterally every 8 h and

1,000 mg ascorbic acid given parenterally daily) [109]. More recent randomized studies, however, have questioned this finding [97, 98]. As with other micronutrients the role and effectiveness of routine supplementation remains unclear.

Conclusion

Artificial nutrition support plays a very real and pervasive role in the management of septic patients. Decisions on how best to feed patients when septic or at risk of developing sepsis are complex and not without significant risk. While many questions remain unanswered there is abundant evidence to suggest that starvation is to be avoided and where possible enteral nutrition should be the first strategy that is implemented.

When this is not possible PN remains a viable (and important) option, although recent evidence would support an adoption of an under-zealous approach to commencement, specifically avoiding the use of PN in the early stages of critical illness. While there have been a plethora of suggested strategies with respect to supplements, antioxidants, etc. we appear to be no closer to realizing a strategy that may have any beneficial impact on patient outcomes and in particular with respect to sepsis.

There remains much work to be done.

References

1. Phillips-Qualigiata JM, Lamm ME. Migration of lymphocytes in mucosal immune system. In: Husband AJ, editor. Migration and Homing of Lymphoid Cells, vol. II. Boca Raton, FL: CRC; 1988. p. 53–75.
2. McGhee JR, Mestecky J, Dertzbaugh MT, Eldridge JH, Hirasawa M, Kiyono H. The mucosal immune system: from fundamental concepts to vaccine development. Vaccine. 1992;10(2):75–88.
3. Schmitz H, Barmeyer C, Fromm M, Runkel N, Foss HD, Bentzel CJ, et al. Altered tight junction structure contributes to the impaired epithelial barrier function in ulcerative colitis. Gastroenterology. 1999;116(2):301–9.
4. Gitter AH, Wullstein F, Fromm M, Schulzke JD. Epithelial barrier defects in ulcerative colitis: characterization and quantification by electrophysiological imaging. Gastroenterology. 2001;121(6):1320–8.
5. Bürgel N, Bojarski C, Mankertz J, Zeitz M, Fromm M, Schulzke JD. Mechanisms of diarrhea in collagenous colitis. Gastroenterology. 2002;123(2):433–43.
6. Janeway Jr CA, Medzhitov R. Innate immune recognition. Annu Rev Immunol. 2002;20:197–216.
7. Medzhitov R, Janeway Jr C. Innate immunity. N Engl J Med. 2000;343(5):338–44.
8. Trinchieri G, Sher A. Cooperation of Toll-like receptor signals in innate immune defence. Nat Rev Immunol. 2007;7(3):179–90.
9. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(7):390–407.
10. Renegar KB, Johnson C, DeWitt RC, King BK, Li J, Fukatsu K, et al. Impairment of mucosal immunity by total parenteral nutrition (TPN): requirement for IgA in murine nasotracheal anti-influenza immunity. J Immunol. 2001;166:819–25.
11. Johnson CD, Kudsk KA, Fukatsu K, Renegar KB, Zarzaur BL. Route of nutrition influences generation of antibody-forming cells and initial defense to an active viral infection in the upper respiratory tract. Ann Surg. 2003;237:565–73.
12. Bernstein CN, Sargent M, Rawsthorne P, Rector E. Peripheral blood lymphocyte beta 2 integrin and ICAM expression in inflammatory bowel disease. Dig Dis Sci. 1997;42(11):2338–49.
13. Bernstein CN, Sargent M, Rector E. Alteration in expression of beta 2 integrins on lamina propria lymphocytes in ulcerative colitis and Crohn's disease. Clin Immunol. 2002;104(1):67–72.
14. Vainer B, Nielsen OH. Changed colonic profile of P-selectin, platelet-endothelial cell adhesion molecule-1 (PECAM-1), intercellular adhesion molecule-1 (ICAM-1), ICAM-2, and ICAM-3 in inflammatory bowel disease. Clin Exp Immunol. 2000;121(2):242–7.
15. Chandra RK. Mucosal immune responses in malnutrition. Ann N Y Acad Sci. 1983;409:345–52.
16. Reddy V, Raghuramulu N, Bhaskaram C. Secretory IgA in protein-calorie malnutrition. Arch Dis Child. 1976;51:871–4.

17. Okamoto K, Fukatsu K, Ueno C, Shinto E, Hashiguchi Y, Nagayoshi H, et al. T lymphocyte numbers in human gut associated lymphoid tissue are reduced without enteral nutrition. JPEN J Parenter Enteral Nutr. 2005;29:56–8.
18. Chang SS, Hsieh WH, Liu TS, Lee SH, Wang CH, Chou HC, et al. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis – a systemic review and meta-analysis. PLoS One. 2013;8(5):e62323.
19. Kudsk KA, Li J, Renegar KB. Loss of upper respiratory tract immunity with parenteral feeding. Ann Surg. 1996;223:629–38.
20. Fukatsu K, Zarzaur BL, Johnson CD, Lundberg AH, Hanna MK, Wilcox HG, et al. Lack of enteral feeding increases expression of E-selectin after LPS challenge. J Surg Res. 2001;97(1):41–8.
21. Li J, Kudsk KA, Gocinski B, Dent D, Glezer J, Langkamp-Henken B. Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. J Trauma. 1995;39:44–52.
22. Wu Y, Kudsk KA, DeWitt RC, Tolley EA, Li J. Route and type of nutrition influence IgA-mediated intestinal cytokines. Ann Surg. 1999;229:662–8.
23. Fukatsu K, Kudsk KA, Wu Y, Zarzaur BL, Hanna MK, DeWitt RC. TPN decreases IL-4 and IL-10 mRNA expression in lamina propria cells but glutamine supplementation preserves the expression. Shock. 2001;15:318–22.
24. 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.
25. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25:210–23.
26. Kudsk KA, Carpenter G, Petersen S, Sheldon GF. Effect of enteral and parenteral feeding in malnourished rats with E. coli-hemoglobin adjuvant peritonitis. J Surg Res. 1981;31(2):105–10.
27. Tanaka S, Miura S, Tashiro H, Serizawa H, Hamada Y, Yoshioka M, et al. Morphological alteration of gut-associated lymphoid tissue after long-term total parenteral nutrition in rats. Cell Tissue Res. 1991;266:29–36.
28. King BK, Li J, Kudsk KA. A temporal study of TPN-induced changes in gut-associated lymphoid tissue and mucosal immunity. Arch Surg. 1997;132:1303–9.
29. Fukatsu K, Zarzaur B, Johnson C, et al. MAdCAM-1 expression in Peyer's patches: a mechanism controlling the gut-associated lymphoid tissue (GALT). Surg Forum. 2000;51:211–4.
30. King BK, Kudsk KA, Li J, Wu Y, Renegar KB. Route and type of nutrition influence mucosal immunity to bacterial pneumonia. Ann Surg. 1999;229:272–8.
31. Moore EE, Moore FA, Franciose RJ, Kim FJ, Biffl WL, Banerjee A. The postischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. J Trauma. 1994;37:881–7.
32. Windsor ACJ, Kanwar S, Li AGK, Barnes E, Guthrie JA, Spark JI, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut. 1998;42:431–5.
33. Lewis SJ, Egger M, Sylvester PA, et al. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled studies, Br Med J. 2001;323:1-5.323:1–5.
34. 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.
35. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr. 2001;74:534–42.
36. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. Intensive Care Med. 2005;31:12–23.
37. 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;20:843–8.
38. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg. 1992;216:172–83.
39. 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;33:213–20.
40. Elke G, Kuhnt E, Ragaller M, Schädler D, Frerichs I, Brunkhorst FM, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis. A secondary analysis of the VISEP trial. Med Klin Intensivmed Notfmed. 2013;108(3):223–33.
41. Arabi YM, Tamim HM, Dhar GS, Al-Dawood A, Al-Sultan M, Sakkijha MH, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr. 2011;93:569–77.
42. 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;39:967–74.

43. 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. Apr;108(3):223–33.
44. 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.
45. Elke G, Heyland DK. Enteral nutrition in critically ill septic patients – less or more? JPEN J Parenter Enteral Nutr. 2015;39(2):140–2.
46. de Haan JJ, Thuijls G, Lubbers T, Hadfoune M, Reisinger K, Heineman E, et al. Protection against early intestinal compromise by lipid-rich enteral nutrition through cholecystokinin receptors. Crit Care Med. 2010;38(7): 1592–7.
47. de Haan JJ, Lubbers T, Hadfoune M, Luyer MD, Dejong CH, Buurman WA, et al. Postshock intervention with high-lipid enteral nutrition reduces inflammation and tissue damage. Ann Surg. 2008;248(5):842–8.
48. Lubbers T, de Haan JJ, Luyer MD, Verbaeys I, Hadfoune M, Dejong CH, et al. Cholecystokinin/Cholecystokinin-1 receptor-mediated peripheral activation of the afferent vagus by enteral nutrients attenuates inflammation in rats. Ann Surg. 2010;252(2):376–82.
49. de Haan JJ, Pastille E, Wirsdörfer F, Lubbers T, Greve JW, Zhang Y, et al. Lipid-rich enteral nutrition improves the defense against an opportunistic infection during polymicrobial sepsis. Shock. 2014;41(2):109–14.
50. Wen H, Hogaboam CM, Gauldie J, Kunkel SL. Severe sepsis exacerbates cell-mediated immunity in the lung due to an altered dendritic cell cytokine profile. Am J Pathol. 2006;168(6):1940–50.
51. Lubbers T, Kox M, de Haan JJ, Greve JW, Pompe JC, Ramakers BP, et al. Continuous administration of enteral lipid- and protein-rich nutrition limits inflammation in a human endotoxemia model. Crit Care Med. 2013;41(5):1258–65.
52. 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.
53. Montejo JC, Zarazaga A, López-Martínez J, Urrútia G, Roqué M, Blesa AL, et al. Immunonutrition in the intensive care unit. A systematic review and consensus statement. Clin Nutr. 2003;22(3):221–33.
54. 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.
55. 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.
56. 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.
57. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. 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.
58. Cangelosi MJ, Auerbach HR, Cohen JT. A clinical and economic evaluation of enteral nutrition. Curr Med Res Opin. 2011;27(2):413–22.
59. Koretz RL, Lipman TO, Klein S, American Gastroenterological Association. AGA technical review on parenteral nutrition. Gastroenterology. 2001;121(4):970–1001.
60. Ippolito P, Larson EL, Furuya EY, Liu J, Seres DS. Utility of electronic medical records to assess the relationship between parenteral nutrition and central line-associated bloodstream infections in adult hospitalized patients. JPEN J Parenter Enteral Nutr. 2014. [Epub ahead of print].
61. Yang SP, Chen YY, Hsu HS, Wang FD, Chen LY, Fung CP. A risk factor analysis of healthcare-associated fungal infections in an intensive care unit: a retrospective cohort study. BMC Infect Dis. 2013;13:10.
62. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006;355(26):2725–32.
63. O'Connor A, Hanly AM, Francis E, Keane N, McNamara DA. Catheter associated blood stream infections in patients receiving parenteral nutrition: a prospective study of 850 patients. J Clin Med Res. 2013;5(1):18–21.
64. Dimick JB, Swoboda S, Talamini MA, Pelz RK, Hendrix CW, Lipsett PA. Risk of colonization of central venous catheters: catheters for total parenteral nutrition vs other catheters. Am J Crit Care. 2003;12(4):328–35.
65. Doig GS, 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.
66. 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.
67. Kutsogiannis J, Alberda C, Gramlich L, Cahill NE, Wang M, Day AG, et al. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. Crit Care Med. 2011;39(12):2691–9.

68. Hayashi N, Tashiro T, Yamamori H, Takagi K, Morishima Y, Otsubo Y, et al. Effects of intravenous omega-3 and omega-6 fat emulsion on cytokine production and delayed type hypersensitivity in burned rats receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr. 1998;22(6):363–7.
69. Melly MA, Meng HC, Schaffner W. Microbiol growth in lipid emulsions used in parenteral nutrition. Arch Surg. 1975;110(12):1479–81.
70. Gilbert M, Gallagher SC, Eads M, Elmore MF. Microbial growth patterns in a total parenteral nutrition formulation containing lipid emulsion. JPEN J Parenter Enteral Nutr. 1986;10(5):494–7.
71. Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. N Engl J Med. 1990;323(5):301–8.
72. Avila-Figueroa C, Goldmann DA, Richardson DK, Gray JE, Ferrari A, Freeman J. Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteremia in very low birth weight newborns. Pediatr Infect Dis J. 1998;17(1):10–7.
73. Pontes-Arruda A, Liu FX, Turpin RS, Mercaldi CJ, Hise M, Zaloga G. Bloodstream infections in patients receiving manufactured parenteral nutrition with vs without lipids: is the use of lipids really deleterious? JPEN J Parenter Enteral Nutr. 2012;36(4):421–30.
74. Yeh SL, Chang KY, Huang PC, Chen WJ. Effects of n-3 and n-6 fatty acids on plasma eicosanoids and liver antioxidant enzymes in rats receiving total parenteral nutrition. Nutrition. 1997;13(1):32–6.
75. Heller AR, Rössler S, Litz RJ, Stehr SN, Heller SC, Koch R, et al. Omega-3 fatty acids improve the diagnosis-related clinical outcome. Crit Care Med. 2006;34(4):972–9.83.
76. Gultekin G, Sahin H, Inanc N, Uyanik F, Ok E. Impact of Omega-3 and Omega-9 fatty acids enriched total parenteral nutrition on blood chemistry and inflammatory markers in septic patients. Pak J Med Sci. 2014;30(2): 299–304.
77. Pradelli L, Mayer K, Muscaritoli M, Heller AR. n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. Crit Care. 2012;16(5):R184.
78. Clinicaltrials.gov. A service of the US National Institutes of Health. Search of: omegaven. http://clinicaltrials.gov/ct2/results?term=omegaven. Accessed 21 Jul 2014.
79. Turpin RS, Canada T, Rosenthal V, Nitzki-George D, Liu FX, Mercaldi CJ, et al. Bloodstream infections associated with parenteral nutrition preparation methods in the United States: a retrospective, large database analysis. JPEN J Parenter Enteral Nutr. 2012;36(2):169–76.
80. Please provide details for reference [80]
81. Buchman AL, Moukarzel A, Goodson B, Herzog F, Pollack P, Reyen L, et al. Catheter-related infections associated with home parenteral nutrition and predictive factors for the need for catheter removal in their treatment. JPEN J Parenter Enteral Nutr. 1994;18(4):297–302.
82. Gillanders L, Angstmann K, Ball P, O'Callaghan M, Thomson A, Wong T, et al. A prospective study of catheter-related complications in HPN patients. Clin Nutr. 2012;31:30–4.
83. Reimund JM, Arondel Y, Finck G, Zimmermann F, Duclos B, Baumann R. Catheter-related infection in patients on home parenteral nutrition: results of a prospective survey. Clin Nutr. 2002;21:33–8.
84. Cotogni P, Pittiruti M, Barbero C, Monge T, Palmo A, Boggio Bertinet D. Catheter-related complications in cancer patients on home parenteral nutrition: a prospective study of over 51,000 catheter days. JPEN J Parenter Enteral Nutr. 2013;37(3):375–8.
85. Buchman AL, Opilla M, Kwasny M, Diamantidis TG, Okamoto R. Risk factors for the development of catheter-related bloodstream infections in patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2013;38(6):744–9.
86. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc. 2006;81(9):1159–71.
87. Touré A, Duchamp A, Peraldi C, Barnoud D, Lauverjat M, Gelas P, Chambrier C. A comparative study of peripherally-inserted and Broviac catheter complications in home parenteral nutrition patients. Clin Nutr. 2014;pii: S0261–5614(13)00340–3.
88. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters(access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365e77.
89. Timsit J-F, Schwebel C, Bouadma L, Geffroy A, Garrouste-Orgeas M, Pease S, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults. JAMA. 2009;301:1231–41.
90. Camargo LF, Marra AR, Büchele GL, Sogayar AM, Cal RG, de Sousa JM, et al. Double-lumen central venous catheters impregnated with chlorhexidine and silver sulfadiazine to prevent catheter colonisation in the intensive care unit setting: a prospective randomised study. J Hosp Infect. 2009;72:227–33.
91. Toure A, Lauverjat M, Peraldi C, Boncompain-Gerard M, Gelas P, Barnoud D, et al. Taurolidine lock solution in the secondary prevention of central venous catheter-associated bloodstream infection in home parenteral nutrition patients. Clin Nutr. 2012;31(4):567–70.

92. Opilla MT, Kirby DF, Edmond MB. Use of ethanol locks therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients. JPEN J Parenter Enteral Nutr. 2007;31:302–5.
93. Jones BA, Hull MA, Richardson DS, Zurakowski D, Gura K, Fitzgibbons SC, et al. Efficacy of ethanol locks in reducing central venous catheter infections in pediatric patients with intestinal failure. J Pediatr Surg. 2010;45:1287–93.
94. Jackson NC, Carroll PV, Russell-Jones DL, Sönksen PH, Treacher DF, Umpleby AM. The metabolic consequences of critical illness: acute effects on glutamine and protein metabolism. Am J Physiol. 1999;276(1 Pt 1):E163–70.
95. Bongers T, Griffiths RD, McArdle A. Exogenous glutamine: the clinical evidence. Crit Care Med. 2007;35(9 Suppl):S545–52.
96. 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.
97. 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.
98. 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.
99. Daly JM, Reynolds J, Thom A, Kinsley L, Dietrick-Gallagher M, Shou J, et al. Immune and metabolic effects of arginine in the surgical patient. Ann Surg. 1988;208(4):512–23.
100. Agay D, Sandre C, Ducros V, Faure H, Cruz C, Alonso A, et al. Optimization of selenium status by a single intraperitoneal injection of Se in Se deficient rat: possible application to burned patient treatment. Free Radic Biol Med. 2005;39:762–8.
101. Angstwurm MW, Schottdorf J, Schopohl J, Gaertner R. Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. Crit Care Med. 1999;27(9):1807–13.
102. Angstwurm MW, Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med. 2007;35(1):118–26.
103. Manzanares W, Biestro A, Torre MH, Galusso F, Facchin G, Hardy G. High-dose selenium reduces ventilator-associated pneumonia and illness severity in critically ill patients with systemic inflammation. Intensive Care Med. 2011;37(7):1120–7.
104. Forceville X, Laviolle B, Annane D, Vitoux D, Bleichner G, Korach JM, et al. Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo-controlled, randomized, double-blind, phase II study. Crit Care. 2007;11(4):R73.
105. 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.
106. Hardy G, Hardy I, Manzanares W. Selenium supplementation in the critically ill. Nutr Clin Pract. 2012;27(1):21–33.
107. Rayman MP. Selenium and human health. Lancet. 2012;379(9822):1256–68.
108. Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. N Engl J Med. 2009;360(18):1912–4.
109. 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(6):814–22.

Chapter 10
Organ Failure and Specialized Enteral Formulas

Ainsley Malone and Farshad Farnejad

Keywords Enteral formulas • Organ failure • Diabetes mellitus • Hepatic encephalopathy • Acute respiratory distress syndrome • Chronic obstructive pulmonary disease • Acute kidney injury • Fish oil • Glycemic control • Branched-chain amino acids

Key Points

- Primary organ failure is a common reason for admission to the intensive care unit (ICU) and many of these patients will experience a second organ failure during their ICU course.
- Specialized enteral nutrition formulations containing selected nutrients are available that may ameliorate the metabolic responses to various organ failure syndromes.
- Evidence demonstrating clinical outcome benefits with the use of various specialized enteral formulations is limited.

Introduction

Critically ill patients commonly present with organ failure. While data pertaining to specific organ failure prevalence is not readily available, some key points can be highlighted. Each year, about 190,000 patients in the USA develop acute respiratory distress syndrome (ARDS) [1]. In the ICU, 7–10 % of admitted patients and 5–8 % of mechanically ventilated patients meet the criteria for ARDS [2, 3]. Acute liver failure affects approximately 2500 patients annually in the USA [4]. Moreover, intensive care unit (ICU) admissions related to cirrhosis in the USA are more than 26,000 per year [5] Acute kidney injury (AKI) occurs in approximately 5–7 % of hospitalized patients [6]. A 2005 multinational, multicenter evaluation documented the prevalence of AKI to be 5.7 % [7]. In addition to individual organ failure syndromes, many ICU patients can and do develop multiple organ failure.

A. Malone, MS, RD, LD, CNSC (✉)
Pharmacy Department, Mt. Carmel West Hospital, 722 W. State Street, Columbus, OH 43222, USA
e-mail: ainsleym@earthlink.net

F. Farnejad, MD, MPH
Department of Surgery, University of Missouri - Kansas City and Truman Medical Center, 2411 Holmes St., Kansas City, MO, 64108, USA

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_10,

Table 10.1 Considerations in evaluation of specialized enteral formulas[a]

• Is the nutrient profile appropriate based on known metabolic abnormalities and nutrient requirements of the specified condition?
• Has the product testing been limited to animal research only?
• Have prospective, controlled, randomized clinical trials evaluating the product been conducted?
• Is the research only product specific?
• Can the study results be generalized to other populations or only that in which the product was studied?
• Has objective criteria been developed to evaluate the specific formula?
• Are recommendations for product use confined only to the population(s) studied or for use with additional population(s)?

[a]Adapted from Malone AM. The clinical benefits and efficacy in using specialized enteral feeding formulas. Support Line 2002; 24(1): 3-11. © (2002) Support Line, Dietitians in Nutrition Support, a dietetic practice group of the Academy of Nutrition and Dietetics. Used with permission

A variety of specialized enteral formulas designed for organ failure syndromes or specific clinical scenarios are available. Specialized formulas may or may not result in improved outcomes for critically ill patients and their use can be controversial [8–10]. Manufacturers market their products for a variety of disease states or conditions, but their use is often not well supported by published clinical studies. It is important to remember that nutrition is only one aspect of a critically ill patient's treatment. It is therefore necessary to ask, what possible difference in outcome will a particular formula offer to the patient? Table 10.1 outlines other important considerations when evaluating specialized formulas. In this chapter, the following enteral formulas for specific organ syndromes or conditions will be reviewed: diabetes mellitus, hepatic disease, pulmonary disease (acute respiratory distress syndrome and chronic obstructive pulmonary disease), and acute kidney injury.

Diabetes Mellitus

Hyperglycemia is a common metabolic disturbance found in both diabetic and nondiabetic critically ill patients. It has been associated with adverse outcomes in both adults and children [11, 12]. Consequently, blood glucose levels must be safely and effectively controlled. To accomplish this goal, exogenous insulin is often required. Aggressive correction of hyperglycemia using insulin has been shown to decrease complications associated with poor glycemic control. This has been well established in prospective randomized trials in perioperative [13–15], cardiac [15], and intensive care settings [13, 14]. Good glycemic control has been widely accepted into clinical practice [16] and is routinely cited in international treatment guidelines [17]. Despite the benefits of euglycemia, the level to which blood glucose should be controlled remains a matter for investigation. Tight glucose control carries a higher risk of hypoglycemia than more moderate control [18]. This may be the reason that some recent studies have failed to show the benefit, or have even shown actual harm, that was seen in initial studies of tight control [19, 20]. This has led many to abandon, or modify, protocols for tight glucose control. Nonetheless, clinicians generally agree that uncontrolled hyperglycemia is harmful, and that some target range for blood glucose should be achieved.

Blood glucose control is a complex process, involving interactions among the pituitary, liver, pancreas, and adrenals. Insulin acts to lower blood glucose, enhancing glucose uptake and glycogen synthesis and suppressing gluconeogenesis. On the other hand, catecholamines, growth hormone, and cortisol all raise blood glucose concentrations through up-regulation of glycogenolysis and gluconeogenesis. Elevation of these hormones is part of the normal response to a stress such as injury, operation, or infection. And critical illness is commonly associated with insulin resistance, rendering both endogenous and exogenous insulin less effective.

Effects of Hyperglycemia

Hyperglycemia is highly prevalent among both diabetics and nondiabetic patients due to physiologic stress. It is reported in up to 68 % of patients admitted to a medical ICU [21]. It is an independent predictor of death in many acute settings, including acute myocardial infarction [22], trauma, head injury [23, 24], and stroke. Postulated mechanisms by which hyperglycemia causes harm include decreased cerebral blood flow, intracellular acidosis, and low ATP levels. These may be similar to the actions of hyperglycemia seen in diabetes mellitus [25]. Cells damaged by hyperglycemia are primarily those unable to effectively control their intracellular glucose concentration. These include neuronal, capillary endothelium, and renal mesangial cells. Raised intracellular glucose levels result in an increased flux through the glycolytic pathway and the Krebs cycle. This in turn causes increased production of the reducing compounds, nicotinamide adenine dinucleotide and succinate. Hyperglycemia is a known risk factor for infection. It is associated with increased mortality in critically ill patients [26–28]. It is also associated with an increased risk of acquiring pathogenic bacteria within the bronchial tree of intubated patients [29]. Diabetics have increased susceptibility to surgical site infections, foot ulcers, and infective diarrhea.

This relative bacterial overgrowth witnessed in hyperglycemia may be partly due to altered host defenses. Hyperglycemia reduces polymorphonuclear leukocyte chemotaxis and bactericidal ability in diabetic patients [30]. Impaired leukocyte phagocytosis in patients with diabetes has also been reported [31, 32].

Hyperglycemia is also recognized as being pro-inflammatory and pro-oxidant. The use of insulin to modulate blood glucose levels can prevent these changes, an effect attributed to maintaining normoglycemia rather than through direct action of insulin. Hyperglycemia also produces a hypercoaguable state. Insulin promotes increased expression of tissue factor, which is both procoagulant and proinflammatory. It activates factor VII of the coagulation cascade [33]. This promotes the generation of thrombin, a protease which converts fibrinogen to fibrin and activates platelets.

Healthy volunteers rendered hyperglycemic and exposed to endotoxin demonstrated evidence of a pro-coagulable state as compared with normal hyperglycemic controls, with raised plasma levels of soluble tissue factor and thrombin–antithrombin complexes [33]. Hyperglycemia is further associated with poor gut motility, a factor that may be important in bacterial overgrowth and translocation. This dysmotility may be due to the inhibitory effects of hyperglycemia on vagal nerve activity [34].

The Diabetic Patient

Nutrition for diabetics has historically consisted of 55–60 % carbohydrate (CHO), 25–30 % fat, and 10–20 % protein. This has changed in recent years. Currently, no one specific macronutrient composition is recommended. Revised recommendations from the American Diabetes Association (ADA) in 2008 for weight loss included either a low-carbohydrate or low-fat calorie-restricted diet. The dietary intake of protein for individuals with diabetes is similar to that of the general population and usually does not exceed 20 %. Individualization of the macronutrient composition will depend upon the metabolic status of the individual patient and may be adjusted depending on weight gain or loss, and other changes in the patient's life. It is important to adjust calorie needs to the metabolic stress status of the patient.

One of the most controversial issues is the distribution of the total calorie requirements and in particular the carbohydrate to lipid ratio. For enteral feeding, the ADA recommends that either a standard enteral formula (50 % CHO) or lower-CHO content formulae may be used [35]. In contrast, the European Association for the Study of Diabetes [36] recommends that fat content in the diet

should not exceed 35 % and that carbohydrate intake should be within 45–60 % of the daily calorie needs. There are specific enteral formulae for diabetics containing fewer carbohydrates (35–40 %) and more fats (40–50 %), with predominance of monounsaturated fatty acids. New formulations have been developed that, in addition to reducing fat content, increase low glycemic index carbohydrates [36]. In studies performed in non-critically ill patients, both types of formula reduce the glycemic and insulin response to intake. Diets rich in slow-digestion carbohydrates do not raise postprandial triglyceride levels, unlike diets rich in fats [35, 37]. Therefore, it is recommended to use low glycemic index carbohydrates, such as starch, fructose at lower doses, and more recently isomaltulose and sucromalt [35]. With regard to lipids, it is recommended to increase monounsaturated fatty acids, as they improve glycemic control, lipid metabolism, and insulin secretion in non-critically ill patients with type 2 diabetes [37]. Furthermore, it is recommended to reduce polyunsaturated fatty acids of the ω-6 series to prevent an increase in pro inflammatory eicosanoids [38]. In general, patients with type 2 diabetes benefit from high-fat diets. Diets very rich in carbohydrates affect the lipid profile of the patient, especially triglycerides, and increase the risk of cardiovascular diseases [39].

Diabetes-Specific Enteral Formulations

Many different enteral formulations have been specifically developed for the diabetic patient or the patient with hyperglycemia due to critical illness. With respect to available nitrogen and total energy, the currently available formulations usually provide values ranging from approximately 40–60 g/L as protein and 1000–1500 kcal/L total energy. These support a diet of 18–20 % total kcal as protein, and differ only marginally from the standard enteral formulas.

The major differences between diabetic specific formulations and standard enteral formulations are the relative amounts and percentages of total energy provided in the form of CHO and fat. The diabetic formulations currently available provide a decreased amount of CHO, and n increased amount of fat. These relatively high fat, low CHO formulations yield values that range from approximately 80–120 g/L CHO (35–50 % of total kcal) and approximately 30–60 g/L as fat (35–50 % of total kcal). The source of CHO often includes increased amounts of fructose relative to standard formulations. Fructose may be 15 % of total calories. The fat in diabetic formulations is usually provided in the form of higher amounts of mono-unsaturated fatty acids than found in standard enteral formulations. These fatty acids can represent over 60 % of the total fat provided. One additional component among diabetic formulations that differs from standard formulations is the amount and source of fiber. The amount of fiber is typically increased relative to standard formulations. The sources of this fiber are usually fruits, vegetables or soy polysaccharide.

The clinical interest in the use of diabetic formulations has focused primarily upon safety and tolerance, in particular on potential short- and long-term effects these preparations may have on various glycemic indicators. There has been some safety concern for the about the relatively higher levels of fat and fructose which may have negative sequelae with respect to lipid metabolism, and the risk for lactic acidosis. Patients with underlying dysmotility disorders may not tolerate fructose and fructo-oligosaccharides. Most importantly, studies have recently begun to focus upon whether or not these diabetic formulations can improve patient outcomes.

The Critically Ill Patient

Critically ill patients with hyperglycemia and particularly those who are diabetics manifest significant metabolic derangements in the absence of insulin. These include an increase in basal energy expenditure and a negative net protein balance. Both insulin and amino acids stimulate protein synthesis.

In hyper-aminoacidemia states, it has been suggested that additional insulin doses do not increase protein synthesis, an effect likely related to the level of insulin resistance [40].

The evidence is not adequate to define protein needs for critically-ill diabetic patients or those with stress hyperglycemia. It is probably best to give 1.3–1.7 g/kg/day of protein or amino acids, according to their metabolic stress level. Antioxidant vitamins at doses higher than maintenance requirements are not necessary, and may not even be safe [41]. It is not clear that oxidative stress contributes to complications in seriously ill diabetic patients. Tissue damage occurs in diabetic patients, but not in hyperglycemic critically ill patients with insulin resistance. There is no proven efficacy of antioxidants in the prevention or control of hyperglycemia associated complications [42].

Although hyperglycemia is an appropriate physiological response to injury or illness, its treatment has been modified recently in the direction of tighter glucose control. This has probably led to improved survival of critically ill patients. Hyperglycemia is compounded by the use of enteral or parenteral nutrition, glucose-containing intravenous fluids, and drugs that potentially increase blood glucose levels. Mechanisms underlying hyperglycemia are complex but include peripheral and hepatic insulin resistance, enhanced hepatic and renal glucose production, and high exogenous glucose from enteral and intravenous nutrition.

A variety of studies have shown that hyperglycemia is an independent risk factor for a worse prognosis in critically ill patients [43, 44]. A study by VandenBergh et al. in a population of critically ill surgical patients, maintained tight glycemic control from 80–110 mg/dl by continuous infusion of insulin [45]. This demonstrated a reduction of 3.4 % of the risk of death in the ICU. But this could not be reproduced in subsequent studies [46, 47]. Publications by others have shown an increased mortality in the group of patients maintaining strict blood glucose levels (80–110 mg/dl). The increased mortality was associated with a high incidence of severe hypoglycemia [20, 48, 49].

The largest multicenter study conducted to date [20, 50] included 6,104 patients from mixed ICUs. It compared two ranges of blood glucose levels: 80–108 mg/dL (strict) versus <180 mg/dL (conventional). The incidence of severe hypoglycemia was higher in the strict control group (6.8 vs. 0.5 %; $p<0.001$). The 90-day mortality in the strict control group was significantly higher (27.5 %) than in the conventional group (24.9 %) (95 % CI, 1.02–1.28; $p=0.02$). The mean blood glucose achieved in the strict control group was 114 mg/dL and in the conventional group 144 mg/dL. Two recent meta-analyses found that in all critically ill patients, strict control of blood glucose levels (80–110 mg/dl) significantly increased episodes of severe hypoglycemia, without improving survival as compared to the conventional control group [50, 51]. The variability of blood glucose levels may affect mortality, even if it occurs between blood glucose ranges considered appropriate [21]. In the cohort of 66,184 patients evaluated by the ANZICS (Australian and New Zealand Intensive Care Society), the variability of blood sugar levels over the first days of illness was associated with an increased adjusted mortality when compared to the appearance of severe hypoglycemia alone [44].

Diabetic Formulations in Critically Ill Patients

In a single-blind, PRCT conducted in two University Hospital Intensive Care Units, Mesejo, et al. compared the use of a high-protein diabetic formula to a standard formula over a 14-day period [52]. Sixty-one patients were enrolled, with diabetes or stress hyperglycemia, basal glycemia ≥60 mg/dL, and an indication for enteral nutrition longer than 5 days. The composition of the two formulas were the following: standard formula: 49 % CHO, 29 % fat, and 22 % protein, and diabetic formula, 40 % CHO, 40 % fat, 20 % protein, plus added fiber. Fifty patients completed the study, 26 diabetic formula and 24 standard. Data was collected on plasma and capillary glucose levels, lipids (cholesterol, triglycerides, HDL, and LDL), visceral proteins (retinol-binding protein, prealbumin, albumin, and transferrin), acute-phase reactantproteins (CRP, alpha-1-antitrypsin, ferritin, and haptoglobin), hormones (glucagon and insulin), HbA1C, immunologic parameters (serum complement components

C3 and C4, CD4+ and CD8+, lymphocytes and total lymphocytes), APACHE II scores, acquired infections, mechanical ventilation, length of ICU stay, and mortality. Both groups received over 92 % of expected kcal. Significant improvements were seen in the diabetic formula group in plasma glucose and capillary glucose levels, insulin/day, insulin per gram of CHO received, and insulin per gram CHO per kg body weight. Broader outcome measures such as infection rate, ICU length of stay, and mortality did not demonstrate significant differences between the two groups. Thus, although a statistically significant improvement in glycemic control of the patients who received diabetic formulation was evident, this improvement did not produce improvements in length of stay or mortality.

Current evidence suggests that the use of a high-fat, lower CHO diabetic formulation is to lower postprandial blood glucose levels relative to a higher CHO, lower fat diet. Importantly, the use of such high-fat diabetic formulations in these patients was tolerated well and did not lead to negative consequences. One must consider the short treatment period when interpreting results in many of these studies. In addition, studies to date are plagued by heterogeneous patient populations, small sample size, combinations of diabetes mellitus types 1 and 2, and stress-induced hyperglycemia. There were high dropout rates. All this makes it difficult to draw reliable conclusions. It seems clear from many studies that improving glycemic control, either through diet or insulin delivery, may avert untoward physiologic changes. While there is no decisive evidence of the optimal glucose level, serum glucose of less than 180 is a reasonable goal. This can be met using a continuous infusion of insulin or as a sliding scale protocol, or with long acting insulin. If diabetic dietary formulations can lower the postprandial glucose response, without altering lipid metabolism, patient outcomes may improve. Most studies have not considered such intermediate term outcomes as hospital length of stay. Although the combined results of these studies are provocative, more robust clinical trials are required for the recommendation and routine adoption of diabetic formulas in clinical practice.

Hepatic Disease

What role might a specialized enteral formula have in the treatment of hepatic failure with resultant encephalopathy? In the late 1970s, research began to appear demonstrating the beneficial use of parenteral formulations high in branched-chain amino acids (BCAA) (valine, leucine, and isoleucine, BCAA) for patients with advanced liver disease. Such patients are often malnourished and require increased amounts of protein to maintain nitrogen equilibrium [53, 54]. These formulas provided increased amounts of BCAA and reduced amounts of the aromatic amino acids, phenylalanine, tyrosine, and tryptophan (AAA). These alterations have been thought to promote a reduced uptake of AAA at the blood–brain barrier, reducing the synthesis of false neurotransmitters and thereby ameliorating the neurological symptoms that occur with hepatic encephalopathy (HE) [55].

Studies evaluating parenteral and enteral BCAA formulas in patients with acute encephalopathy have yielded conflicting results [56–59]. A meta-analysis conducted by Naylor et al. reviewed nine randomized controlled trials evaluating parenteral BCAA [60]. Five of the studies showed a highly significant improvement in mental recovery from acute encephalopathy and a significant reduction in mortality. But these authors concluded that, due to short-term follow-up times and mortality discrepancy across the trials, recommendation of parenteral BCAA over conventional therapy is not indicated.

Several trials evaluating BCAA in chronic encephalopathy have been conducted in an attempt to determine whether BCAA improve neurological outcome or improve tolerance to dietary protein. In a multi-center trial, Horst et al. compared a BCAA-enriched versus a mixed protein enteral supplement [58]. The BCAA-supplemented group achieved nitrogen balance equal to that of the control group without precipitation of HE. Additional studies in which patients were randomized to receive either oral diets enriched with BCAA or control failed to demonstrate clinical benefit of the

BCAA-enriched diet [8]. In a more recent (2003) evaluation, Marchesini and colleagues compared the use of oral BCAA supplementation versus standard protein or carbohydrate without protein on death, disease deterioration and the need for hospital admission in ambulatory patients with advanced cirrhosis [61]. BCAA supplementation resulted in a significant decrease in the primary occurrence events, death, and disease deterioration. The authors concluded that there are benefits to routinely supplementing BCAA in patients with advanced cirrhosis. While this study offers a possible benefit to routine BCAA supplementation, generalizing these results to the critically ill patient with HE is not recommended. In a 2009 Cochrane Review the following results were demonstrated: BCAA appeared to have a modest effect in improving encephalopathy. However, this effect was not seen when only trials of high quality were included [62]. The review also concluded there is still no convincing evidence to support the use of BCAA for patients with hepatic encephalopathy.

The routine use of BCAA-enriched enteral formulas does not appear to be clinically beneficial in patients with advanced liver disease and/or HE. Standard enteral formulas can successfully be used with most patients. However, in those patients who are unable to tolerate standard protein intakes without precipitation of HE, the use of BCAA enriched enteral formulas may be better tolerated, thus permitting achievement of desired protein intakes [8, 9, 63, 64]. Evidence-based guideline recommendations favor this approach. The 2009 Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition. recommends, "Standard enteral formulations should be used in ICU patients with acute and chronic liver disease. Branched chain amino acid formulations should be reserved for the rare encephalopathic patient who is refractory to standard treatment with luminal acting antibiotics and lactulose" [65]. This recommendation is hardly a ringing endorsement, and makes clear that the only indication for BCAA use is in a very few patients.

Respiratory Failure

Perhaps the most common reason for ICU admission and assisted ventilation is acute respiratory failure. The underlying causes of acute respiratory failure are usually multifactorial. Common reasons for ICU admission are exacerbation of chronic obstructive pulmonary disease and acute lung injury manifesting as ARDS [1]. ARDS is a combination of physiologic derangements, among which are a pro-inflammatory response associated with hyper-catabolism. This may predispose the patient to significant nutrition deficits. These patients are at high risk for malnutrition due to underlying disease, altered catabolism, and the use of mechanical ventilation.

Mechanically ventilated patients cannot eat, and if nutrition is not addressed for long periods become malnourished. Malnutrition is associated with poor outcomes in critically ill patients. Nutritional support is especially important in patients with acute respiratory failure and ARDS as they have an expected longer duration of mechanical ventilation. Whenever feasible, enteral nutrition targeting caloric needs is recommended over parenteral nutrition [65, 66].

Several observational studies have shown improved clinical outcomes, including fewer infections, shorter duration of mechanical ventilation, and lower mortality for patients receiving a higher percentage of calculated caloric needs [67, 68]. Nonetheless, the best timing, formulation, and amount of enteral nutrition remain unknown. Recent data suggest that hypocaloric feeding, or permissive underfeeding, may result in shorter duration of mechanical ventilation and improved mortality [69, 70]. Even minimal amounts of enteral feedings, sometimes called trophic nutrition, have beneficial effects, such as preserving intestinal epithelium, stimulating secretion of brush border enzymes, enhancing immune function, preserving epithelial tight cell junctions, and preventing bacterial translocation, despite not meeting daily caloric needs [71–73].

In all critically ill patients regardless of the etiology, the energy supply must meet the patient requirements. The goal is optimizing nutrition delivery and avoiding overfeeding. It is also important to ensure at least 50–65 % of calorie requirements estimated during the catabolic phase, though only observational studies demonstrate the beneficial effect of meeting energy requirements [67, 74, 75]. Large multicenter studies aimed at evaluating strict glycemic control have demonstrated the difficulty in trying to achieve mean calorie intake above this percentage (from 11 to 16 kcal/kg/day), regardless of the administration route used. Current data does not support meeting these calorie requirements from the first day [76–79].

This debate is also applicable to protein supplies. There is a consensus on the need to provide proteins above –1.2 g/kg/day, but the level of evidence is also very low [80]. In fact, and taking into account the mean calorie supplies, in all above mentioned studies protein supplies are below 1 g/kg/day [67]. In a observational study of the Metabolism and Nutrition Working Group, 20 kcal/kg/day of calorie intake and 1 g/kg/day of protein intake were reached in 50 % of the patients, though 30 % of them received parenteral nutrition and enteral nutrition, simultaneously [81].

Pharmaconutrients

The use of ω-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), gamma linoleic acid (GLA), and antioxidants have been studied to elucidate their influence on outcomes. Omega-3 fatty acids, contained in fish oil, are essential in critically ill patients. They have been postulated to modulate the systemic inflammatory response. One of the findings in uncontrolled activation of the inflammatory response, as seen in ARDS and in sepsis, is the role of cytokines and eicosanoids derived from lipids. Three clinical trials with enteral nutrition using a commercial formula containing omega-3 fatty acids, GLA, and antioxidants showed improvements in clinical outcomes, both in ICU length of stay and days on mechanical ventilation. One of these studies actually found a reduction in mortality [82–84]. This has been confirmed in a subsequent meta-analysis [85]. In addition, an observational study in surgical patients with intra-abdominal sepsis treated with parenteral nutrition enriched with omega-3 fatty acids found a relative mortality reduction [86].

These studies [79–81] used control diets containing high amounts of fat (up to 50 % of energy requirements in two of them), and high amount of linoleic acid. When several pharmaconutrients are combined, it is difficult to establish the actual benefit of each of them. Three recent studies addressed this topic. The first compares the effect of omega-3 fatty acid supplements with antioxidants, administered as a bolus every 12 h in addition to the standard enteral diet versus the control. This trial was discontinued for treatment futility after recruiting 272 patients [87]. The second study analyzes the inflammatory response in broncheoalveolar lavage of these patients, with no significant differences [88]. And, finally, a multicenter study using a commercial diet with omega-3 fatty acids, GLA, and antioxidants in the treatment of patients with sepsis and ARDS did not find any improvements in gas exchange or decrease in the incidence of organ failure. Although the ICU length of stay was shorter than in the control group, no differences were seen in infectious complications [89]. All studies have used enteral preparations, although a parenteral form of omega-3 fatty acids has been developed. There are no studies assessing the effect of omega-3 fatty acids, given parenterally in patients with ARDS, nor with other pharmaconutrients given parenterally.

Based on the evidence currently available, the following recommendations can be made. It is important to pay special attention to potassium, phosphorus, magnesium, and antioxidant intake in patients with chronic respiratory failure. Current evidence does not support the use of enteral formulas with low-carbohydrate content and high-fat content in chronic respiratory failure. In patients with acute respiratory failure, calorie and protein supply should be similar to that recommended for other critically ill patients. An enteral diet enriched with omega-3 diet fatty acids, GLA, and antioxidants may have

beneficial effects in patients with ARDS. There are no specific recommendations for the use of ω-3 fatty acids by parenteral route. Further, there are no specific recommendations for the single use of glutamine, vitamins, or antioxidant supplements.

Chronic Pulmonary Disease

The practice of altering macronutrient distribution to avoid detrimental respiratory effects became common in the mid-1980s [90–92]. Their use remains controversial as outlined below.

Multiple studies exist comparing the effects of macronutrient metabolism on respiratory function and status. Most have studied ambulatory patients making it difficult to generalize to patients in the ICU, but selected details can be highlighted. In 1985 Angelillo et al. [93] studied the effect of fat and carbohydrate content on carbon dioxide (CO_2) production in ambulatory COPD patients with hypercapnia. The authors found that use of a high-fat formula reduced CO_2 production and respiratory quotient compared to those receiving a lower fat formula. In a more recent study, Akrabawi et al. [94] in 1996 evaluated pulmonary function and gas exchange in ambulatory COPD patients. Patients received both a high-fat (55 %) and a moderate-fat (41 %) formula "meal" on two separate days. No significant differences in respiratory quotient were demonstrated between the moderate and high fat meals.

In an effort to compare the differences in gas exchange and ventilation between normal patients and those with COPD, Kuo et al. evaluated a high fat oral liquid diet and a high CHO oral liquid diet) in 12 stable ambulatory COPD patients and 12 healthy volunteers [95]. Significantly greater increases in O_2 consumption (VO_2) ($p<0.05$), CO_2 production (V CO_2) ($p<0.001$), and minute ventilation (Ve) ($p<0.001$) occurred in the COPD patient group receiving the high CHO diet compared to those receiving the high-fat diet. The healthy controls demonstrated no change in respiratory parameters. In 2001 Vermeeren et al. conducted an evaluation of both high fat and high CHO nutritional supplements and higher versus lower calories on metabolism and exercise capacity in stable COPD patients [96]. Significant increases in VCO_2 ($p<0.05$), VO_2 ($p<0.05$), and RQ ($p<0.01$) were observed when the higher calorie load was consumed. There were no significant differences in VCO_2 or VO_2 between the high CHO and high-fat supplements.

Two studies have been conducted evaluating the role of high-fat formulas in weaning patients from mechanical ventilation. Al-Saady et al., in 1988, studied the effects of a modified enteral formula on 20 ventilated patients in an intensive care unit [97]. Patients were randomized to receive either a high-fat formula or a standard formula in amounts equal to their estimated energy requirements. Significant decreases in $PaCO_2$ ($p<0.03$), tidal volume ($p<0.009$), and peak inspiratory pressure ($p<0.046$) were observed in the high-fat group whereas these parameters all increased in the group receiving the standard formula. Time spent on artificial ventilation was 42 % less in the high-fat group compared to the standard formula group ($p<0.001$). Van den Berg et al. in 1994, conducted a similar study with slightly differing results [98]. Their unblinded study compared a high-fat formula with a standard formula in 32 medical patients in the intensive care unit. The RQ during weaning was significantly lower in the high-fat formula group (0.72 ± 0.02 vs. 0.86 ± 0.02; $p<0.01$). There were however, no significant differences in VCO_2 during weaning and both groups had similar successful weaning episodes.

It is important to note that in most of the early reports citing adverse effects with large dextrose intakes, patients received excessive calories (1.7–2.25 times the measured energy expenditure) [99–101]. In a study by Talpers et al, 20 mechanically ventilated patients received either varying amounts of carbohydrate (40, 60, and 75 %) or total kcals (1.0, 1.5, and 2.0 times the basal energy expenditure) [102]. There was no significant difference in $VC0_2$ among the varying carbohydrate regimens. However $VC0_2$ significantly increased as the total kcal intake increased ($p<0.01$). The authors concluded that avoidance of overfeeding is of greater significance than CHO intake in avoiding

nutritionally related hypercapnia. This, along with early anecdotal reports of excessive overfeeding and the results demonstrated by Vermereen and colleagues, lends support for the argument that total calorie intake is more important than intake of CHO in preventing adverse ventilatory effects.

In summary, current clinical guideline recommendations do not support the use of an altered macronutrient enteral formula in patients with chronic pulmonary disease [65, 103, 104]. As with most nutrition support practices, patient monitoring is essential. If challenges in ventilatory management occur with the use of a standard enteral formula, offering an altered macronutrient formula is a potential option.

Acute Kidney Injury

Patients with acute kidney injury are typically hypercatabolic and hypermetabolic, due to their underlying disease state and to the derangements in renal function. This, together with the type of renal replacement therapy (RRT) utilized, greatly influences the patient's energy and protein requirements [105]. Up to 73 % of ICU patients with AKI will require RRT during the course of their ICU stay [7]. Protein requirements in these patients may be significantly higher than the general recommendation of 1.5–2 g/kg body weight [65]. In an evaluation of patients undergoing continuous veno-venous hemofiltration, Bellomo and colleagues reported that a high-protein intake of 2.5 g/kg/day of parenteral amino acids resulted in a slightly negative overall nitrogen balance. The authors attributed this high requirement to losses during the filtration process [106]. Similar results were obtained by Scheinkestel and colleagues in 2003, thus confirming the need for high protein intakes in patients undergoing this type of renal replacement therapy [107].

Standard calorically dense enteral formulas are frequently appropriate for patients with acute kidney injury although to achieve higher protein requirements, supplemental protein may often be required. Ongoing laboratory monitoring of renal excreted electrolytes; potassium, phosphorus and magnesium, is essential when using standard enteral formulas. In patients undergoing continuous veno-venous hemodialysis (CVVHD), renal formulas may not be the most appropriate formula choice. These patients may not require significant fluid restriction and have higher protein requirements as noted above. In addition, losses of electrolytes, specifically phosphorous [108] during CVVHD coupled with very low intakes provided by renal formulations often results in the need for significant electrolyte supplementation. A standard high-protein formula may be best suited for this type of patient.

In patients in whom RRT is delayed or unintended, a calorically dense, reduced protein formula is indicated [10]. Protein requirements for the non-dialyzed patient with chronic renal failure range from 0.55 to 1.0 g/kg/day [105] and can be achieved with reduced protein formulas. In addition to modified protein levels, renal formulas offer alterations in electrolytes. This variation may offer benefit to those patients who are not RRT or in whom the therapy is not achieving its desired results.

Conclusion

Organ failure is common in the critically ill patient. Understanding the metabolic alterations and pathophysiology associated with organ failures including acute and chronic respiratory disease, kidney injury, hepatic disease, and diabetes will allow the clinician to better anticipate challenges in providing adequate nutrition support therapy. The use of specialized formulations may offer clinical benefit in selected patients. However, careful review of the evidence, along with consideration of current evidence-based guideline recommendations, is necessary to determine if use of these formulations is warranted.

References

1. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;5:1–13.
2. Ruberfield G, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353:1685.
3. Cartes I, Penuelas O, Esteban A. Acute respiratory distress syndrome: evaluation and management. Minerva Antesiologica. 2011;78:343–57.
4. Trotter J. Practical management of acute liver failure in the intensive care unit. Curr Opin Crit Care. 2009;15:163–7.
5. Saliba F, Ichai P, Levesque E, Samuel D. Cirrhotic patients in the ICU: prognostic markers and outcome. Crit Care. 2013;19:154–60.
6. Lamiere N, Van BW, Vanholder R. The changing epidemiology of acute renal failure. Nat Clin Pract Nephrol. 2006;2:364–77.
7. Uchino S, Kellum BR, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294:813–8.
8. Matarese LE. Rationale and efficacy of specialized enteral and parenteral formulas. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice: a clinical guide. 2nd ed. Philadelphia: WB Saunders; 1998. p. 263–75.
9. A.S.P.E.N. Board of Directors and Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr 2002;26.
10. Malone AM. The clinical benefits and efficacy in using specialized enteral feeding formulas. Support Line. 2002;24(1):3–11.
11. Ulate KP, Lima Falcao GC, Bielefeld MR, Morales JM, Rotta AT. Strict glycemic targets need not be so strict: a more permissive glycemic range for critically ill children. Pediatrics. 2008;122(4):e898–904.
12. Kong MY, Alten J, Tofil N. Is hyperglycemia really harmful? A critical appraisal of "Persistent hyperglycemia in critically ill children" by Faustino and Apkon (J Pediatr 2005; 146:30-34). Pediatr Crit Care Med. 2007;8(5): 482–5.
13. Thomas MC, Mathew TH, Russ GR, Rao MM, Moran J. Early peri-operative glycaemic control and allograft rejection in patients with diabetes mellitus: a pilot study. Transplantation. 2001;72(7):1321–4.
14. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA, et al. Intra-operative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc. 2005;80(7):862–6.
15. Doenst T, Wijeysundera D, Karkouti K, Zechner C, Maganti M, Rao V, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2005;130(4):1144.
16. Brunkhorst FM, Engel C, Ragaller M, Welte T, Rossaint R, Gerlach H, German Sepsis Competence Network (SepNet), et al. Practice and perception–a nationwide survey of therapy habits in sepsis. Crit Care Med. 2008;36(10):2719–25.
17. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296–327.
18. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med. 2007;35(10):2262–7.
19. Arabi YM, Dabbagh OC, Tamim HM, Al Shimemeri AA, Memish ZA, Haddad SH, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008;36(12):3190–7.
20. 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(13):1283–97.
21. Freire AX, Bridges L, Umpierrez GE, Kuhl D, Kitabchi AE. Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. Chest. 2005;128(5):3109–16.
22. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355(9206):773–8.
23. Mowery NT, Gunter OL, Guillamondegui O, Dossett LA, Dortch MJ, Morris Jr JA, et al. Stress insulin resistance is a marker for mortality in traumatic brain injury. J Trauma. 2009;66(1):145–51.
24. Prakash A, Matta BF. Hyperglycaemia and neurological injury. Curr Opin Anaesthesiol. 2008;21(5):565–9.
25. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6): 1615–25.
26. Lin JN, Tsai YS, Lai CH, Chen YH, Tsai SS, Lin HL, Huang CK, Lin HH. Risk factors for mortality of bacteremic patients in the emergency department. Acad Emerg Med. 2009;16(8):749–55.
27. Del Rio A, Cervera C, Moreno A, Moreillon P, Miro JM. Patients at risk of complications of Staphylococcus aureus bloodstream infection. Clin Infect Dis. 2009;48 Suppl 4:S246–53.

28. Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, AmarCand Study Group, et al. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). Crit Care Med. 2009;37(5):1612–8.
29. Philips BJ, Redman J, Brennan A, Wood D, Holliman R, Baines D, et al. Glucose in bronchial aspirates increases the risk of respiratory MRSA in intubated patients. Thorax. 2005;60(9):761–4.
30. Mowat A, Baum J. Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. N Engl J Med. 1971;284(12):621–7.
31. Bybee JD, Rogers DE. The phagocytic activity of polymorphonuclear leukocytes obtained from patients with diabetes mellitus. J Lab Clin Med. 1964;64:1–13.
32. Bagdade JD, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. Diabetes. 1974;23(1):9–15.
33. Stegenga ME, van der Crabben SN, Blumer RM, Levi M, Meijers JC, Serlie MJ, et al. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood. 2008;112(1):82–9.
34. Takahashi T, Matsuda K, Kono T, Pappas TN. Inhibitory effects of hyperglycemia on neural activity of the vagus in rats. Intensive Care Med. 2003;29(2):309–11.
35. American Diabetes Association. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2007;30 Suppl 1:S48–65.
36. Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and metaanalysis. Diabetes Care. 2005;28:2267–79.
37. McMahon MM, Miles JM. Glycemic control and nutrition in the intensive care unit. Curr Opin Clin Nutr Metab Care. 2006;9:120–3.
38. Yokoyama J, Someya Y, Yoshihara R, Ishii H. Effects of highmonounsaturated fatty acid enteral formula versus high-carbohydrate enteral formula on plasma glucose concentration and insulin secretion in healthy individuals and diabetic patients. J Int Med Res. 2008;36:137–46.
39. Coulston AM. Enteral nutrition in the patient with diabetes mellitus. Curr Opin Clin Nutr Metab Care. 2000;3:11–5.
40. Hebert SL, Nair KS. Protein and energy metabolism in type 1 diabetes. Clin Nutr. 2010;29:13–7.
41. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care. 2003;26:1277–94.
42. Scott JA, King GL. Oxidative stress and antioxidant treatment in diabetes. Ann N Y Acad Sci. 2004;1031:204–13.
43. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78:1471–8.
44. Bagshaw SM, Egi M, George C, Bellomo R, Australia New Zealand Intensive Care Society Database Management Committee. Early blood glucose control and mortality in critically ill patients in Australia. Crit Care Med. 2009;37:463–70.
45. 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.
46. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449–61.
47. Arabi YM, Tamin HM, Rishu AH. Hypoglucemia with intensive insulin therapy in critically ill patient: predisposing factors and association with mortality. Crit Care Med. 2009;37:2536–44.
48. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, German Competence Network Sepsis (SepNet), et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39.
49. Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, et al. A prospective randomised multicentre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009;35:1738–48.
50. Griesdale DE, De Souza R, Van Dam R, Heyland DK, Cook DJ, Malhotra A, et al. Intensive insuline therapy and mortality among critically ill patients. A meta-analysis including NICESUGAR study data. CMAJ. 2009;180:821–7.
51. Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and meta-analysis. Chest. 2010;137:544–51.
52. Mesejo A, Acosta JA, Ortega C, Vila J, Fernández M, Ferreres J, et al. Comparison of a high-protein disease-specific enteral formula with a high-protein enteral formula in hyperglycemic critically ill patients. Clin Nutr. 2003;22(3):295–305.
53. Raup SM, Kaproth P. Hepatic failure. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice: a clinical guide. 2nd ed. Philadelphia: W.B. Saunders; 1998. p. 445–59.

54. Fischer JE. Branched-chain enriched amino acid solutions in patients with liver failure: an early example of nutritional pharmacology. JPEN J Parenter Enteral Nutr. 1990;14:249S–56.
55. Fischer JE. The role of plasma amino acids in hepatic encephalopathy. Surgery. 1975;78:276–90.
56. Cerra FB, Cheung NK, Fischer JF. Disease specific amino acid infusion in hepatic encephalopathy: a prospective, randomized, double-blinded controlled trial. JPEN J Parenter Enteral Nutr. 1985;9:288–95.
57. Michel H, Bories P, Aubin JP, Pomier-Layrargues G, Bauret P, Bellet-Herman H. Treatment of acute hepatic encephalopathy in cirrhotics with branched-chain amino acid enriched versus a conventional amino acid mixture. Liver. 1985;5:282–9.
58. Horst D, Grace ND, Conn HO, Schiff E, Schenker S, Viteri A, et al. Comparison of dietary protein with an oral, branched chain enriched amino acid supplement in chronic portal-systemic encephalopathy: a randomized controlled trial. Hepatology. 1984;4:279–87.
59. Rossi-Fanelli F, Riggio O, Cangiano C, Cascino A, De Conciliis D, Merli M, et al. Branched-chain amino acids vs lactulose in the treatment of hepatic coma: a controlled study. Dig Dis Sci. 1982;27:929–35.
60. Naylor CD, O'Rourke K, Detsky AS, Baker JP. Parenteral nutrition with branched-chain amino acids in hepatic encephalopathy. Gastroenterology. 1989;97:1033–42.
61. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003;124:1792–801.
62. Als-Nielsen B, Koretz R, Gluud L, Gluud C. Branched-chain amino acids for hepatic encephalopathy. Cochrane Database Syst Rev. 2003;2:CD001939.
63. Russell MK, Charney P. Is there a role for specialized enteral nutrition in the intensive care unit? Nutr Clin Pract. 2002;17:156–68.
64. Mizok BA. Nutritional support in hepatic encephalopathy. Nutrition. 1999;15:220–8.
65. McClave S, Martindale R, Vanek V, 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 the American Society for Parenteral and Enteral Nutrition. JPEN J Parenter Enteral Nutr. 2009;33:277.
66. 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.
67. Barr J, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. Chest. 2004;125(4):1446–57.
68. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med. 2004;32(2):350–7.
69. Dickerson RN, Boschert KJ, Kudsk KA, Brown RO. Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition. 2002;18(3):241–6.
70. Arabi YM, Haddad SH, Tamim HM, Rishu AH, Sakkijha MH, Kahoul SH, et al. Near-target caloric intake in critically ill medical-surgical patients is associated with adverse outcomes. JPEN J Parenter Enteral Nutr. 2010;34(3):280–8.
71. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. Am J Respir Crit Care Med. 1995;152((5, pt 1)):1545–8.
72. Hernandez G, Velasco N, Wainstein C, Castillo L, Bugedo G, Maiz A, et al. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care. 1999;14(2):73–7.
73. McClure RJ, Newell SJ. Randomised controlled study of clinical outcome following trophic feeding. Arch Dis Child Fetal Neonatal Ed. 2000;82(1):F29–33.
74. Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, Mechanical Ventilation International Study Group, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA. 2002;287:345–55.
75. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, Nutrition Guidelines Investigators of the ANZICS Clinical trials Group, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA. 2008;300:2731–41.
76. Heyland DK, Dhaliwal R, Day A, Jain M, Drover J. Validation of the Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients: results of a prospective observational study. Crit Care Med. 2004;32:2260–6.
77. Braunschweig CA, Sheean PM, Peterson SJ, Perez SG, Freeis S, Lateef O, et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). JPEN J Parenter Enteral Nutr. 2015;39:13–20.
78. 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;307:795–803.
79. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. Am J Respir Crit Care Med. 2013;188:567–76.

80. Berger MM, Mechanick J. Continuing controversy in the intensive care unit: why tight glycemic control, nutrition support, and nutritional pharmacology are each necessary therapeutic considerations. Curr Opin Clin Nutr Metab Care. 2010;13:167–9.
81. Bonet A, Grau T, Grupo de trabajo de Metabolismo y Nutrición de la SEMICYUC. Multicenter study on incidence of total parenteral nutrition complications in the critically-ill patient. ICOMEP study. Part I. Nutr Hosp. 2005;20:268–77.
82. 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. Crit Care Med. 1999;27:1409–20.
83. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentanoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med. 2006;34:1033–8.
84. Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentanoic acid, gamma-linolenic acid and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med. 2006;34:2325–33.
85. 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;32:596–605.
86. Heller AR, Rossler S, Litz RJ, Stehr SN, Heller SC, Koch R, et al. Omega-3 fatty acids improve the diagnosis-related clinical outcome. Crit Care Med. 2006;34:972–9.
87. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Early versus delayed enteral feeding and omega-3 fatty acid/antioxidant supplementation for treating people with acute lung injury or acute respiratory distress syndrome (the EDEN omega Study) [consultado 16–2-2010]. http://clinicaltrials.gov/show/NCt00609180. Accessed october 14, 2015.
88. Stapleton RD, Martin TR, Weiss NS, Crowley JJ, Gundel SJ, Nathens AB, et al. A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. Crit Care Med. 2011;39:1655–62.
89. Grau-Carmona T, Morán-García V, García-de-Lorenzo A, Herasde-la-Calle G, Quesada-Bellver B, López-Martínez J, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and antioxidants on the outcome of mechanically ventilated, critically ill, septic patients. Clin Nutr. 2011;30(5):578–84.
90. Garfinkel F, Robinson R, Price C. Replacing carbohydrate calories with fat calories in enteral feedings for patients with impaired respiratory function. JPEN J Parenter Enteral Nutr. 1985;9:106.
91. Baker JP, Detsky AS, Stewart S, Whitwell J, Marliss EB, Jeejeebhoy KN. Randomized trial of total parenteral nutrition in critically ill patients: metabolic effects of varying glucose-lipid ratios as the energy source. Gastroenterology. 1984;87:53–9.
92. Brown RO, Heizer WD. Nutrition and respiratory disease. Clin Pharm. 1984;3:152–61.
93. Angelillo VA, Sukhdarshan B, Durfee B, Dahl J, Patterson AJ, O'Donohue Jr WJ. Effects of low and high carbohydrate feedings in ambulatory patients with chronic obstructive pulmonary disease and chronic hypercapnia. Ann Intern Med. 1985;103:883–5.
94. Akrabawi SS, Mobarhan S, Stoltz R, Stoltz R, Ferguson PW. Gastric emptying, pulmonary function, gas exchange, and respiratory quotient after feeding a moderate versus high fat enteral formula meal in chronic obstructive pulmonary disease patients. Nutrition. 1996;12:260–5.
95. Kuo CD, Shiao GM, Lee JD. The effects of high-fat and high-carbohydrate diet loads on gas exchange and ventilation in COPD patients and normal subjects. Chest. 1993;104:189–96.
96. Vermeeren MA, Wouters EF, Nelissen LH, van Lier A, Hofman Z, Schols AM. Acute effects of different nutritional supplements on symptoms and functional capacity in patients with chronic obstructive pulmonary disease. Am J Clin Nutr. 2001;73:295–301.
97. Al-Saady NM, Blackmore CM, Bennett ED. High fat, low carbohydrate, enteral feeding lowers PaCO2 and reduces the period of ventilation in artificially ventilated patients. Intensive Care Med. 1989;15:290–5.
98. van den Berg B, Bogaard JM, Hop WC. High fat, low carbohydrate, enteral feeding in patients weaning from the ventilator. Intensive Care Med. 1994;20:470–5.
99. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with CopD: a meta-analysis. Chest. 2000;117:672–8.
100. Covelli HD, Black JW, Olsen MS, Beekman JF. Respiratory failure precipitated by high carbohydrate loads. Ann Intern Med. 1981;95:579–81.
101. Askanazi J, Rosenbaum SH, Hyman AI, Silverberg PA, Milic-Emili J, Kinney JM. Respiratory changes induced by the large glucose loads of total parenteral nutrition. JAMA. 1980;243:1444–7.
102. Dark DS, Pingleton SK, Kerby GR. Hypercapnia during weaning. A complication of nutritional support. Chest. 1985;88:141–3.
103. 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.

104. Critical care nutrition. Canadian clinical practice guidelines for nutrition support in adult critically ill patients; http://www.criticalcarenutrition.com/docs/cpg/4.2ahighfat_FINAL.pdf. Accessed 23 Mar 2014.
105. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25:210–23. doi:10.1016/j.clnu.2006.01.021.
106. Goldstein DJ, Abrahamian-Gebeshian C. Nutrition support in renal failure. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice: a clinical guide. 2nd ed. Philadelphia: W.B. Saunders; 1998. p. 447–71.
107. Bellomo R, Tan H, Bhonagiri S, Gopal I, Seacombe J, Daskalakis M, et al. High protein intake during continuous hemodiafiltration: impact on amino acids and nitrogen balance. Int J Artif Organs. 2002;25:261–8.
108. Scheinkestel C, Adams F, Mahony L, Bailey M, Davies AR, Nyulasi I, et al. Impact of increasing parenteral protein loads on amino acid levels and balance in critically ill anuric patients on continuous renal replacement therapy. Nutrition. 2003;19:733–40.

Chapter 11
Management of the Obese Patient

Roland N. Dickerson

Keywords Obesity • Enteral nutrition • Parenteral nutrition • Hyperglycemia • Insulin resistance • Insulin • Hypercapnia • Steatosis • Fatty liver disease • Nitrogen balance • Nitrogen • Protein • Weight loss • Fat oxidation • Lipolysis • Diabetes mellitus • Carbohydrate • Clinical outcomes • Body mass index • Requirements • Vitamins • Thiamine • Vitamin B12 • Essential fatty acid deficiency • Energy • Energy deficit • Hypercaloric • Hypocaloric • Eucaloric • Energy expenditure

Key Points

- Hospitalized patients with obesity are at high risk for overfeeding complications due to prevailing comorbidities and difficulty for estimating caloric requirements.
- Hypocaloric, high-protein nutrition therapy promotes nitrogen accretion with less potential for hyperglycemia, hypercapnia, and fatty liver disease when compared to hypercaloric nutrition therapy.
- Hypocaloric, high-protein nutrition therapy is more difficult to achieve with enteral nutrition than parenteral nutrition.
- Nitrogen balance is the most practical clinical marker for determining the anabolic success of a hypocaloric, high-protein nutrition regimen. High-quality prospective randomized trials, however, are lacking to support this approach.

Introduction

Data from the USA (2009–2010) indicates that 36 % of adult men and women are obese, at least as defined by a body mass index (BMI) of $\geq$30 kg/m^2 [1]. The prevalence of obesity is also increasing worldwide [2]. As many as 25 % [2] to 31 % [3] of patients in the intensive care unit (ICU) are obese. Thus, the intensive care clinician will encounter dilemmas associated with the metabolic care of the obese patient. Unfortunately, the availability of outcomes research guiding optimal nutrition therapy

R.N. Dickerson, PharmD, BCNSP (✉)
Department of Clinical Pharmacy, University of Tennessee Health Science Center,
881 Madison Avenue, Suite 345, Memphis, TN 38163, USA
e-mail: rdickerson@uthsc.edu

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_11,

for hospitalized patients with obesity is limited. This chapter focuses on the scientific evidence for the metabolic care of hospitalized patients with obesity. In addition, practical suggestions and techniques for delivering, managing, and monitoring nutrition therapy are provided.

Impact of Obesity upon Clinical Outcome in Hospitalized Patients

The diagnosis of obesity is currently based on body mass index (BMI) and is organized into three classes of obesity (Table 11.1). However, BMI alone is not sufficient for assessing the severity of obesity and its associated risk. The risk of adverse clinical outcomes is influenced by the presence of comorbid conditions, including diabetes, hyperglycemia, hypoventilation syndrome, and other associated metabolic perturbations. These outcomes are further influenced by any modifications made to the patient's clinical care due to their obesity.

Studies comparing clinical outcomes for obese versus non-obese patients are conflicting. Some studies indicate patients with obesity have worse outcomes, others show no difference, whereas some suggest improved outcomes. Many of these studies have limitations and are often fraught by retrospective study design and an inadequate number of patients [4]. Further limiting some of the large studies is that multivariate analysis is used to control for the presence of diabetes, hyperglycemia, cardiovascular disease, and other comorbidities associated with obesity. By negating these factors, the data may be biased towards omitting those obese patients with an unfavorable metabolic profile [3]. For example, in one study, hyperglycemia was discovered to be an independent predictor of outcome for obese patients [5]. The investigators concluded that when controlling the dataset for hyperglycemia, there was no effect of Class III obesity when compared to those patients with Class I or II obesity upon survival. However, patients with Class III obesity have a greater incidence of insulin resistance, diabetes, and a pre-existing inflammatory state, all of which are due to obesity. In turn, these factors predispose to hyperglycemia. By statistically eliminating the effect of hyperglycemia, this analysis may be unintentionally eliminating the adverse effects of obesity itself.

Moderate to severe obesity (Class II and III) is a risk factor for increased morbidity or mortality compared to non-obese patients [6–10]. Other studies indicate that obesity increases mortality [1], has no effect [11–14], or reduces mortality [15]. These divergent findings are likely due to heterogeneity regarding the etiology for admission to the intensive care unit, presence of single versus multi-system organ failure [16], adjustment for confounders that may be attributed to or augmented by the presence of obesity [5], duration of stay in the ICU [11], and duration of ventilator dependency [8, 12, 14, 17]. The reason for the patients' admission (the acuity of the initial stressor leading to hospitalization) and subsequent stress-inducing events (or "multiple metabolic hits") such as multiple operative procedures dictates their propensity towards adverse clinical outcomes.

The presence or impact of nutrition therapy was not evaluated in many studies that examined the relationship between severity of obesity and clinical outcomes. Lack of evaluation of nutrition therapy is a significant shortcoming as nutrition therapy may influence clinical outcomes. Early initiation of nutrition therapy decreases infectious morbidity for critically ill surgical and trauma patients [18]. Provision of

Table 11.1 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

higher amounts of protein has been associated with improved survival during critical illness in some studies [19, 20]. Preliminary evidence also indicates excessive caloric intake worsens morbidity for critically ill patients with obesity [21]. Thus, early or delayed nutrition therapy, as well as the composition and amount of nutrition therapy, could have influenced mortality and morbidity in these studies.

Recent data suggests an inverse J-shaped curve may be present when relating BMI to survival [1, 15, 22, 23]. 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, 15, 22, 23]. Etiologies for this presumed "obesity paradox" are not clear [4]. Emerging research indicates that adipose cells may mediate a range of short-term beneficial functions in response to sepsis or stress. Adipose tissue is not just a passive depot for excess energy but also is a functional organ capable of altering metabolism by secretion of immune-modulating chemokines, apoproteins, and eicosanoid-derived compounds that may augment the immune response by neutralizing lipopolysaccharide, stimulate the clearance of inflammatory debris, and improve bacterial clearance [24–26]. Based on the current evidence, 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.

Nutritional Assessment

Nutritional assessment of the patient with morbid obesity is challenging as physical assessment techniques are not precise. A potential detriment to achieving positive clinical outcomes for 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 [27, 28]. Obesity with a history of limited mobility or physical activity prior to hospital admission is a clue for the presence of significant sarcopenia, as is prolonged illness or hospitalization. Gross physical examination of the sarcopenic obese patient by a naïve or inexperienced clinician may erroneously assume that the patient is nutritionally adequate because of their caloric abundance. Even worse, nutrition therapy may be a low priority in the mind of the uniformed clinician during that patient's hospitalization.

Delayed or intentional avoidance of nutrition therapy may speed depletion of lean tissues. Recent data indicates that obese patients have a higher protein turnover rate with a higher breakdown rate than synthesis, which leads to a more negative net protein balance when compared to non-obese counterparts [29]. This phenomenon has been partially attributed to obesity-associated insulin resistance, which impairs insulin's anabolic action on protein metabolism [29]. When obesity is compounded by critical illness, body protein losses become exaggerated as the critically ill patient experiences a protein catabolic rate 3–4 times higher than that of a non-stressed normal subject [30]. Lack of attention to nutrition therapy of the obese patient could result in worsened clinical outcomes including delayed recovery and the need for subsequent physical rehabilitation. Recent guidelines from the American Society for Parenteral and Enteral Nutrition recommend that nutritional assessment and development of a nutrition support plan be implemented within 48 h of ICU admission for the critically ill patient with obesity [4].

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

Obesity-related comorbidities (Table 11.2) complicate the metabolic management of the hospitalized patient with obesity. It is common for hospitalized obese patients to exhibit more than a single comorbidity. Excessive caloric intake leads to a worsening effect on these comorbidities and extends beyond amplifying pre-existing abundant caloric reserves. The patient's nutritional regimen may also need to be modified for hyperglycemia, hyperlipidemia, hypercapnia, congestive heart failure, or nonalcoholic fatty liver disease.

Table 11.2 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

Insulin resistance is common for patients with obesity, especially those with Class III obesity [31]. Critically ill patients with sepsis or traumatic injuries experience a post-receptor insulin resistance with increased counter-regulatory hormone production resulting in substantial hyperglycemia [32]. When obesity and critical illness compound nutrition therapy, hyperglycemia is a prevalent complication and requires vigilance. Trauma [33–35], cardiothoracic surgery [36], and thermally injured [37] patients benefit from tighter glycemic control (e.g., blood glucose concentrations [BG] less than 140–150 mg/dL) than that required of other populations (e.g., medical ICU patients) [38]. A lower target BG range for the critically ill obese patient is challenging to achieve. Choban found a detrimental influence of increased caloric intake upon glycemic control in obese patients [39]. Despite similar carbohydrate intakes, these data indicate 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 [40].

Hypertriglyceridemia is more prevalent in patients with obesity versus the non-obese. Impaired intravenous triglyceride clearance may occur in obese in patients given intravenous lipid emulsion as part of parenteral nutrition or as propofol pharmacotherapy. Severe hypertriglyceridemia can impair immune function and reticuloendothelial system clearance, cause hepatic fat accumulation, and induce acute pancreatitis. Improvement in glycemic control with insulin therapy can improve hypertriglyceridemia in patients with insulin-dependent diabetes mellitus [41] and may allow for the use and clearance of intravenous lipid emulsion. However, hypertriglyceridemia may not be fully corrected with appropriate glycemic control for those with non-insulin dependent diabetes mellitus [41] and lipid emulsion clearance may remain impaired.

Patients with morbid obesity have a prolonged duration of mechanical ventilation compared to their non-obese counterparts [8, 14, 17, 42]. Approximately 10–20 % of patients with obesity are presumed to have obesity hypoventilation syndrome [2]. This is separate from obstructive sleep apnea which may occur in up to 45 % of patients with obesity [2]. Obesity hypoventilation syndrome is characterized by hypercapnic respiratory failure (e.g., $pCO2 > 45$ mmHg) and alveolar hypoventilation ($pO2 < 75$ mmHg) [43]. These changes result in greater minute ventilation requirements. Aggressive nutrition therapy with higher amounts of total calories worsens hypercapnia [44, 45]. A significant increase in carbon dioxide production from parenteral nutrition therapy occurs when total energy intake exceeds 1.3 times the predicted or measured resting energy expenditure [44, 45]. Thus, caution regarding the amount of calories given to ventilator-dependent patients with obesity is pivotal when planning a nutritional regimen.

Because of extreme body mass and the requirement for an increased circulating blood volume, patients with morbid obesity can develop myocardial hypertrophy, decreased compliance, and hypertension. These cardiovascular alterations may eventually lead to congestive heart failure, total body fluid overload, a higher risk for arrhythmias, and sudden death [43]. In severe cases of obesity hypoventilation syndrome, extreme pulmonary failure may lead to right heart failure with pulmonary edema [43]. Restriction of fluid intake may be required. However, use of weight or body surface area estimates of fluid requirements could result in a marked overestimate of fluid requirements. Conversely,

underestimation of fluid requirements is also common, especially during resuscitation. Obese patients are more prone to hypovolemic shock, mortality, and organ failure with inadequate fluid resuscitation, than patients of normal BMI [46]. In summary, extreme care in avoiding fluid overload and dehydration is mandatory for the critically ill patient with obesity.

Caloric overfeeding with parenteral nutrition for a duration as short as 10–14 days is an established cause of fatty infiltration of the liver and hepatic steatosis [47], and must be avoided, in general. The critically ill patient with morbid obesity is at risk for development of non-alcoholic fatty liver disease (NAFLD) and hepatic steatosis relative to their non-obese counterparts. The prevalence of NAFLD ranges from 57 % of overweight subjects to 98 % of nondiabetic obese patients; one-third of obese patients have advanced disease (e.g., hepatic steatosis) [48]. Older patients with obesity are at risk for NFALD due to their prolonged duration of hypertension, obesity, hyperlipidemia, and diabetes [47, 48].

Defining Energy and Protein Requirements for the Hospitalized Patient with Obesity

To avoid overfeeding, an accurate assessment of energy needs is required. Without measurement of resting energy expenditure by indirect calorimetry, defining caloric requirements for the hospitalized patient with obesity by the use of predictive formulas is limited [49]. The 2013 guidelines for the nutrition support of the hospitalized adult patients with obesity from the American Society of Parenteral and Enteral Nutrition [4] recommends the use of the Penn State equation or the modified Penn State equation (for patients over 60 years of age) for estimating energy expenditure of ventilator-dependent, critically ill patients (Table 11.3) [50–52]. However, these equations tend to accurately estimate ($\pm$10 %) resting energy expenditure, determined by indirect calorimetry, of critically ill, mechanically ventilated patients only about 70 % of the time [50–52]. For less sick, nonmechanically ventilated, hospitalized patients with obesity, clinicians have favored the use of the Mifflin equations [53] to estimate resting energy expenditure [4] (see Table 11.3). However, the Mifflin equations [53] were developed in unstressed obese subjects. This may limit their accuracy in the hospitalized population.

Because of the high risk for overfeeding complications in hospitalized patients with obesity and the uncertainty of accurately estimating resting energy expenditure, many clinicians have adopted the use of a hypocaloric, high-protein nutrition regimen [21, 31, 39, 54–57]. According to clinical guidelines, hypocaloric, high-protein nutrition therapy may be considered as long as the patient does not have severe renal or hepatic dysfunction [4]. To understand the rationale for this type of therapy, it is

Table 11.3 Predictive methods for estimating resting energy expenditure (REE) for hospitalized patients with obesity

1. Ventilator-dependent, critically ill patients with obesity <60 years of age [51, 52]:
REE (kcal/day) = (Mifflin REE × 0.96) + (Tmax × 167) + (Ve × 31) − 6212
whereas Tmax is maximum temperature for the day (°C) and Ve is minute ventilation (L/min)
2. Ventilator-dependent, critically ill patients with obesity ≥60 years of age [100]:
REE (kcal/day) = (Mifflin REE × 0.71) + (Tmax × 85) + (Ve × 64) − 3085
whereas Tmax is maximum temperature for the day (°C) and Ve is minute ventilation (L/min)
3. Non-ventilator-dependent, non-critically ill hospitalized patients with obesity
Mifflin-St. Jeor Equation [53] (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

necessary to first review determination and interpretation of nitrogen balance, the influence of caloric and protein intakes upon nitrogen balance, and the impact of differing caloric-protein intake combinations upon changes in body composition.

The most common clinical technique to assess adequacy of a nutritional regimen with respect to protein requirements is nitrogen balance. Nitrogen balance is 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 "nitrogen equilibrium."

To determine nitrogen balance, a 24-h urine collection for urea nitrogen excretion is obtained and protein intake from the parenteral or enteral nutrition from that same 24-h period is ascertained. The following equation [58] may be used for assessing nitrogen balance (NB) during critical illness:

NB (g/day) = Protein Intake (g/day)/6.25 − Urine Urea Nitrogen (g/day)/0.85 − 2 [1]

This nitrogen formula is more accurate for critically ill patients than the following classic NB formula:

NB = Protein Intake/6.25 − Urine Urea Nitrogen − 4

The former equation is more accurate for critically ill patients as the factor of 4 g in the latter assumes only 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 (e.g., ammonia, creatinine, free amino acids) is usually significantly greater than the assumed 2 g and sometimes as much as 4–6 g/day [58].

In current practice the goal is considered to be achieving a 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 [59, 60]. It is accepted that a nitrogen balance of about −5 g/day or better during an aggressive protein intake within 2–2.5 g/kg/day is a reasonable goal among obese and non-obese critically ill patients with multiple traumatic injuries until the catabolic stress is diminished or abated [30]. The rationale for use of nitrogen balance as a marker for adequate protein intake may be questioned due to the lack of large, prospective randomized trials examining nitrogen balance-guided protein intake upon clinical outcomes for critically ill patients. However, limited evidence from small studies in non-obese critically ill patients suggest increasing protein intake above normal maintenance requirements with improvement in nitrogen balance may be of benefit. Data from one prospective observational cohort study in 113 critically ill, mixed ICU patients, a higher protein intake (1.5 ± 0.3 g/kg/day versus 1.1 ± 0.2 g/kg/day or 0.8 ± 0.3 g/kg/day) led to a significantly improved nitrogen balance (-2.6 ± 7.5 g/day versus -4.6 ± 5.4 g/day and -6.6 ± 5.4 g/day, respectively) as well as a trending improvement in ICU mortality (16 % versus 24 % and 27 %, respectively) [19]. In a prospective randomized design, 50 critically ill patients who required continuous renal replacement therapy received either 1.5, 2, or 2.5 g/kg/day of protein with a caloric intake designed to match measured or predicted energy requirements. Nutrition therapy was given via the parenteral route. The investigators found that nitrogen balance was improved by increasing protein intake and for every 1 g/day increase in nitrogen balance, the probability of survival increased by 21 % ($p = 0.03$, odds ratio of 1.21) [61]. Current guidelines recommend use of nitrogen balance for assessing adequacy of protein intake for hospitalized patients with obesity [4]. Despite the lack of clinical outcomes data to support the use of nitrogen balance in critically ill patients with obesity, its use is recommended; however, further research is clearly needed.

Achievement of nitrogen equilibrium or positive nitrogen balance has been accomplished in unstressed non-obese nutritionally depleted patients by altering caloric intake, protein intake, or both. The relationship between calorie and protein intake upon nitrogen balance in these patients is depicted in Fig. 11.1 [62, 63]. At a fixed protein intake, nitrogen balance increases rapidly as calories are

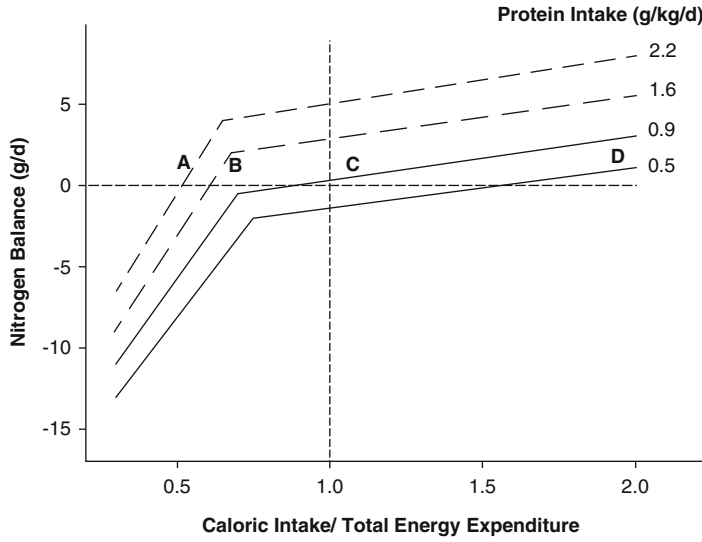


Fig. 11.1 Potential relationship between calorie and protein intakes on nitrogen balance. The *dashed lines* represent protein intakes that could achieve net protein anabolism during hypocaloric nutrition therapy. Points *A* and *B* illustrate achievement of nitrogen equilibrium at caloric intakes less 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

increased until a caloric intake of about 60–70 % of total energy expenditure is achieved. Once 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. 11.1 illustrate achievement of nitrogen equilibrium at a caloric intake less than energy expenditure when provided a higher 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 achievement of nitrogen equilibrium with a low protein intake and a very high caloric intake. Thus, the same nitrogen balance (slightly positive or equilibrium) can be achieved by four 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 among each regimen, each of these regimens when given to unstressed, nutritionally depleted, non-obese patients will result in different body composition changes. The low-calorie, high-protein regimens (points A and B) will likely result in lean body mass gain and body fat loss whereas the moderate-calorie and -protein regimen (point C) will result in lean body and body fat maintenance (possibly some minor gain in both compartments) [64–66]. 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 [64–66].

During critical illness, however, 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-labelled 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 resolves [59, 60]. Although total body protein declines during critical illness in non-obese patients despite nutrition support [67], the rate of net protein catabolism and total body protein loss is reduced in patients receiving adequate nutrition, as opposed to those who are not fed [59, 60]. An aggressive protein intake of 2–2.5 g/kg/day will achieve nitrogen equilibrium in only about half of non-obese critically ill patients during the first 5–14 days post-admission to the trauma ICU [30]. To ascertain if increases in caloric intake will improve nitrogen balance and decrease skeletal muscle catabolism (as reflected by urinary 3-methylhistidine excretion) in critically ill trauma

patients, Frankenfield randomized 30 non-obese 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 [68]. 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) was noted among the different caloric intake groups.

Increasing caloric delivery to critically ill, thermally injured patients will result in a significant increase in total body fat especially when caloric intake exceeds 1.2 times the measured resting energy expenditure [69]. Additionally, increasing caloric intake had no significant impact upon improving lean body mass [69]. These data suggest that protein intake has a more profound effect than caloric intake on total body protein synthesis, net protein catabolism, and nitrogen balance [70], but has minimal impact on skeletal muscle loss during critical illness [69, 70].

These data serve as the theoretical basis for providing hypocaloric, high-protein nutrition therapy for hospitalized patients with obesity. By providing a conservative caloric intake, the risk of developing complications associated with overfeeding such as worsening hyperglycemia, hypercapnia, and hepatic fat accumulation would likely be minimized. A conservative caloric intake may also result in increased lipolysis and net fat oxidation with fat weight loss [56], which may be a welcome secondary benefit particularly if the patient demonstrates morbid complications from their obesity

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

It is important to differentiate between hypocaloric high protein feeding and permissive underfeeding. There is confusion among practitioners and researchers regarding use of these terminologies. Often used interchangeably, these two terms describe distinctly different therapies. Permissive underfeeding indicates that the patient is intentionally allowed to receive less than "goal intake" for BOTH calories and protein. The intent of a hypocaloric, high protein regimen is to provide only a calorie deficit while ensuring a protein intake higher than would be required for maintenance needs. In one study, 60-day mortality was worse when inadequate protein intake (46 g of protein/day or 0.4 g/kg/day) was given during hypocaloric (1000 kcal/day or 9 kcal/kg/day) feeding [71]. Therefore, it is recommended that caloric underfeeding with a low protein intake be avoided for the seriously ill, hospitalized patient with obesity.

Table 11.4 summarizes the current literature on hypocaloric, high protein nutrition therapy for surgical and trauma patients with obesity. Dickerson et al. reported the first case series of use of hypocaloric, high protein parenteral nutrition therapy in 13 postoperative obese patients with complications of sepsis from gastric anastomotic leaks, abscesses, fistulae, or wound dehiscence [56]. Patients received 52 % of measured resting energy expenditure as nonprotein calories (or about 70 % of measured resting energy expenditure as total calories) and 2.1 g/kg ideal body weight/day of protein. Patients achieved positive nutritional and clinical outcomes as assessed by nitrogen balance and by closure of fistulae, resolution of abscess cavities, and wound closure.

This case series was followed by two small prospective, randomized, controlled trials from the Ohio State University Medical Center comparing a hypocaloric, high-protein regimen to a higher calorie and isonitrogenous parenteral nutrition regimen [39, 54]. In the first study [54], caloric intake was based on measured resting energy expenditure. Patients received either hypocaloric (50 % of measured energy expenditure as nonprotein calories) or eucaloric (100 % of measured energy expenditure) parenteral nutrition therapy [54]. Protein intakes were similar at 2.0 and 2.2 g/kg ideal body weight/day, respectively. No significant differences in nitrogen balance or clinical outcomes were observed between groups. In the second study [39], calorie dosing was weight based rather than

Table 11.4 Summary of clinical studies with hypocaloric, high-protein therapy in hospitalized patients with obesity

Author, year	Study design	Patient population	Study groups	Route	No. Pts	WT/ BMI/%IBW	Total caloric intake (kcal/ kg/day)	Protein intake (g/kg IBW/day)	Duration of PN/EN (d)	Nutritional outcomes	Clinical outcome
Dickerson, 1986 [56]	Prospective case series	Surgical	Not applicable	PN	13	127±60 kg 208±114 %	25 IBW	2.1±0.6	48±31	NB: +2.4±1.9 g/day Incr Alb, TIBC, decr RQ, weight loss	Healed wounds, closed fistulae
Burge, 1994 [54]	Randomized controlled trial	Surgical	Hypocaloric vs. eucaloric	PN	9	90±12.5 kg 33±6 kg/m^2 152±22 %	22 IBW	2.0±0.6	10±3	NB: +1.3±3.6 g/day	Not evaluated
					7	102±20 kg 35±4 kg/m^2 167±20 %	42 IBW	2.2±0.4		NB: +2.8±6.9 g/day	
										Both groups lost weight; lower RQ with hypocaloric group	
Choban, 1997 [39]	Randomized controlled trial	Surgical, SICU	Hypocaloric vs. eucaloric	PN	16	97±19 kg 36±5 kg/m^2 165±26 %	22 IBW	2.0±0.1	10±3	NB: +4.0±4.2 g/day	No difference in mortality, LOS
					14	90±17 kg 34±6 kg/m^2 160±26 %	36 IBW	2.0±0.1	11±2	NB: +3.6±4.1 g/day	
										No difference in Alb, SUN change, weight change; trending incr in insulin requirements for eucaloric group	
Liu, 2000 [76]	Retrospective	Surgical	Age<60 yo	PN	18	97±16 kg 34±5 kg/m^2 143±26 %	18 CBW	1.8±0.4	13±13	NB: +3.4±3.9 g/day	No difference in morbidity or mortality
			Age≥60 yo		12	84±20 kg 31±5 kg/m^2 141±14 %	18 CBW	1.9±0.3	13±8	NB: +0.2±5.0 g/day	
										No difference in Alb, transferrin change, minimal weight change	

(continued)

Table 11.4 (continued)

Author, year	Study design	Patient population	Study groups	Route	No. Pts	WT/ BMI/%IBW	Total caloric intake (kcal/ kg/day)	Protein intake (g/kg IBW/day)	Duration of PN/EN (d)	Nutritional outcomes	Clinical outcome
Dickerson, 2002 [21]	Retrospective	Trauma ICU	Hypocaloric vs. eucaloric	EN	28	118±41 kg 41±14 kg/m^2 188±65 %	22 IBW	2.0±0.5[a]	15±11	NB: −2.7±5.9 g/day	Decreased ICU stay, decreased antibiotic days, trending decrease in ventilator days. No diff in mortality
					12	102±36 kg 36±12 kg/m^2 168±62 %	30 IBW	2.0±0.4[a]	26±15	NB: −1.4±5.8 g/d	
										Both groups increased PA, no change Alb	
Choban and Dickerson, 2005 [31]	Retrospective	Surgical, SICU, trauma ICU	BMI 30-39.9 vs. BMI≥40	PN and EN	48	97±31 kg 35±9 kg/m^2	Regression analysis for determination of protein requirements to achieve nitrogen equilibrium from two different medical centers			ICU patients: BMI 30–39.9: ~2 g/kg IBW/d BMI>40: ~2.5 g/kg IBW/d	
					22	122±33 kg 44±12 kg/m^2				Non ICU patients: BMI 30–39.9: ~1.7 g/kg IBW/d BMI>40: ~1.8 g/kg IBW/d	
Hamilton, 2011 [57]	Retrospective case series	Post-bariatric surgery	Not applicable	PN	23	113 kg 40 kg/m^2	14 CBW	1.2 CBW	1.5 months.	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 [55]	Retrospective	Trauma ICU	<60 yo	PN and EN	41	105±21 kg 35±5 kg/m^2	18 IBW	1.9	31±24	NB: -4.9±9.0 g/day	No difference in ICU LOS, ventilator days, hospital LOS, mortality
			≥60 yo		33	105±26 kg 35±6 kg/m^2	21 IBW	2.1	29±13	NB:-3.2±5.7 g/day	
										Both groups at 2.3 g/kg during NB	
										Similar changes in PA; higher SUN for older patients	

Alb serum albumin concentration, *BMI* body mass index (kg/m^2), *CBW* current body weight, *decr* decreased, *EN* enteral nutrition, *IBW* ideal body weight, *ICU* intensive care, *Incr* increased, *LOS* length of stay, *mo* months, *No* number of, *NB* nitrogen balance, *Pts* patients, *PN* parenteral nutrition, *RA* respiratory quotient, *SICU* surgery intensive care unit, *SUN* serum urea nitrogen, *TIBC* total iron binding capacity, *yo* years old

[a]During the NB study

titrated to measured resting energy expenditure. Patients were given either 22 kcal/kg of ideal body weight/day or 30 kcal/kg of ideal body weight/day. Protein intake was 2 g/kg of ideal body weight/day for both groups. No differences in nitrogen balance or clinical outcomes were observed between groups (see Table 11.4).

In 2002, Dickerson and colleagues retrospectively examined the impact of hypocaloric versus eucaloric enteral feeding in 40 critically ill trauma patients with obesity. This study was different from the previously published work that was available at that time in that all patients were given enteral nutrition rather than parenteral nutrition. Additionally, all patients were critically ill, ICU patients [21] as opposed to a non-ICU or mixed ICU/non-ICU population with the previous studies. Patients received either hypocaloric feeding (<25 kcal/kg ideal body weight/day) or eucaloric feeding (25–30 kcal/kg ideal body weight/day). Protein goals were 2 g/kg ideal body weight/day for both groups. There was no difference in nitrogen balance between groups. Both groups were in negative nitrogen balance on average (see Table 11.4), presumably due to the hypercatabolic state following multiple traumatic injuries [30]. Unlike previous studies that indicated no difference in clinical outcomes between hypocaloric and eucaloric feeding groups, hypocaloric feeding in this study was associated with improved clinical outcomes compared to eucaloric feeding [21]. This was a small, retrospective cohort study and 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 limited amount of published studies and unavailability of large trials, the use of hypocaloric, high protein nutrition therapy for the hospitalized obese patient has been gaining popularity. Two guidelines and an opinion paper [4, 72, 73] recommend this mode of therapy for hospitalized patients with obesity, as long as the patient does not have severe renal or hepatic dysfunction.

Specialized Considerations and Potential Exceptions to the Use of Hypocaloric, High-Protein Nutrition Therapy

Significant Renal or Hepatic Disease

Patients with significant renal or hepatic disease may not be able to tolerate a large protein load due to impending uremia or worsening encephalopathy. One empiric approach for those is to liberalize the caloric intake and reduce protein intake. This approach stems from the interrelationship between calorie and protein intake upon nitrogen balance (see Fig. 11.1). If a reduced protein intake is mandatory, than an increased caloric intake will be required to achieve an equivalent nitrogen balance.

Under protein-restrictive conditions, the clinician could design a regimen that will provide a caloric intake similar to or less than the Penn State equations [50–52] for ventilator-dependent ICU patients or the Mifflin-St. Joer equations for non-ICU hospitalized patients (see Table 11.3). Extreme care must be undertaken when liberalizing calories, and the patient must be closely monitored for complications such as hyperglycemia and hypercapnia. It is important to note that this empiric approach, which reflects the author's clinical practice, has not been studied, but is provided for potential consideration. Once hemodialysis or continuous renal replacement therapy (CRRT) is initiated, the picture alters considerably. Hemodialysis or CRRT remove amino acids from the plasma, requiring a higher protein intake. A higher protein intake can be tolerated once dialysis is initiated [72, 74, 75]. However, it is unclear what amount of calories should be provided under these conditions. In critically ill patients with obesity and with acute kidney injury and who are on dialysis, there are no data to support the use of low-calorie high-protein nutritional intake.

Class III Obesity

Data from Choban and Dickerson [31] indicated that critically ill patients with Class III obesity required a protein intake of about 2.5 g/kg ideal body weight/day to achieve nitrogen equilibrium, as compared to about 2 g/kg ideal body weight/day for those with Class I and II obesity. For non-critically ill, hospitalized patients with obesity, protein requirements were similar at 1.8 and 1.7 g/kg ideal body weight/day, respectively. Thus, the severity of obesity may mandate different initial protein goals. As with most similar studies, clinical outcomes were not studied.

Older Patients

It has been questioned whether older (e.g., ≥ 60 years of age) hospitalized patients with obesity respond effectively to hypocaloric, high protein nutrition therapy [76]. Despite similar protein and energy intakes, Liu and colleagues noted that nitrogen balance was lower for the older patient group compared to younger patients during hypocaloric, high-protein feeding (see Table 11.4) [76].

Decreased sensitivity of muscle to anabolic stimuli, including amino acids, occurs during aging [77, 78]. As a result, older healthy subjects may need more protein to achieve the same nitrogen balance as younger subjects. Recent data indicates that this age-dependent phenomenon also occurs during critical illness in non-obese patients, but can be overcome by giving a sufficient amount of protein [55]. The potential for azotemia is a concern when providing high protein intakes to older patients, as required for hypocaloric, high-protein nutrition therapy. Aging is associated with a decline in renal function that may not be detected by serum creatinine concentration alone. A serum creatinine concentration in the "normal range" for an elderly person may be equivalent to an abnormally increased serum creatinine concentration for a young person because older patients have less muscle mass (the source of creatinine appearance in the serum). Thus, the healthy older person with good renal function should have a lower serum creatinine concentration than that of a healthy younger person with the same glomerular filtration rate [79]. Although the decrease in glomerular filtration rate that occurs with aging is much less than necessary to elicit symptoms of renal failure [80], concern is often expressed by clinicians about prescribing aggressive protein intakes to older patients due to anticipation of a decreased renal functional reserve [81], resulting in an increase in serum urea nitrogen concentration.

Dickerson and colleagues examined nitrogen balance and clinical outcomes in response to Liu's study [76] regarding hypocaloric, high-protein nutrition therapy in older (≥60 years of age) versus younger adult critically ill trauma patients with obesity (see Table 11.4) [55]. When given an isonitrogenous regimen of 2.3 g/kg ideal body weight/day (0.4–0.5 g/kg ideal body weight/day higher dose than that given in the Liu study), nitrogen balance was equivalent between older and younger age groups. These data indicate that if sufficient protein is given, anabolic resistance associated with aging can be overcome. Clinical outcomes of survival, duration of ICU stay, hospital length of stay, and duration of mechanical ventilation were similar between age groups. However, older patients experienced a greater mean serum urea nitrogen concentration than the younger patients (30 ± 14 mg/dL vs. 20 ± 9 mg/dL). Four older patients (12 % of the population) experienced serum urea nitrogen concentrations ≥ 60 mg/dL. This supports the conclusion that older patients are at greater risk for developing azotemia and should be closely monitored.

Hyperglycemia with Hypertriglyceridemia

Because hyperglycemia is prevalent in critically ill obese patients [40, 82], 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 hypertriglyceridemia that doesn't

improve when the hyperglycemia resolves. This limits the use of fat, and suggests that increased lipids should be used with caution in obese patients. During hypercaloric, fat-free, continuous parenteral nutrition, biochemical evidence (eicosatrienoic acid to arachidonic acid ratio also known as the triene to tetraene ratio which had to be >0.4) for the development of essential fatty acid deficiency occurred in 30, 66, 83, and 100 % of patients after 1, 2, 3, and 4 weeks, respectively [83]. Two out of 32 patients in the study developed clinical symptoms suggestive of essential fatty acid deficiency. Once the biochemical abnormality developed, intravenous lipid emulsion was initiated if the parenteral nutrition could not be discontinued. However, during hypocaloric feeding, lipolysis would be expected to occur for energy and also provide a source for essential fatty acids. Respiratory quotient measurements from the case series regarding hypocaloric, high protein parenteral feeding of hospitalized patients with obesity from Dickerson et al. [56] (see Table 11.4) indicated that 68 % of non-protein energy originated from net fat oxidation during fat-free hypocaloric parenteral nutrition. These data are supported by 15 overweight cancer patients who were hypocalorically fed a continuous, fat-free, parenteral nutrition regimen for 2–5 weeks [84]. None of the patients experienced biochemical or clinical evidence for essential fatty acid deficiency [84]. Therefore, in the presence of hypertriglyceridemia and impaired clearance of intravenous lipid emulsion, it is the author's belief that fat-free hypocaloric high-protein parenteral nutrition therapy may be safely prescribed to hospitalized patients with obesity for at least 4–5 weeks without development of essential fatty acid deficiency.

Despite these data, whether endogenous fat is available for use as an energy source during critically illness in patients with obesity is the subject of debate [85]. Jeevanadam and colleagues studied seven obese patients and ten non-obese, ventilator-dependent patients with multiple traumatic injuries 2–4 days following injury and before the provision of nutrition therapy [85]. Lipolysis and net fat oxidation were reduced in the obese group compared to the non-obese controls. These and other data [56, 84, 85] suggest that obese patients may exhibit a transient impairment in fat metabolism early after injury, but this resolves later during the patients' hospital course. Just how effectively the body can use endogenous fat stores during hypocaloric high-protein nutrition therapy following traumatic injury remains uncertain, and more research on this issue is clearly needed.

Metabolic Support After Bariatric Surgery

Bariatric surgery causes substantial weight loss, decreases obesity-related comorbidities, and improves quality of life and survival [86]. A small portion of patients develop postoperative complications requiring use of parenteral nutrition therapy. 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 [56, 57].

Long-term monitoring is mandatory as bariatric surgery results in malabsorption of both macronutrients and micronutrients [4, 87–91]. Reported vitamin and mineral deficiencies include iron, folate, vitamin B12, calcium, thiamine, copper, selenium, and vitamins A, D, and K. In addition to a physical exam and patient interview directed towards signs and symptoms of such deficiencies, laboratory evaluation is also necessary. For patients with a microcytic anemia, serum ferritin concentration should be obtained for evaluation of potential iron deficiency. Bariatric surgery patients can develop microcytic anemia from copper deficiency [88]. Patients with a macrocytic anemia should be evaluated for folate or vitamin B12 deficiency using serum methylmalonic acid and homocysteine concentrations, which are sensitive markers for folate and vitamin B12 depletion [92]. 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, since neurologic sequelae from vitamin B12 deficiency may not be reversible. Metabolic bone disease and secondary hyperparathyroidism, attributed to calcium and vitamin D deficiency, can also occur [93].

Aasheim reviewed 84 of 104 reported cases of Wernicke's encephalopathy from thiamine depletion following bariatric surgery [89]. Most cases occurred within 6 months after restrictive or gastric bypass surgery. Intravenous glucose administration without thiamine supplementation was determined to be a risk factor in 18 % of the hospitalized patients. Ominously, 49 % of patients failed to completely recover, despite thiamine therapy. Thiamine-depleted patients can also develop beriberi which presents either as a lactic acidosis ("dry" beriberi) or a congestive cardiomyopathy with gravity-dependent edema ("wet" beriberi). Similar to the management of patients with alcoholism, it is recommended that patients who have previously undergone bariatric surgery and who are admitted to the hospital receive parenteral thiamine supplementation prior to the administration of dextrose or carbohydrate-containing solutions [88].

The American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic and Bariatric Surgery guidelines recommend that bariatric surgery patients receive a daily regimen of two daily doses of multivitamins plus minerals, calcium citrate 1200–1500 mg, $\geq$3000 units of vitamin D (titrated to a serum 25-hydroxy vitamin D concentration of $>$30 ng/mL), and vitamin B_{12} (in quantities sufficient to maintain normal concentrations) [87]. Supplemental vitamin A, thiamine, copper, zinc, and selenium may also be necessary for some patients. It is recommended that routine vitamin and trace mineral laboratory monitoring be performed every 3–6 months and a bone density evaluation be performed at 2 years following bariatric surgery [87].

Optimal Nutrition Support for Hospitalized Patients with Obesity

Development of a nutrition regimen for the hospitalized patient with obesity can be complicated and is dependent on the presence of influencing comorbidities. It is recommended that hypocaloric high-protein feeding be implemented only for patients who do not have severe renal or hepatic disease. Target caloric intakes should be about 50–70 % of measured (if available) or predicted energy requirements based on the Penn State equations for critically ill, ventilator-dependent patients or the Mifflin-St. Jeor equations for non-ventilated patients [4] (see Table 11.3 for calculation of equations). An alternative to the use of predictive equations is to use a weight-based dosing method of either $\leq$14 kcal/kg actual weight/day [4] or $\leq$25 kcal/kg ideal body weight/day [21, 31, 55]. It is imperative that the clinician use good clinical judgment regarding caloric dosing. It is reasonable to temporarily delay achievement of caloric goals if the patient is experiencing hyperglycemia, intracellular electrolyte depletion, or hypercapnia [94]. Initial target protein target goals should be 1.2 g/kg actual weight/day or within 2–2.5 g/kg ideal body weight/day [4]. For critically ill patients with a BMI of $\geq$40 kg/m^2, this author targets a protein intake of ~2.5 g/kg ideal body weight/day as use of 2 g/kg ideal body weight/day may underestimate protein requirements for those with Class III obesity [31]. Based on current clinical guidelines [4], it is suggested that an adjustment of initial goal protein intake be considered dependent upon the results of the nitrogen balance determination. Hoffer and Bistrian suggest that a maximum protein dose between 2.5 and 3 g/kg/day are safe for use except in critically ill patients with refractory hypotension, overwhelming sepsis, or serious liver disease [95]. This author would also include acute kidney injury without continuous renal replacement therapy and chronic kidney disease with azotemia or uremia as additional exceptions for the safety of high-protein dosing.

Practical methods for successfully delivering a hypocaloric high-protein nutrition regimen require creativity on the part of the clinician, especially for enteral nutrition. A patient case scenario is provided for parenteral (Table 11.5) and enteral (Table 11.6) nutrition therapy to demonstrate potential prescribing methods to achieve a hypocaloric high-protein regimen by these routes. However, these cases may be considered simplified in that the patients in these cases do not have comorbidities from their obesity.

Table 11.5 Case study: Development of a hypocaloric high-protein parenteral nutrition regimen

Case: 42-year-old female admitted to the trauma intensive care unit for multiple traumatic injuries has developed a paralytic ileus. Parenteral nutrition is requested
Nutritional and clinical assessment:
Height: 5 ft, 5 in.. Pre-resuscitation body weight: 100 kg. BMI: 36.7 kg/m^2. Ideal body weight (IBW): 57 kg. Serum Albumin: 2.5 g/dL. Normal renal/hepatic function. No history of diabetes mellitus, hyperlipidemia, cardiomyopathy, obstructive lung disease, or fatty liver disease. Current blood glucose is 110 mg/dL and triglycerides are 105 mg/dL prior to initiation of nutrition therapy. Patient is ventilator dependent but without significant hypercapnia
Nutritional requirements:
Energy: 20–25 kcal/kg IBW/day or 1140–1425 kcal/d
Protein: 2–2.5 g/kg IBW/d or 114–143 g/d
The assumption is made that the PN solution is compounded from 70 % dextrose, 15 % amino acids, 20 % lipid emulsion, electrolytes, vitamins, trace minerals, and sterile water for injection
Two common methods for prescribing parenteral nutrition regimens are given below:
Goal parenteral nutrition regimen 1
Dextrose 10 %
Amino acids 8 %
Lipid emulsion 2 %
Infusion rate: 65 mL/h
Regimen 1 will provide 1341 kcal/day (24 kcal/kg IBW/day or 13 kcal/kg current body weight) and 125 g protein/day (2.2 g/kg IBW/day or 1.3 g/kg current body weight/day)
Goal parenteral nutrition regimen 2
Dextrose 150 g/day
Amino acids 125 g/day
Lipids 30 g/day
Infusion rate: 65 mL/h
Total volume: 1560 mL/day
Regimen 2 will provide 1310 kcal/day (23 kcal/kg IBW/day or 13 kcal/kg current body weight) and 125 g protein/day (2.2 g/kg IBW/day or 1.3 g/kg current body weight/day)

Parenteral Nutrition

Parenteral nutrition has the advantage over enteral nutrition for developing a hypocaloric high-protein formulation in that each macronutrient can be independently prescribed. The primary limitation with 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 volume overload: dextrose 70 % in water, 15 or 20 % amino acid solution, and 20 or 30 % lipid emulsion. However, due to cost considerations, hospital formulary management, and perception of institutional need, not all hospital pharmacies have the most concentrated macronutrient solutions for compounding the most fluid restricted base formulas. The case study given in Table 11.5 provides two methods for prescribing a parenteral nutrition solution for a hospitalized patient with obesity.

Enteral Nutrition

Providing a hypocaloric, high-protein enteral nutrition regimen is technically more difficult than parenteral nutrition. The primary limitation with enteral nutrition is enteral formulas are only

Table 11.6 Case study: Development of a hypocaloric high-protein enteral nutrition regimen

Case: 42-year-old female admitted to the trauma intensive care unit for multiple traumatic injuries. A nasoenteric feeding tube has been placed for continuous enteral nutrition
Nutritional and clinical assessment:
Height: 5 ft, 5 in.. Pre-resuscitation body weight: 100 kg. BMI: 36.7 kg/m^2. Ideal body weight (IBW): 57 kg. Serum albumin: 2.5 g/dayL. Normal renal/hepatic function. No history of diabetes mellitus, hyperlipidemia, cardiomyopathy, obstructive lung disease, or fatty liver disease. Current blood glucose is 110 mg/dL and triglycerides are 105 mg/dL prior to initiation of nutrition therapy. Patient is ventilator dependent but without significant hypercapnia
Nutritional requirements:
Energy: 20–25 kcal/kg IBW/d or 1140–1425 kcal/day
Protein: 2–2.5 g/kg IBW/d or 114–143 g/day
Two different prescriptions for achieving this goal with enteral feeding are given below:
Goal enteral regimen 1
Use of a commercial formula designed for bariatric patients: 1 kcal/mL, 93 g protein/L
"Bariatric formula" at 55 mL/h (1320 mL/day)
Provides 1320 kcal/day (23 kcal/kg IBW/day or 13 kcal/kg actual body weight/day) and 123 g of protein/day (2.2 g/kg IBW/day or 1.2 g/kg actual body weight/day). The above regimen will achieve 88 % of US Dietary Reference Intakes for vitamins and minerals. Liquid multivitamin supplementation via the feeding tube is optional
Goal enteral regimen 2
Use of a commercial high-protein formula for stressed patients: 1 kcal/mL, 62 g/L of protein PLUS use of commercial liquid protein supplement (15 g of protein per 30 mL which provides 100 total kcal: 60 kcal from protein and 40 kcal from carbohydrate/flavoring) to be administered as a bolus via feeding tube. Other institutions may have a different protein supplement
"High-protein formula" at 40 mL/h plus 30 g of Liquid Protein twice daily (via feeding tube)
Provides 960 kcal and 60 g of protein daily from the enteral formula, 400 total kcal and 60 g of protein from liquid protein supplement, for a total of 1360 kcal/day (24 kcal/kg IBW/day or 14 kcal/kg actual body weight/day) and 120 g protein/day (2.1 g/kg IBW/day or 1.2 g/kg actual body weight/day). The above regimen will achieve 96 % of US Dietary Reference Intakes for vitamins and minerals. Liquid multivitamin supplementation via the feeding tube is optional

commercially available in fixed macronutrient concentrations. Use of protein supplements, along with a reduction in enteral formula feeding rate, may be necessary to achieve the intended target caloric and protein intakes. 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. Incomplete mixing of the powder may also occur which will result in clumping and tube clogging. If a powdered protein product is to be added to the enteral feeding solution, it is preferred that the protein powder be admixed with the enteral solution under aseptic or clean conditions in the pharmacy and blenderized to reduce clumping. Given the wide use of "ready to hang" enteral products, an alternative strategy is to give the supplemental protein by bolus administration via the feeding tube. Use of a liquid protein solution can further reduce nursing workload. A caveat to the use of a liquid protein solution is that some products are viscous and difficult to administer via a small-bore feeding tube. A 50:50 dilution of the liquid protein solution with water can alleviate difficulty in administration via a small bore (10, 12 or 14 Fr) feeding tube [96].

Since the hypocaloric high-protein technique often requires a low enteral formula feeding rate (due to the contribution of calories 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 (Peptamen® Bariatric, Nestlé Health Science, Florham Park, NJ, USA)

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 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, 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 desirable. Intermittent administration of protein supplements along with the specialized bariatric formula may be required in an effort to restrict caloric intake while providing an aggressive protein intake. Table 11.6 illustrates a case study with two different methods for achieving a hypocaloric high-protein nutrition regimen via enteral nutrition for a critically ill obese patient.

Metabolic Monitoring of the Hospitalized Patient with Obesity

Monitoring should be designed to insure efficacy of the prescribed regimen as well as avoidance of complications associated with overfeeding [97]. In the ICU, despite its limitations, the marker recommended for assessing the efficacy of the nutrition regimen is nitrogen balance. During the acute phase of illness following trauma or surgery, if nitrogen equilibrium (e.g., a nitrogen balance of about −4 g/day to +4 g/day) can be achieved, the regimen is considered successful. For some highly catabolic patients, nitrogen equilibrium cannot be achieved until the stress is resolved [59, 67]. Nitrogen balance determinations are performed weekly while the patient is in the ICU at this author's institution [97].

Body weight is not routinely used as a marker of efficacy for multiple reasons. The difficulty of accurately determining weight in the ICU often limits its interpretation. Weight is also a poor marker due to fluid perturbations following resuscitation and throughout their course of stay in the ICU. Finally, weight loss, or maintenance, is not necessarily a primary clinical outcome or goal for critically ill patients, whether or not receiving hypocaloric, high protein nutrition therapy. The primary intent is to avoid hyperglycemia, hypercapnia, hypertriglyceridemia, fluid overload, and worsening of nonalcoholic fatty liver disease while meeting nutritional goals based on the best available techniques while keeping in mind that much more study is required to verify that this approach results in the best outcomes. Fat weight loss should be considered as a welcome secondary benefit.

The impact of obesity upon insulin sensitivity and a higher incidence of diabetes mellitus complicate glycemic control management. Despite hypocaloric feeding with low carbohydrate intakes, use of a continuous intravenous regular human insulin infusion [40] or intermittent sliding scale insulin [82] is often warranted to maintain blood glucose concentrations within a desirable target range [45].

Other routine monitoring markers include fluid intake and output, serum urea nitrogen and creatinine concentrations, and arterial blood gas measurements. 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. Arterial blood gases are closely monitored for rises in pCO_2 concentrations not attributable to other causes as evidence of overfeeding for patients who require mechanical ventilation [45]. A small proportion of older patients [55] or those with a modestly compromised renal function may exhibit azotemia during hypocaloric, high protein therapy. Therefore, serial serum urea nitrogen and creatinine concentrations should also be closely monitored. 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 elevated serum aminotransferase concentrations associated with nonalcoholic fatty liver disease [98], it would be important to avoid overfeeding. Unfortunately, routine monitoring of liver function tests is of somewhat limited value as the presence of sepsis and inflammation confounds interpretation of these tests [99].

Conclusion

Metabolic management of the hospitalized patient with obesity is difficult. Implementation of nutrition therapy for this population requires unique considerations to avoid complications of overfeeding while attempting to achieve net protein anabolism. Implementation of hypocaloric, high protein nutrition support may be challenging, but is achievable. This therapeutic strategy appears beneficial for achieving nutritional goals and positive clinical outcomes for the hospitalized and critically ill patient with obesity, but further research is required to confirm these preliminary findings. In particular, outcome-oriented clinical studies of nutritional strategies in obese patients are needed. Finally, close monitoring of the patient and individualization of the regimen 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;37:714–44.
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. Glance LG, Li Y, Osler TM, Mukamel DB, Dick AW. Impact of obesity on mortality and complications in trauma patients. Ann Surg. 2014;259:576–81.
7. 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;34:964–9771.
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;204:1056–10644.
9. Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med. 2014;370:233–44.
10. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309:71–82.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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. Intern Care Med. 2009;35:1152–70.
16. 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.
17. Hoffmann M, Lefering R, Gruber-Rathmann M, Rueger JM, Lehmann W, Trauma Registry of the German Society for Trauma S. The impact of BMI on polytrauma outcome. Injury. 2012;43:184–8.
18. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264–70.
19. 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.
20. 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.

21. Dickerson RN, Boschert KJ, Kudsk KA, Brown RO. Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition. 2002;18:241–6.
22. 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.
23. 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.
24. Druml W. ICU patients: fatter is better? Intensive Care Med. 2008;34:1961–3.
25. Bornstein SR, Licinio J, Tauchnitz R, Engelmann L, Negrão AB, Gold P, et al. 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.
26. Wendel M, Paul R, Heller AR. Lipoproteins in inflammation and sepsis. II: clinical aspects. Intensive Care Med. 2007;33:25–35.
27. 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.
28. Prado CMM, Wells JCK, Smith SR, Stephan BCM, Siervo M. Sarcopenic obesity: a Critical appraisal of the current evidence. Clin Nutr. 2012;31:583–601.
29. Guillet C, Masgrau A, Boirie Y. Is protein metabolism changed with obesity? Curr Opin Clin Nutr Metab Care. 2011;14:89–92.
30. Dickerson RN, Pitts SL, Maish 3rd GO, Schroeppel TJ, Magnotti LJ, Croce MA, et al. A reappraisal of nitrogen requirements for patients with critical illness and trauma. J Trauma Acute Care Surg. 2012;73:549–57.
31. Choban PS, Dickerson RN. Morbid obesity and nutrition support: is bigger different? Nutr Clin Pract. 2005;20:480–7.
32. Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW. Mechanisms of insulin resistance following injury. Ann Surg. 1982;196:420–35.
33. 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;29:353–8. discussion 359.
34. 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.
35. 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.
36. 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.
37. Jeschke MG. Clinical review: glucose control in severely burned patients – current best practice. Crit Care. 2013;17:232.
38. Finfer S, Chittock DR, Su SY, Blair D, Foster D, NICE-SUGAR Study Investigators, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
39. 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.
40. Dickerson RN, Swiggart CE, Morgan LM, Maish 3rd GO, Croce MA, Minard G, et al. Safety and efficacy of a graduated intravenous insulin infusion protocol in critically ill trauma patients receiving specialized nutritional support. Nutrition. 2008;24:536–45.
41. Goldberg IJ. Clinical review 124: diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab. 2001;86:965–71.
42. 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.
43. Brown CV, Velmahos GC. The consequences of obesity on trauma, emergency surgery, and surgical critical care. World J Emerg Surg. 2006;1:27.
44. 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.
45. 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.
46. Nelson J, Billeter AT, Seifert B, Neuhaus V, Trentz O, Hofer CK, et al. Obese trauma patients are at increased risk of early hypovolemic shock: a retrospective cohort analysis of 1,084 severely injured patients. Crit Care. 2012;16:R77.
47. Sheldon GF, Peterson SR, Sanders R. Hepatic dysfunction during hyperalimentation. Arch Surg. 1978;113:504–8.
48. 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.

49. Feurer ID, Crosby LO, Buzby GP, Rosato EF, Mullen JL. Resting energy expenditure in morbid obesity. Ann Surg. 1983;197:17–21.
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. 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.
52. 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.
53. 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.
54. 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.
55. Dickerson RN, Medling TL, Smith AC, Maish 3rd GO, Croce MA, Minard G, et al. Hypocaloric, high-protein nutrition therapy in older vs younger critically ill patients with obesity. JPEN J Parenter Enteral Nutr. 2013;37:342–51.
56. 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.
57. 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.
58. 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.
59. 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.
60. 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.
61. Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulasi I, et al. Prospective randomized trial to assess caloric and protein needs of critically ill, anuric, ventilated patients requiring continuous renal replacement therapy. Nutrition. 2003;19:909–16.
62. Elwyn DH. Nutritional requirements of adult surgical patients. Crit Care Med. 1980;8:9–20.
63. 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.
64. Hill GL, Church J. Energy and protein requirements of general surgical patients requiring intravenous nutrition. Br J Surg. 1984;71:1–9.
65. Macfie J, Smith RC, Hill GL. Glucose or fat as a nonprotein energy source? A controlled clinical trial in gastroenterological patients requiring intravenous nutrition. Gastroenterology. 1981;80:103–7.
66. Smith RC, Burkinshaw L, Hill GL. Optimal energy and nitrogen intake for gastroenterological patients requiring intravenous nutrition. Gastroenterology. 1982;82:445–52.
67. 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.
68. 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.
69. Hart DW, Wolf SE, Herndon DN, Chinkes DL, Lal SO, Obeng MK, et al. Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. Ann Surg. 2002;235:152–61.
70. Wolfe RR, Goodenough RD, Burke JF, Wolfe MH. Response of protein and urea kinetics in burn patients to different levels of protein intake. Ann Surg. 1983;197:163–71.
71. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. 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.
72. 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.
73. 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 Parenter Enteral Nutr. 2011;35:88–96S.
74. Scheinkestel CD, Adams F, Mahony L, Bailey M, Davies AR, Nyulasi I, et al. Impact of increasing parenteral protein loads on amino acid levels and balance in critically ill anuric patients on continuous renal replacement therapy. Nutrition. 2003;19:733–40.

75. Brown RO, Compher C, American Society for Parenteral and Enteral Nutrition Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support in adult acute and chronic renal failure. J Parenter Enteral Nutr. 2010;34:366–77.
76. Liu KJ, Cho MJ, Atten MJ, Panizales E, Walter R, Hawkins D, et al. Hypocaloric parenteral nutrition support in elderly obese patients. Am Surg. 2000;66:394–9. discussion 399-400.
77. Guillet C, Prod'homme M, Balage M, Gachon P, Giraudet C, Morin L, et al. Impaired anabolic response of muscle protein synthesis is associated with S6K1 dysregulation in elderly humans. FASEB J. 2004;18:1586–7.
78. 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.
79. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
80. Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. Clin Nutr. 2008;27:675–84.
81. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. J Am Soc Nephrol. 1993;3:1371–7.
82. 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.
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, et al. 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. 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 (Silver Spring). 2013;21 Suppl 1:S1–27.
88. 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.
89. Aasheim ET. Wernicke encephalopathy after bariatric surgery: a systematic review. Ann Surg. 2008;248:714–20.
90. Aasheim ET, Bjorkman S, Sovik TT, Engström M, Hanvold SE, Mala T, et al. Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch. Am J Clin Nutr. 2009;90:15–22.
91. Malone M. Recommended nutritional supplements for bariatric surgery patients. Ann Pharmacother. 2008;42:1851–8.
92. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Intern Med. 1999;159:1289–98.
93. Slater GH, Ren CJ, Siegel N, Williams T, Barr D, Wolfe B, et al. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. J Gastrointest Surg. 2004;8:48–55.
94. Dickerson RN. Optimal caloric intake for critically ill patients: first, do no harm. Nutr Clin Pract. 2011;26:48–54.
95. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr. 2012;96:591–600.
96. 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.
97. Dickerson RN, Drover JW. Monitoring nutrition therapy in the critically ill patient with obesity. JPEN J Parenter Enter Nutr. 2011;35:44S–51.
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 Intern Med. 1989;149:2246–8.
100. 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.

Chapter 12
Ethical Considerations in Nutrition Support in Critical Care

Albert Barrocas and Denise Baird Schwartz

Keywords Patient-centered care • Artificial nutrition and hydration • Informed consent • Futility • Evidence-based medicine • Quality of life • Transdisciplinary • End of life • Palliative care • Shared decision making • Preventive ethics • Health literacy • Teach-back method • Advance directives • Low yield interventions • Troubling trichotomy

Key Points

- Critically ill patients and family members may experience contradictions among what *can* be done technologically, what *should* be done ethically, and what *must* be done legally, resulting in a "Troubling Trichotomy."
- Respecting the patient's wishes and dignity is essential in patient-centered care.
- Four basic tenets/principles (Autonomy, Beneficence, Non-maleficence, Distributive Justice) drive ethical decisions in western bioethics.
- The fully educated patient or surrogate decision maker is the ultimate decision maker of whether a medical intervention, as recommended by the physician, will be undertaken.
- Discussing a time limited trial of "low yield" therapy prior to starting the therapy is often helpful in dealing with family expectations.
- Discussing artificial nutrition and hydration with patients, family members, and surrogate decision makers is crucial when the prognosis points to forgoing therapies or interventions.
- Consideration of ethnic, religious, and cultural sensitivity is essential in dealing with ethical nutrition support issues in the critically ill.
- Application of ethics to the critically ill requires a transdisciplinary approach, focused on the wishes and best needs of the patient.
- Development of a proactive, integrated, systematic process is required to prevent ethical dilemmas in critical care.

A. Barrocas, MD, FACS, FASPEN (✉)
Atlanta Medical Center, 4050 Spalding Drive, Atlanta, GA 30312, USA
e-mail: abarroc@tulane.edu

D.B. Schwartz, MS, RD, CNSC, FASPEN
Food and Nutrition Services, Providence Saint Joseph Medical Center, Burbank, CA, USA

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_12,

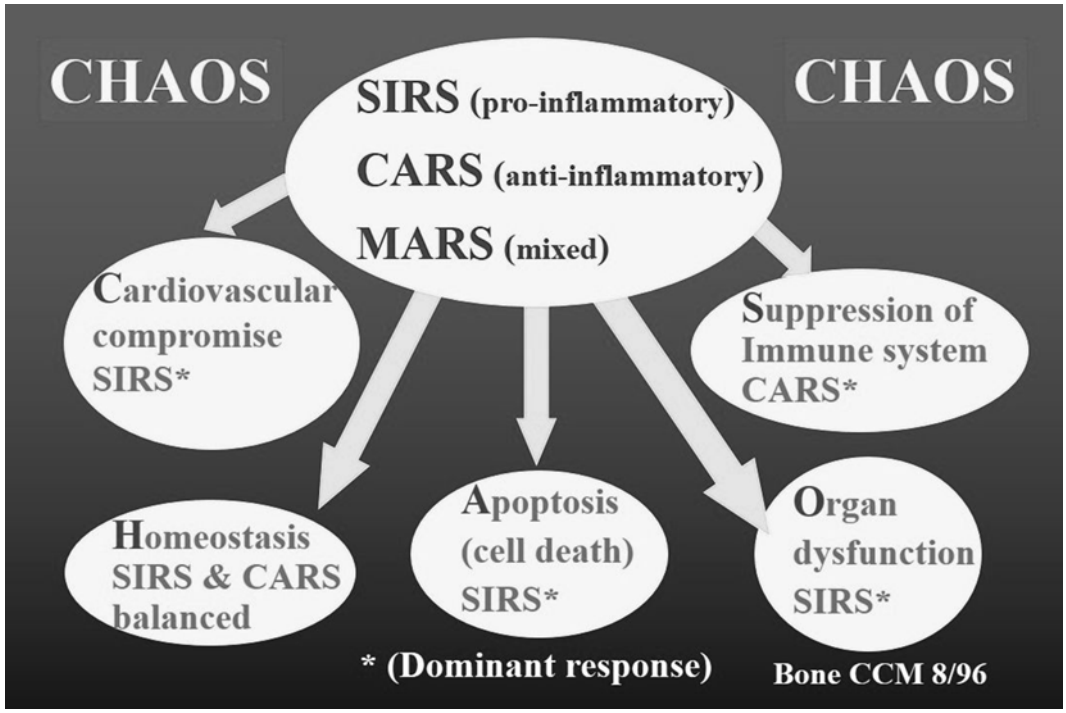


Fig. 12.1 Schematic of Bone's CHAOS often experienced by critically ill patients. *SIRS* systemic inflammatory response syndrome, *CARS* compensatory anti-inflammatory syndrome, *MARS* mixed antagonistic response syndrome. Adapted from ref. [1]

- Expert and consistent application of ethics to nutrition support in the critically ill and optimizing the communication process prevent unnecessary care and promote utilization of fewer resources during the end-of-life period, while improving patient and family satisfaction. These benefit the hospital, facilitating administrative support for the ethics team.
- Development of standardized policies and procedures for nutrition support in the intensive care unit helps insure consistent ethical practice.
- Shared decision making, preventive ethics, health literacy, and teach-back method are all tools in patient-centered care.
- Resources are available to health care clinicians and the public to help with understanding ethical considerations in health care decision making.

Introduction

The intensive care unit (ICU) is a cold, intimidating environment for critically ill patients and their families. Most often they arrive as a result of an unexpected serious illness or injury requiring the most sophisticated technology, medical treatments, and intense monitoring. As designated by Bone almost two decades ago, the critically ill patient can experience CHAOS (Fig. 12.1). Bone's Clinical CHAOS encompasses *C*ardiovascular compromise, altered *H*omeostasis, *A*poptosis, *O*rgan dysfunction, and *S*uppression of the immune system [1, 2].

Paralleling Bone's Clinical CHAOS is the real chaos regarding decisions of interventions in the critically ill patient. In many instances available therapies and interventions may provide little or no benefit to patients. These interventions, now designated as "low yield," often contribute to the chaos experienced by the critically ill patient, families and the entire health care team. There are built-in contradictions among what *can* be done technologically, what *should* be done ethically, and what *must* be done legally [3], resulting in a "Troubling Trichotomy" [4]. Countering the "Troubling Trichotomy" is the concept of patient-centered care and respecting his/her wishes and dignity.

The Honorable William Brennan, Associate Justice. US Supreme Court, in the Case of Nancy Cruzan, 1990, put it this way:

> "Medical technology has created a twilight zone of suspended animation where death commences while life, in some form, continues. Some patients, however, want no part of a life sustained only by technology. Instead, they prefer a plan of medical treatment that allows nature to take its course and permits them to die with dignity." [5].

That is easier said by a judge than determined by a physician. The health care team must balance the patient's wishes with reality to determine if the patient has indeed arrived at "the twilight zone of suspended animation."

In this chapter we will focus on the ethical considerations of nutrition support and applied clinical ethics in the critically ill patient. We recognize that other technological and legal aspects exist and are equally important considerations. Ethical chaos is often the result of multiple factors. Knowledge, communication, and teamwork encompassing the patient, family, caregiver, and other decision makers are the cornerstones for prevention of ethical conflicts and dilemmas. This chapter is intended to provide "navigation buoys on a stormy sea" of critical communications "uncertainty" [6].

Basic Principles of Ethics

Four basic tenets, Autonomy, Beneficence, Non-maleficence, and Distributive Justice drive ethical decisions in Western bioethics [6, 7]. These principles underpin all ethical decision making, whether at the bedside or at the policy level.

Autonomy

The individual's right to self-determination is the main ethical tenet, trumps all others, and is one area in which law and ethics agree. Judge Cardozo's 1914 New York Supreme Court Decision [9] and subsequent decisions [5, 8, 10], established that any adult of sound mind shall have the right to determine what will be done or not done to his or her body. Health care decisions must be made based on what is best for the patient after an educated conversation has taken place.

Two additional factors should be considered when applying the principle of autonomy. First, does autonomy of the individual negatively impact the interests of others or of the state? Clinicians and administrators may be reluctant to follow the patient's wishes if they fear reprisal by the state. Criteria for brain death have only been defined in the last generation, as in the Uniform Determination Act of 1981 [11]. Note also the American Academy of Neurology definition [12]. These are not accepted by everyone in the USA, much less elsewhere in the world [13]. The following cases describe conflicts between the interests of the patient and those of the state. Commonly, a patient is legally dead based on brain death, but still has a beating heart. The conflict applies specifically to nutrition support, which may be legally life-sustaining treatment.

Case 1

Thirty-three-year-old Marise Muñoz was 14 weeks pregnant when she collapsed at home on November 26, 2013 where her husband found her on the kitchen floor. She was subsequently diagnosed with a massive pulmonary embolus. Initially apneic, she was intubated. But she was declared brain dead shortly after arriving at John Peter Smith Hospital in Fort Worth, Texas. Mrs. Muñoz and her husband Erick, both emergency medical technicians, had previously discussed their feelings concerning such scenarios. Mr. Munoz, with the concurrence of other family members, asked for withdrawal of ventilation and other supportive measures [14].

However, the patient was pregnant. To protect the rights of the fetus, the Texas Advance Directive Law [15] prohibits the forgoing of cardiopulmonary resuscitation or "certain other life sustaining treatment" for pregnant women. Interpretation of this law by hospital attorneys resulted in a determination to keep the patient on full life support, despite the diagnosis of brain death. This demonstrates both the "troubling trichotomy" and conflict between the patient's autonomy and the state's interest in the survival of the fetus. After considerable legal efforts, the courts asserted that the law was not applicable to pregnant individuals who had been declared dead. Brain death is, despite a beating heart, considered death. Mrs. Muñoz's support was withdrawn on January 26, 2014.

Many questions and commentaries have resulted from this case. For instance, referring to "life support" or "life sustaining treatment" in a legally deceased patient is a contradiction in terms, which contributed in this case to the misapplication of the law. This case of brain death is different from many historical cases, which have dealt with individuals in persistent vegetative states (PVS) [16–18].

Case 2

Jahi McMath was 13 years old when she underwent removal of tonsils, adenoids, and sinus tissue to alleviate her sleep apnea at Children's Hospital and Research Center Oakland, CA. After surgery, she bled severely, arrested, and was resuscitated. But she was declared brain dead on the third postoperative day. The diagnosis was confirmed by several independent neurologists, including one appointed by the court. The health care team and hospital were in agreement that the patient needed to be removed from support. The family disagreed, both on religious grounds and because they believed that she was still alive [19].

When the case came to legal action, the court agreed that the patient was brain dead. But it ruled that the patient remain on ventilator support for an additional period of time. The family sought alternative facilities for transfer, one of which required that the patient have a tracheostomy and a gastrostomy. The hospital refused the request on the grounds that performing surgical procedures on deceased patients is wrong. The patient was eventually transferred on a ventilator to an undisclosed site per a court supervised agreement, with added nutrition support. There, she underwent tracheostomy and gastrostomy.

This case illustrates that, while autonomy provides for the individual to refuse an intervention or treatment, the same is not true when the patient is demanding treatment. Autonomy also applies to the health care provider, who may have ethical and moral beliefs that cannot be overridden. If the physician feels that the requested intervention is inappropriate, harmful or not in the patient's best interest, he or she is not compelled to provide it. In that situation, every effort should be made for the orderly transfer to another willing and qualified physician and facility. Otherwise the original physician would be violating his ethical and legal duty through abandonment. It should be noted that all four core ethical principles were at play in the refusal of the hospital to carry out tracheostomy and gastrostomy. Finally, the demand by many nursing homes that patients receiving nasogastric tube feeding undergo gastrostomy

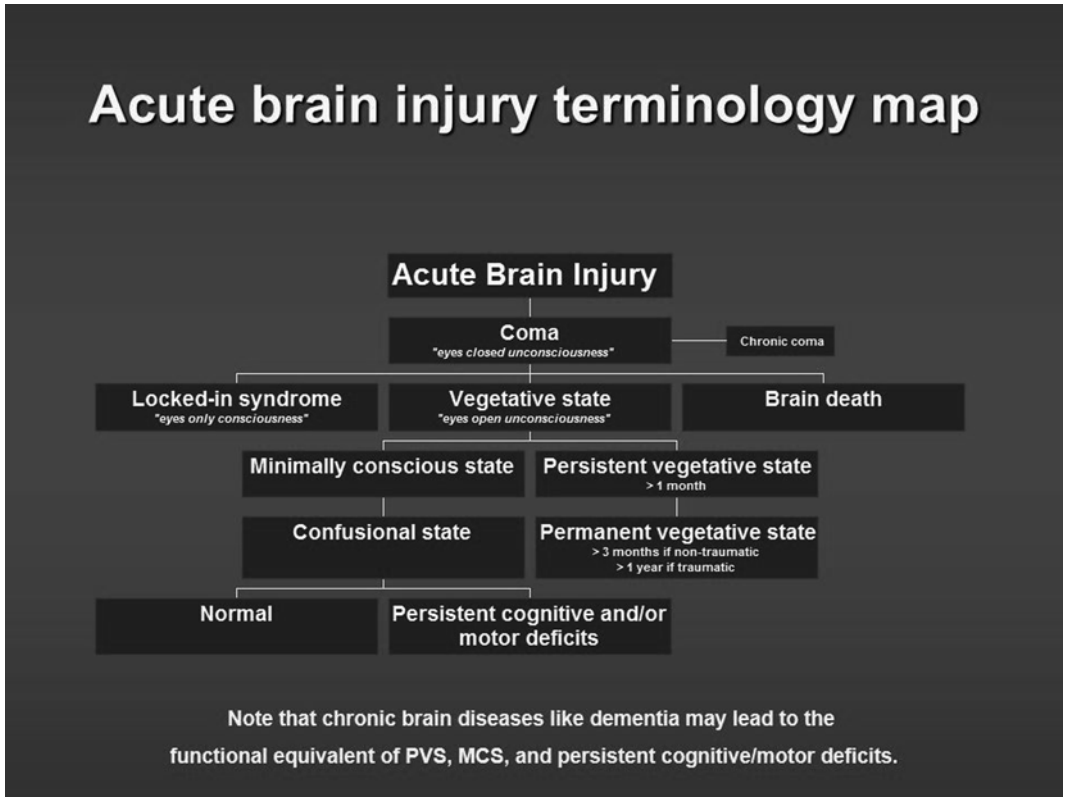


Fig. 12.2 Fine's acute brain injury schematic. Adapted from ref. [57]

prior to admission is not supported by the evidence. While gastrostomy tubes may be more reliable than nasal tubes for feeding, there is no difference in the incidence of complications [20].

Cases 1 and 2 both represent conflicts over brain death as a legal state of death. While the legal definition and criteria are stated clearly in statutory law, individuals and the public may simply disagree on whether a given individual is no longer alive [21, 22].

A second consideration relevant to the application of respect for autonomy principle is the determination of the patient's mental and cognitive capacity. Decisional capacity is clinically established. Competence is a legal issue, usually determined in a court of law or its agents. A competent patient may be rendered incapable of making decisions either temporarily or permanently by medications, e.g., narcotics and anesthetics, or by disease, e.g., head trauma, metabolic derangements, severe dementia, persistent/permanent vegetative state, and coma. The various states of brain injury are depicted in Fig. 12.2, and are well defined in the literature [16, 17].

Beneficence

Doing "good" for patients and always acting in the best interests of the patient are encompassed by beneficence, a basic precept not only in bioethics, but also the Hippocratic Oath [23] and the Declaration of Helsinki [24]. Fluid resuscitation, endotracheal intubation and initiation of artificial nutrition and hydration (ANH), when the benefits outweigh the burdens/risks, are examples of

beneficence in action. Similarly, forgoing ANH where the burdens/risks outweigh the benefits is also an act of beneficence, since such action, objectively, is in the patient's best interest. Judgments and beliefs about what constitutes benefit, however, may conflict.

Beneficence also requires that the interventions recommended and provided are based on the most updated evidence. Continuing education is thus an ethical imperative. In many cases, especially considering ANH, recommendations are based on experience rather than conclusive randomized studies. The health care team needs to understand this difference and continually update their collective knowledge to provide optimal nutrition intervention [25]. Beneficence also encompasses the role of the nutrition support clinician to assure that specialized ANH is provided appropriately. More generally, all health care professionals have a duty to assure that appropriate nutrition is available and provided to patients [26]. Intentional starvation by omission or commission is counter to beneficence. This is all the more challenging because so much of what we believe to be "appropriate nutrition" is based on observation and experience.

Non-maleficence

Primum non nocere (first do no harm) epitomizes non-maleficence. Non-maleficence is not limited to avoiding harm. The health care team is obligated to refrain from providing ineffective treatments as well. Because almost all interventions have the potential for harm, it is incumbent on the practitioners managing the patient's care to be able to discern the proportional risks of the intervention and balance them against the potential short- and long-term benefits. The available information, and recommendations, should be discussed with the patient, family, caregiver, or surrogate decision maker who will make the final decision [27].

Initiation of ANH, early in the critical patient's course of treatment, is appropriate, even when the prognosis is uncertain. Continuing such intervention, when the intervention is thought to be ineffective or associated with more harm than good, may not be the right thing to do. Preventive clinical ethics provides guidance in managing situations in which treatments become "near death" rather than life-sustaining.

Even while providing treatments and interventions driven by beneficence, adverse events occur. Beauchamp and Childress [7] refer to these negative outcomes as the "rule of double effect" which requires that four criteria are met for the act to be ethically acceptable:

1. The goal is to relieve suffering (beneficence).
2. Act must be good or at least morally neutral (non-maleficence).
3. Response must be proportionate, i.e., "mercy killing" is not a means to relieve suffering.
4. The hastening of death is not intended, although it may be foreseen, e.g., high doses of morphine for pain.

Distributive Justice

Under distributive justice, patients should all be treated equally, allowing for the differences in their clinical requirements [3]. Patients should be treated fairly and justly. The challenge to distributive justice occurs when individual needs compete with community/state needs in an environment of limited total resources [28]. Cost-effective medicine should be embraced by all members of the health care team to preserve and allocate resources in a just manner. Decisions by the health care team should be based on the ethical principles previously discussed, but the individual health care provider must also assure that the same level of care will be delivered to all patients.

Table 12.1 Benefits versus burdens/risks of nutrition, and artificial nutrition and hydration (ANH) according to routes of intake

Benefits	Burdens/risks
Oral • Natural • Easy • Symbolic • Inexpensive • Low tech	Oral • Requires alertness • Aspiration • May require feeding assistance • Religious/dietary restriction • Taste, appetite dependent
Enteral (tube feeding) • Alertness not required • Convenient • Relatively safe • Mildly invasive • Inexpensive • Maintenance/restoration of mucosal integrity • Flexibility of cyclic or continuous • Independent of taste, appetite • Utilizes usual physiologic process for digestion and absorption • Supports concept "If the gut works, use it" • Simultaneous provision with other routes	Enteral (tube feeding) • Monitoring/supervision required • Aspiration • Bloating, early satiety • Nausea, vomiting • Gastroesophageal reflux • Diarrhea • Access required • Perforation • Mechanical (erosion, necrosis, bleeding, dislodgement sinusitis) • Refeeding syndrome • Metabolic complications (fluid, electrolytes, glycemic control) • May require restraints
Parenteral (intravenous) • GI tract not required • No associated GI complaints • Specific nutrients provided • Independent of taste, appetite • Precise intake • Potential for provision of all necessary nutrients for growth and maintenance • Home infusion safe under strict protocols	Parenteral (intravenous) • Requires access • Pneumothorax • Catheter infections, thrombosis • Metabolic complications (fluid overload/dehydration, electrolytes, glycemic control, mucosal integrity) • Increase monitoring required • Relatively more expensive than other routes • More technologically demanding

Payers, governmental and regulatory agencies, and hospitals impose restrictions on the type of interventions allowed, or for which they will pay. De facto care rationing occurs in such an environment. Individuals without financial resources may be unable to obtain excluded services. Payers, both government and private, may clearly state that they do not prohibit the particular procedure or medication, but they will not provide reimbursement. They are operating within the broad umbrella of distributive justice, since all enrollees are equally affected. But they are practicing the evolving "golden rule" of health care: "he who has the gold makes the rule." Instead of primum non nocere (first do no harm) they exercise the principle of "primum pecuniae parcere" (first save money). The challenge for the health care team is to practice ethically in an environment that has financial and regulatory limitations [29].

Applications of Medical Ethics

Informed Consent

Respect for autonomy requires that the fully educated patient, or surrogate, is the ultimate decision maker as to whether any given therapy is undertaken. Informed consent should be comprehensive, with updated and accurate information and involvement of the patient and family in the final decision. The health care team is responsible for providing the most up to date information regarding the purpose of the intervention including alternatives, and short- and long-term burdens/risks and benefits [30] Examples of nutrition-related risks and benefits are listed in Table 12.1.

Inserting a long-term enteral access device such as a percutaneous endoscopic gastrostomy (PEG) is a common source of ethical conflict in the ICU. In many instances the patient is not capable and a surrogate decision maker is involved. Advanced dementia, or severe dementia, is not uniformly defined in the literature [31–33]. In this chapter, advanced dementia refers to the stage of dementia when the individual cannot self-feed, walk or perform the activities of daily living (ADLs). It progresses to dysphagia, muteness, and cognitive deficits that impedes normal nutrition intake while the rest of gastrointestinal function is not compromised [33]. Many of the persistent cognitive and motor deficits seen in advanced dementia are similar to those seen in patients with brain injuries [6].

Informed consent for artificial nourishment is often obtained via phone, due to scheduling conflicts between the physician and the surrogate decision maker. The discussion is often, as a result, limited to the physician stating that the patient is unable to ingest oral feedings or fluids and without such intervention malnutrition and complications may occur. Potential risks of the procedures, including bleeding, peritonitis from leakage, dislodgement, or perforation of another viscous (transverse colon) are also discussed. However, the urgency and permanent or temporary nature of the PEG is not often discussed. Neither are the poor long-term outcomes in specific populations, such as those with advanced dementia and terminal illnesses. There is overwhelming evidence to recommend avoiding the use of a PEG tube in such patients [34]; see Table 12.2 [35–46].

The patient, family and/or surrogate decision maker, while accepting the evidence against PEG tubes in the limited sub-population noted above, usually have additional questions. One of the major concerns is suffering and discomfort in the absence of ANH. Table 12.3 summarizes some published material addressing these questions, often not proactively included in the informed consent conversations [34, 48–51].

Futility vs. Low Yield Therapies/Treatments

The problematic term *futility* is often used in conversations regarding treatments and/or interventions when recovery is not expected. Continuing ANH in a terminally ill patient is often considered "futile" by the health care team. The same may not be the case for the surrogate decision maker. The patient's family members simply may not subscribe to the same concept of futility as the physician. On the other hand, designating the intervention as "low yield" therapy based on risk/burden versus benefit may be more readily accepted by all. This semantic shift seems minor, but is far less emotionally laden than "futile," and may be important in helping the family to understand the patient's condition.

The authors believe that the use of "low yield" as a substitute for "futile" will result in more frequent consensus regarding specific interventions. There are additional considerations. First is an appreciation for the relation of the individual to the patient, providing him with the appropriate information and time to process all that is taking place. Second, it may be best to propose a *time limited trial* of the intervention with the interested parties prior to starting the therapy. Then, when the health care team determines that the intervention is no longer of benefit, it will be discontinued without further discussion, as a strictly clinical decision. Of course, informing the family is still necessary. Third, if the "low yield" intervention is considered by the health care team as not being in the patient's best interest, the ethical principles of beneficence and non-maleficence should be applied. Lastly, "low yield" like "termination" or "forgoing" should always refer to treatments or interventions and not "care." We should always reassure patients, families, and the health care that the team will continue to care for the patient until the end.

Table 12.2 Support for forgoing PEG tubes in advanced dementia and end-of-life

Authors	Findings/conclusions
Haddad,Thomas [35]	High mortality and morbidity rates Questionable effectiveness except in critical illness and ALS
Oyoga, Schein, Gardegi,Wise [36]	41% 30 day mortality 4 % related to procedure
Abuksis, Mor, Segal, et al. [37]	87 % NH demented patients 39.5 % mortality rate
Grant, Rubberg, Brody [38]	Mortality rates (81,105 patients) 23 %—30 day 63 %—1 year 81.3 %—3year
Finucane, Christmas, Travis [39]	Meta-analysis—5,266 NH residents No improvement in rates of aspiration pneumonia, pressure sores, decline in ADL, survival Avoid tube feedings in advanced dementia patients
Murphy, Lipman [40]	PEGs do not prolong survival in patients with dementia
Cervo, Bryan, Farber [41]	PEG in advanced dementia No reduction in oral or gastric aspiration, or pneumonia
Gillick [42]	PEG in advanced dementia: Increase mortality, morbidity Often require physical and chemical restraints Increased discomfort Comprised human dignity
Schwartz DB, Barrocas A, Wesley JR, Kliger G, Pontes-Arruda A, Arenas Márquez H, James RL, Monturo C, Lysen LK, DiTucci [43]	Decision to withhold or withdraw tube feeding in end-stage disease is supported by current scientific literature Advanced dementia should be seen by the health care team as a terminal illness, and health care team members should clearly communicate this perspective to the patient's family, significant others, caregivers, and/or surrogate decision makers
Meier, Ahronheim, Morris [44]	Reduced short-term survival after in hospital placement in chronically demented patients with superimposed delirium
Sampson, Candy, Jones [45]	Cochrane database systematic review Insufficient evidence to suggest enteral nutrition benefits in patients with advanced dementia Lacking data on adverse events associated with enteral nutrition
O'Sullivan Maillet, et al. [51] Position of the American Dietetic Association	"In the case of the patient with advanced dementia, terminal illness and those persistently unconscious, feeding may not be the best answer"
Korner, Dondolfi, Buhler, et al. [46] Introduction, ESPEN guidelines on enteral nutrition, ethical and legal aspects	Balance of evidence supports that artificial nutrition should not be undertaken (in advanced dementia) "… loss of appetite and thirst are terminal features in this fatal condition, as in other terminal illnesses at a late stage"
Barrocas, Geppert, Durfee, et al. [34] A.S.P.E.N. Ethics Position Paper	ANH may not provide any benefit and may have associated risks in patients with advanced dementia

Table 12.3 Advanced dementia and end-of-life suffering/discomfort with or without ANH

Author	Findings/conclusions
A.S.P.E.N. ethics position paper [34, 47]	"Scientific evidence in the physiology of patients with brain death, coma or PVS indicates that these patients do not experience thirst or hunger, and therefore not likely to suffer" "Artificial hydration of terminally ill patient can lead to discomfort due to fluid overload, pulmonary and generalized edema, shortness of breath, etc., and may be discontinued on clinical and ethical grounds provided such determination is not in conflict with existing laws, institutional policies and consent/consensus of decision makers" Additional interventions associated with ANH which have discomfort potential include: • Catheters • Additional laboratory tests-blood draws • Medications, electrolytes • ANH complications • Physical restraints
Ciocon, Silverstone, Graver, Foley [48]	ANH in dying patients: Increased diarrhea, nausea, vomiting, and repeated aspiration pneumonia
Ellenshaw, Sutcliffe, Saunders [49]	Fluids: • Cause/exacerbate dyspnea • Bronchial secretions • Urinary frequency • Bladder distension • Pulmonary edema/effusions • Ascites
Friederich [50]	• Infections at surgical site • Perforations • Leakage • Does not prevent skin breakdown or pressure ulcers despite greater protein intake
McCann, Hall, Groth-Juncker [51]	Ketosis and dehydration, in absence of ANH, provide anesthetic/sedative effects to the terminally ill or advanced demented patients who may retain the ability to experience discomfort or suffering

Withholding, Withdrawing, or Forgoing

Clinicians, ethicists, lawyers, and theologians generally do not differentiate between withholding and withdrawing medical interventions. But clinicians should be sensitive to the reality that these may have very different emotional impacts on the family. To help drive a less emotional discussion, the use of the term "forgoing" has been proposed to encompass both. Interventions with questionable benefit are sometimes withheld due to concerns that once started is difficult to discontinue, particularly in the area of ANH. Risk/burden/benefit analyses according to evidence-based (EBM) should precede the final decision. Some would further argue that agreement and assent should be reached that the intervention will be discontinued solely based on the judgment of the clinicians, with notification of all stakeholders when the termination occurs [28]. In any case, agreement with the patient or surrogates should be based on the situation.

The Crucial/Critical Conversation(s): 5 Ws and an H

One of the most challenging aspects of critical care in general, and ANH specifically, is discussing with patients and surrogates that the prognosis is so poor that forgoing therapies or interventions is indicated. This is the crucial or critical conversation. An excellent means to prepare, execute and follow-up this conversation is organizing the discussion utilizing the journalistic tenets of the 5 Ws (Why? What? Who? When? Where?) and the H (How?).

Why?

The four basic ethical principles provide for respecting the autonomy and dignity of the patient or surrogates by involving them in the decision making process. Informed consent is not only ethical, but also is a legal requirement, at least in the USA. Conducting the crucial/critical conversation is in keeping with the concept of shared decision making and patient-family centered care. Lastly, since medicine is not an exact science and forgoing ANH may have "double effect" consequences, and is an emotionally laden decision, it is best to have consensus among all stakeholders in the process.

What?

A well prepared outline of the goals and expectations of the conversation should be developed prior to the meeting and discussed by the care team. The presenters should endeavor to be as transparent as possible about the scientific rigor of any recommendations. The existing varieties of grading systems are quite helpful [53, 54]. A more general, but practical classification is E_3BM. E_3BM refers to Evidential (true EBM, the strongest), Experiential (collective past experiences) and Eminence (expert opinion) Based Medicine. A recent editorial by Braithwaite [55] points out that the most dangerous words in EBM conclusions are "There is no evidence to suggest…." He cites Altman and Bland's admonition that "absence of evidence is not evidence of absence" [56].

The patient's course in the hospital serves as the cornerstone for the discussion. The format and content of the data to be presented should be determined by the known or perceived educational level of the patient/surrogate. In the context of simplifying the information, diagrams, pictures, or other images such as x-rays may be useful. A schematic developed by Fine (see Fig. 12.2) [57] may be

useful as background information and/or actual presentation to the patient/surrogate in discussions regarding cognitive impairment acute versus chronic, traumatic versus non-traumatic, etc. The literature also provides credible evidence as to the experience of hunger, thirst and suffering/discomfort in the various facets of consciousness and cognitive derangements, as shown on Table 12.3.

Who?

Given that the patient is the most important presence in the conversation, the team should have as much information as possible about the patient's perceptions: their likes, dislikes, quality of life, and opinions regarding interventions in the event they became incapable of making decisions. If this information is not known to the care team, it may be advisable to have a preliminary conversation in which the focus is solely getting to know the patient.

The surrogate's perception of the patient's quality of life is highly subjective, and may be at odds with the patient's when the surrogate is uncertain, and applies his own values. While assessment tools [53, 54] have been developed and validated that may be useful when dealing with decisions regarding ANH in the critically ill patient, such tools are dependent on the patient or surrogate's ability to appropriately respond to the questionnaire or checklist. If there is an executed advance directive, every effort should be made to review it prior to the conversation.

In preparing for the conversation, it must be established who will be making the ultimate decisions, the patient or a surrogate decision maker. To respect autonomy, when a patient has the capacity to make the decision at hand, the patient is always the primary decision maker. This includes the designation of a surrogate if the patient *chooses* not to participate in the process, as sometimes happens.

There are important differences between decisional capacity and competence. Although some variation may exist between the states in the USA, competency is usually a condition legally determined by the court. Decisional capacity, on the other hand, is a clinical determination made by one or (preferably) more physicians, relating to whether the patient has the ability to understand the consequences of the specific decision under discussion. Decisional capacity is situational. As an example, a competent individual on narcotics for pain management may be considered decisionally incapable to consent for risky surgery until 4–6 h following the last medication dose [54]. On the other hand, a patient with a mild sedation from narcotics may be capable of assigning a surrogate.

If the patient is not considered to be decisionally capable and/or competent, it behooves all concerned that the surrogate decision maker be designated as early as possible to avoid any challenges at a later time. Representatives from case and risk management, and if necessary legal, should assist in the process. The patient or surrogate decision maker should recommend other non-hospital individuals to participate in the conversation, if so desired [58].

It is important to have key members of the health care team participate in the conversation. Those that cannot be physically present should make every effort to join by conference call. The expected individuals include, but are not limited to: attending and consulting physicians, staff nurse caring for the patient and/or charge nurse, care manager, social worker, palliative care team, spiritual care team, and nutrition support team (or in absence of a team, dietitian, pharmacist). The individual's spiritual leader, or other personal advisors, may be included if desired/acceptable to patient or surrogate decision maker, etc. The role of the nutrition support team in the conversation is to provide, in a concise manner, the reason why the particular intervention is low yield and why forgoing is recommended, as well as what changes are expected following the discontinuance of ANH.

Transdisciplinarity is a useful concept in the conduct of a crucial/critical conversation. It describes what often occurs in the delivery of health care but not often mentioned in ethical decision-making processes. It focuses on the function of the team rather than the individual disciplines [59]. In some institutions the monitoring of ANH is conducted by a team that includes physicians, nurses, dietitians, and pharmacists. In others it may be conducted only by the dietitians and/or the pharmacists.

Fig. 12.3 Kubler-Ross five stages of grief

In the context of the crucial conversation, those assembled act in a transdisciplinary fashion by assuming roles that they may not usually execute under their traditional roles. The entire team participates in designing, in this case, the ethical discussion. For instance, if the physician is not available, it may be the dietitian or pharmacist who assumes the role of presenting the case and recommendations regarding nutrition support. As health care reforms continue to emphasize function over form, health care teams such as nutrition support teams, are undergoing the metamorphosis from organizationally multidisciplinary, through compositionally interdisciplinary, to functionally transdisciplinary [60].

When?

The conversation should be held sooner rather than later. Often the patient and/or family are aware of the situation but uncomfortable introducing the conversation. They become frustrated by conflicting information from different physicians and other members of the health care team. Despite expectations to resolve issues at the conclusion of the initial conversations, additional sessions may be required to allow all parties concerned to think through all possible scenarios. Both the patient and the family will be going through some or all of the traditional five stages of grief: denial, anger, bargaining, depression and acceptance (Fig. 12.3). Communication may be difficult as a result.

Dr. Elisabeth Kubler Ross introduced the five stages of grief in her pivotal book "On Death and Dying" in 1969 [61]. While proposed for these individuals facing the end-of-life, the five stages are applicable to many life experiences [62]. Some of the characteristics of each stage are outlined in Table 12.4. The stages are neither sequential nor time limited, and to-and-fro movement between stages occurs in an individual fashion. While the patient may be at the bargaining stage, his or her spouse may be at the stage of denial. Recognizing the particular stage the individuals are traveling through at the time of the crucial conversation will add to the effectiveness and success of the process [63].

Holding the conversation as early as possible allows everyone involved to "sing from the same songbook." The timing of the conversation should be determined by the availability of the patient or surrogate decision maker, and may take into consideration the availability of the major members of the clinical team, e.g., attending physician and social worker. The goal should be to maximize participation to avoid second hand information without the ability to provide input, but significant delays should be avoided, and, as discussed above, may be avoided by transdisciplinary practice, and remote access to the meeting.

Table 12.4 Kubler–Ross's five stages of grief (change) [61][a]

Stage	Presentation [62]	Interpretation
Denial and Isolation	"No, not me" • The patient leaves the physician's office or hospital believing that he/she does not have a serious illness and seeks other causes for symptoms	• Conscious/unconscious refusal to accept reality • Natural defense mechanism • Some become locked in this stage • Death not easy to avoid or evade indefinitely
Anger	"Why me? • I've lived a clean life giving to others • What did I do to deserve this?"	• May manifest in different ways • Angry with themselves, others, particularly those close to them • Acknowledging the above helps in being detached and non-judgmental in our interaction with those who are very angry and upset
Bargaining	"Yes it's me, but…" • Dr. Kubler-Ross cites a case of a terminal cancer woman requiring frequent pain medication • She bargained by making several promises to herself to live long enough to attend her son's wedding. • With the help of nurses for grooming and self-hypnosis for pain control, she was comfortable through the wedding. • On her return to the hospital, she was asked about her experience and stated "Don't forget, I have another son"	• Can involve bargaining with the God they believe in • Those facing less serious trauma can bargain or negotiate a compromise, e.g., "Can we still be friends?" if break-up is anticipated • Rarely provides sustainable solution particularly if it's a matter of life or death
Depression	"Yes, it's me" • Does not speak much • Usually bed bound • Slow eater	• A.k.a. Preparatory grieving • Different meaning depending on the involved individual • Acceptance with emotional attachment? • Natural to feel regret, sadness, uncertainty, etc. • Demonstrates the start of accepting reality
Acceptance	"Yes, its me, I am dying • Want to be remembered by family and friends • Need to get my affairs in order • Want to be comfortable • Do not want to die alone" • Easiest stage to deal with	• Also varies according to personal situation • Demonstrates some detachment and objectivity • Often enter this stage long before those they live behind

[a]Adapted from interpretation by Alan Chapman 2006–2013

Where?

The place to have the conversation will depend on the institution, but should be safe from distractions and private. The patient's room and a conference or consultation room are frequent sites. Patients' family members may be reluctant to have the conversation in the patient's room due to the concern that the patient might hear information that would cause them to lose hope, even if the patient is comatose or near death. Teleconferencing as a substitute for face-to-face meetings may be offered to health care team members and family, as well. Recent advances in internet communications have broadened the possibilities to participate remotely. There should be ample seating and adequate room for all, good acoustics, and a warm and nurturing environment, thus setting the tone of caring comfort, collaboration rather than intimidation.

How?

The facilitator, designated by the transdisciplinary concept of "the best person for the job," welcomes all. Each participant is asked to introduce themselves and state their relationship to the patient. Another team member is designated as a scribe who will provide a summary of the conversation and list of attendees for inclusion in the medical records. Attendees are often given the opportunity to review a draft of the summary before it is entered into the record.

Before discussing the case, and as discussed above, the family members are asked to provide more information regarding the patient prior to hospitalization in terms of values, profession family interaction, quality of life, etc. This helps insure that all know the patient better, helps humanize the patient to the health care team, and provides a more unified picture of the patient. The facilitator, or another designated team member, presents the case from the medical perspective, with recommendations from the health care team. This is followed by offering all representing the patient to speak or ask questions. Additional comments are subsequently solicited by the health care team. The scribe then provides a summary of the conversation including any subsequent steps or action plans as well the tentative time and place of the next meeting if deemed necessary. It is important, prior to departure that individuals be identified to be the respective contact and representative for the patient and the medical team for subsequent communications. This aids in avoiding confusion and miscommunication.

Ethnic, Cultural and Religious Diversity

Food and water are symbolic sources of life, nurturing, and caring, are tightly tied to socialization. They have significant spiritual and ritual connotations, different from any other aspect of medical treatment. A common experience in critical care is that it is difficult to effectively and optimally treat that which we cannot diagnose. A similar concept applies in clinical ethics. Each individual represents a unique persona, like a quilt composed of values, beliefs and practices united by a thread of culture, ethnicity and religion as exemplified in Case 2. It is essential that the health care team be knowledgeable as to the patient's and family's background along these lines. While an encyclopedic treatise on the subject is not possible in this chapter, some examples of various tenets of a sampling of religions and ethnicities are summarized in Table 12.5.

Table 12.5 Characteristics of patient-centered versus family-centered perspective on end-of life treatment decision making [27, 57, 80–94]

Patient-centered	Family-centered	Physician-centered
African-American, Black • Prefer more life-sustaining treatment compared to white patients • Feel that patient should be primary decision maker in end-of-life care • May view overly individualistic focus as disrespectful to family heritage • Perceive suffering as spiritually meaningful, and life as always having some value • Ceasing aggressive therapies may be equated with giving up • Perspective that end-of-life is in God's hands • Less likely to grieve openly and publicly *Catholicism* • Person has a moral obligation to use ordinary or proportionate means of preserving his or her life • Person may forgo extraordinary or disproportionate means of life • Medically assisted nutrition and hydration become morally optional when they cannot reasonably be expected to prolong life or when they would be excessively burdensome for individual or would cause significant physical discomfort, for example resulting from complications in use of means employed • Free and informed judgment made by a competent adult individual concerning use or withdrawal of life-sustaining procedures should always be respected and normally complied with, unless it is contrary to Catholic moral teaching *Caucasian, White (Non-Hispanic)* • Prefer less life-sustaining treatment than black patients • Feel that patient should be primary decision maker for end-of-life care • Concerned about dying individuals undergoing needless suffering *Judaism* • Withdrawal of continuous life-sustaining therapy is not allowed, but withholding further treatment is allowed as part of dying process, if it is an intermittent life-sustaining treatment, and if it was clear wish of patient • Food and fluid are regarded as basic needs and not treatment • It is permissible to withhold food and fluid if this is the individual's expressed wishes, when individual approaches final days of life, when food and even fluids may cause suffering and complications • Differs amongst Orthodox, Conservative and Reform *North American* • Emphasis placed on autonomy and openly discuss treatment decisions, norm is for individual medical care decision making • Rely on friends, church/synagogue/temple members, neighbors and non-relatives when death of loved one occurs *Protestantism* • Most will, if there is little hope of recovery, accept and understand the withholding or withdrawal of therapy *Mormon* • Individual choice • Promote a peaceful death when death is inevitable *Islam* • Most medical treatment accepted • Efforts to shorten life not permitted *Jehovah's Witness* • Use of extraordinary means is an individual choice • Administration of blood and blood products strictly forbidden *Australian* • Palliative care at home, but physician does not have to comply • Euthanasia not legal	*Asian (specific ethnic group not designated)* • Value physician's obligation to promote patient welfare by encouraging patient hope, even in terminal illness • Special status of elderly, should not be burdened with bad news • Illness is considered a family event rather than individual occurrence • Family members and physicians share decisional duties *Chinese* • Hope is considered very important in care of dying, as hope prevents suffering by avoiding despair, prefer family-centered decision making • Food represents more than source of energy; it embodies family, love, and caring • Much distress in terminal persons can be attributed to or related to anorexia and cachexia • Medical decision is usually based on best interests of person; treatment utility is often open to interpretation • Family members protect terminally ill individuals from knowledge of condition • Individuals and families do not discuss possible death due to belief that direct acknowledgement of mortality may be self-fulfilling • Stoic and fatalistic towards terminal illness and death *Hispanic* • Prefer less aggressive, comfort-focused end-of-life care • Favor family-centered decision making and limited patient autonomy • Family members actively protect terminally ill person from knowledge of condition • Consider family members, rather than individual alone, as holding decision making power regarding life support • May be reluctant to formally appoint a specific family member to be in charge because of concerns about isolating these persons or offending other relatives • Consensually oriented decision making approach appears to be more acceptable • Difficulty accepting death • Often stay with hospitalized loved one (shifts of vigil) • Encourage open expression of anger and grief *Korean* • Consider family members, rather than individual alone, as holding the decision making power regarding life support *Lebanese* • With every interaction at end-of-life, importance given to role of family • Loyalty to family is first in importance, even before religion, nationality, or ethnicity • Important to acknowledge family-oriented outlook and make family one of central elements in communication protocol *Pakistani* • Family members protect terminally ill individuals from knowledge of condition • Physicians may be adopted into family unit and addressed as parent, aunt, uncle, or sibling; this family status provides physician with role sanctioning involvement in intimate discussions *Christian Science* • Will not seek medical help to prolong life • May request a practitioner or reader *Confucianism* • Central concern is family, not individual • Decisions made by family elders or oldest son • Younger family members charged to care for elder members • Driven by "doing everything possible" to maintain life and hope despite physician designation of futile (low yield) interventions *Buddhism and Taoism* • Acceptance of inevitable regarded as taboo • Interventions, e.g., tube feedings, supported despite other considerations *Japanese-American* • May not ask questions regarding care or prognosis • Family members aware of dying but avoid discussing situation • Request to stay with dying patients *Armenian-American* • Designated family spoke person, decision maker • Subject of death may be avoided • Presence of family member critical • Terminal care preferred at home	*Bosnian* • Prefer physician, due to expert knowledge, make independent decisions to reduce burden on individuals and families • Expect physician to maintain individual's optimism by not revealing terminal diagnosis *Eastern European* • Tradition of physician-centered, paternalistic decision making • Physician rather than person or family often determines a person's level of life support

Ethics Committees

Active involvement and a strong partnership with the hospital ethics committee can help reduce conflict in the ICU. Consultation with the ethics committee, recommended by The Joint Commission since the 1970s, can provide the path to resolution when ethical chaos is encountered in the critical care unit. The composition of the committee varies, but it is recommended that it include representatives from various disciplines, including, but not limited to, medicine, nursing, nutrition, spiritual/religious, risk/legal, etc. In addition, many ethics committees also include public/patient representatives. The functions of the committee are carried out in a transdisciplinary fashion. Cases are referred to the committee for evaluation. They are first evaluated by a single individual or a designated subgroup of the committee to determine whether or not an ethical issue persists. If not, the issue is referred to another institutional department, i.e., administration, legal, risk/case management. The committee discusses and deliberates about the ethical issues of the case, and presents their recommendations. Conclusions of the committee are usually considered consultative, but in some institutions they may be binding [27].

The "Must" of the Law

Law often overlaps with ethics. A simplified schematic of the US legal system is provided in Fig. 12.4, demonstrating the components of criminal and civil law. The latter is the one most frequently associated with health care, whether tort (negligence, malpractice) and abandonment, or product liability.

Many legal decisions have been provided regarding end-of-life treatments and forgoing various interventions, particularly artificial nutrition, over the past five decades. Three seminal and precedent-setting cases are briefly mentioned here.

The case of Karen Ann Quinlan in 1976 prompted states to enact living will legislation and the development of hospital ethics committees. The Nancy Cruzan case prompted the US Supreme Court in 1990 to: (1) establish the authority of individual states to apply higher standards of evidence; (2)

Fig. 12.4 Schematic of US legal system. Reprinted from ref. [3]

determine that artificial nutrition and hydration are life sustaining interventions similar to ventilation and hemodialysis; (3) promote the increased use of Durable Powers of Attorney for Health Care Decisions or Healthcare Proxies. This case led to the enactment of the patient Self-Determination Act of 1990 [27].

The case of Terri Schiavo in 2004 [64, 65] led to the refinement of living will legislation in various states. In some states, legislation was enacted that required clear and convincing evidence before allowing the forgoing of artificial nutrition and hydration, as opposed to other medical interventions. This evidence might include a specific statement in an advance directive, or the trustworthy recall of a conversation in which specific wishes were made known.

Advance directives, powers of attorney for health care decision, health care proxies, and guardians ad litem are legal alternatives for the decisionally incapable or incompetent individual. Optimally an executed, annually revised, and readily available advance directive should be accompanied by a proxy (the document assigning the surrogate decision maker). It is preferable for the surrogate decision maker to review the advance directive and further discuss it with the author to ensure the surrogate understands clearly the wishes of the person they are representing. Further information regarding substituted judgment and surrogate decision making is found in the resource section of this chapter.

Health care providers have legal duties and/or obligations that cross-react with their ethical duties. Among the most common ones is the duty to provide safe, reasonable care within acceptable standards. It is the duty of the health care nutrition professional to assure that patients are nutritionally assessed and nourished in the most optimal fashion possible, including forgoing feeding when appropriate. However forgoing feeding should be an active decision and not a result of lack of attention. Likewise appropriate monitoring and frequent reassessment should be conducted. Failure to discharge these obligations may result in charges of unintentional negligence and malpractice not only against the practitioner but also the health care institution [66]. Legal action must be based on four elements summarized in the ABCD Rule of Palmisano [67]. The health care professional must *A*ccept the patient in an established relationship; *B*reach the duty to provide the acceptable standard of care; *C*ause by an act of omission or commission; and cause *D*amage that is directly related to the cause.

As seen in the case of Jahi McMath (Case 2, above), patients and families often demand interventions that are not acceptable to the health care provider. The same respect for autonomy principles apply to the providers who have to make individual decisions as to their professional and personal ethics. Unless in a dire emergency, a provider is not under any ethical or legal obligation to acquiesce to demands of care he or she does not feel is appropriate. In the case of an unresolvable conflict between caregiver and patient or surrogate, the ethical and legal duty to maintain continuity of care still exists. Thus, transferring care to another qualified professional should be sought as diligently as possible. Otherwise, the provider will be vulnerable to charges of abandonment. Abandonment can be defined as "the unilateral severance of the professional relationship without reasonable notice under the circumstances when continued attention is required" [3]. Refusal to treat, insufficient or delayed treatment, withdrawal without adequate notice and premature discharge are potential triggers for allegations of abandonment [57]. It is rare for health care professionals to be charged with intentional tort or criminality in relation to omission or commission acts related to ANH. However, malpractice cases have been brought over inappropriate or lack of nutrition support in the hospital.

Applied Nutrition Support Clinical Ethics for the Critically Ill

The following case is presented to identify the importance of engaging the family in a collaborative process for ethical decision making. Family dynamics including religion impact on the decision maker, nutrition therapies, and the ethical components will be discussed.

Case 3

A 60-year-old man was admitted with intra-cerebral hemorrhage and a history of hypertension and bipolar disorder. He had extensive bilateral subarachnoid hemorrhage, requiring enteral and parenteral nutrition, and mechanical ventilation. He progressed to multiple organ failure.

The nutrition component of the patient's care was an easy concept for the patient's family to understand. Although the nutrition was provided through tubes, this represented love and nurturing to the family. The artificial nutrition was comparable to food to them and provided a sense of normalcy. Due to the altered metabolic and gastrointestinal function, changes were made in the alimentation throughout the patient's course. This resulted in frequent discussion between the patient's family and nutrition support clinician. Indirect calorimetry was incorporated into the nutrition assessment parameters, which added to the family's understanding that the nutrition therapy was tailored specifically for their family member. Enteral feeding was stopped due to abdominal distention with possible bowel obstruction, and parenteral nutrition was then initiated.

Multiple medical interventions to stabilize his metabolic derangements added to the complexity of the case and to the family member's heightened emotional state. Coming into the hospital room and seeing their loved one connected to so many intravenous solutions and tube feeding with numerous pumps and a ventilator created a startling picture in comparison to normality for this family. The progression of respiratory failure, hemodynamic failure, renal failure, gut failure, skin integrity failure, in addition to the overwhelming damage to the brain, led the health care team to conclude that continuing low yield medical interventions would not improve the patient's eventual outcome from this acute illness leading to death.

Family/health care team conferences were held throughout the hospitalization. These meetings included physicians, social worker, nutrition support clinician, chaplain, case manager, the patient's son (the decision maker) and older family members. The older family members recognized the clinical status, as presented by the medical team, would not result in a quality of life presumed acceptable to the patient. If he survived his multiple organ failures, he would require a tracheostomy, gastrostomy, and transfer to a long-term care facility for an indefinite period of time, without anticipated improvement in his current clinical status. In fact, even if he were to be able to survive to that point, further deterioration in his condition was the expectation. The decision to place a gastrostomy feeding tube was problematic, especially with the continued inability to tolerate nasogastric tube feedings.

During the course of the acute illness, the palliative care team was consulted to support the patient's decision maker and other family members to determine the best choices for treatment options, reflective of what the patient would have wanted in this situation. Unfortunately the patient did not have an advance directive, nor was there any prior family discussion on quality of life goals and wishes for medical treatments in the face of an acute, progressive, declining organ function illness.

The older family members were supportive of the patient's son being the final decision maker, patiently providing him time and being careful to avoid forcing him into a decision before he could comprehend the whole picture of his father's condition. However, the decision maker expressed difficulty in ceasing medical treatments based on the following: (1) there was such a short period of time from being normal to the patient's current clinical state of total body failure, especially the brain; (2) the son had seen opening of his father's eyes, which represented improvement to the son, but not to the medical team.

After repeated meetings with the team, discussions with the family, the decision maker decided to forgo tracheostomy and gastrostomy. Instead, compassionate extubation was chosen. Some of the determinants that made the decision possible for him included the following:

1. The son ultimately did not see improvement in his father's clinical status, only deterioration over 3 weeks.
2. The patient could not be fed enterally, despite several attempts to transition from TPN. Cessation of efforts to feed the patient enterally was eventually recognized as more appropriate to the patient's son than it was initially.

3. The palliative care team physician director indicated to the decision maker that all of the physicians on the case were in agreement that the patient's clinical status would not improve.
4. Acceptance by the son that the patient's presumed quality of life wishes would not be achieved were he to remain in a long-term care facility connected to tubes for mechanical ventilation and nutrition for the remainder of his life.
5. Reasonable requests by the decision maker for the scheduling of the compassionate extubation had been implemented by the health care team. This included delaying the extubation due to the family's religious holiday and having the extubation occur outside the hospital.
6. Health care team members supported both the decision maker and older family members, providing insight on the medical treatments provided, including ANH therapies.

Development of a Proactive, Integrated, Systematic Process to Prevent Ethical Dilemmas in Critical Care

Organizational Performance Improvement in the Intensive Care Unit

Performance improvement in ethical decision making in the ICU has been proven to decrease the unnecessary utilization of resources during the end-of-life period without impacting mortality rates, is viewed positively by patients and families [68, 69], and results in a reduction in cost of care [70]. As a result, supporting a strong ethics program should be a priority for hospital administration.

Organizational performance improvement follows the IDEAL method: (1) Identify the problem; (2) Describe and measure the current process; (3) Explore solutions and generate ideas from a transdisciplinary health care clinician group; (4) Act and modify the process; (5) Look back and remeasuring the parameters identified to determine improvement and sustainability. Further, results should be shared with other organizations. Simple, yet important examples of organizational performance improvement projects are the quantification of the number of patients in ICU on ANH, the percentage of patients with an advance directive, the number of family care conferences, and the frequency of palliative care consults and ethics consults. The development of a policy for ethical decision making for artificial nutrition will assist in memorializing changes made via the performance improvement process, and help to guide practice more broadly. Examples of policies for ethical decision making for ANH are available in the literature [57]. Ongoing quality data collection might include such things as ventilator days, length of ICU stay, decrease overall hospital length of stay, earlier transfer to lower level of care within the hospital or to outside facilities, ICU readmission, and use of interventions such as ANH designated as low yield in specific contexts.

Engagement and education of clinicians, as well as feedback on adherence on the policies and procedures promotes those processes to insure the successful implementation and sustainability for the interventions. Figure 12.5 provides an example of a flow chart that could be used to develop and present the process of implementation of ICU patient-centered health care communication for ANH practice. Figure 12.6 summarizes important cultural and religious attitudes.

Bridging the Communication Gap between Clinicians and Patients/Family/ Surrogate Decision Makers

Table 12.6 presents actual conversations between the ICU health care clinicians and patient's family members or surrogate decision makers. These conversations provide an example of transdisciplinary discussions, as the conversations are not led by just one discipline.

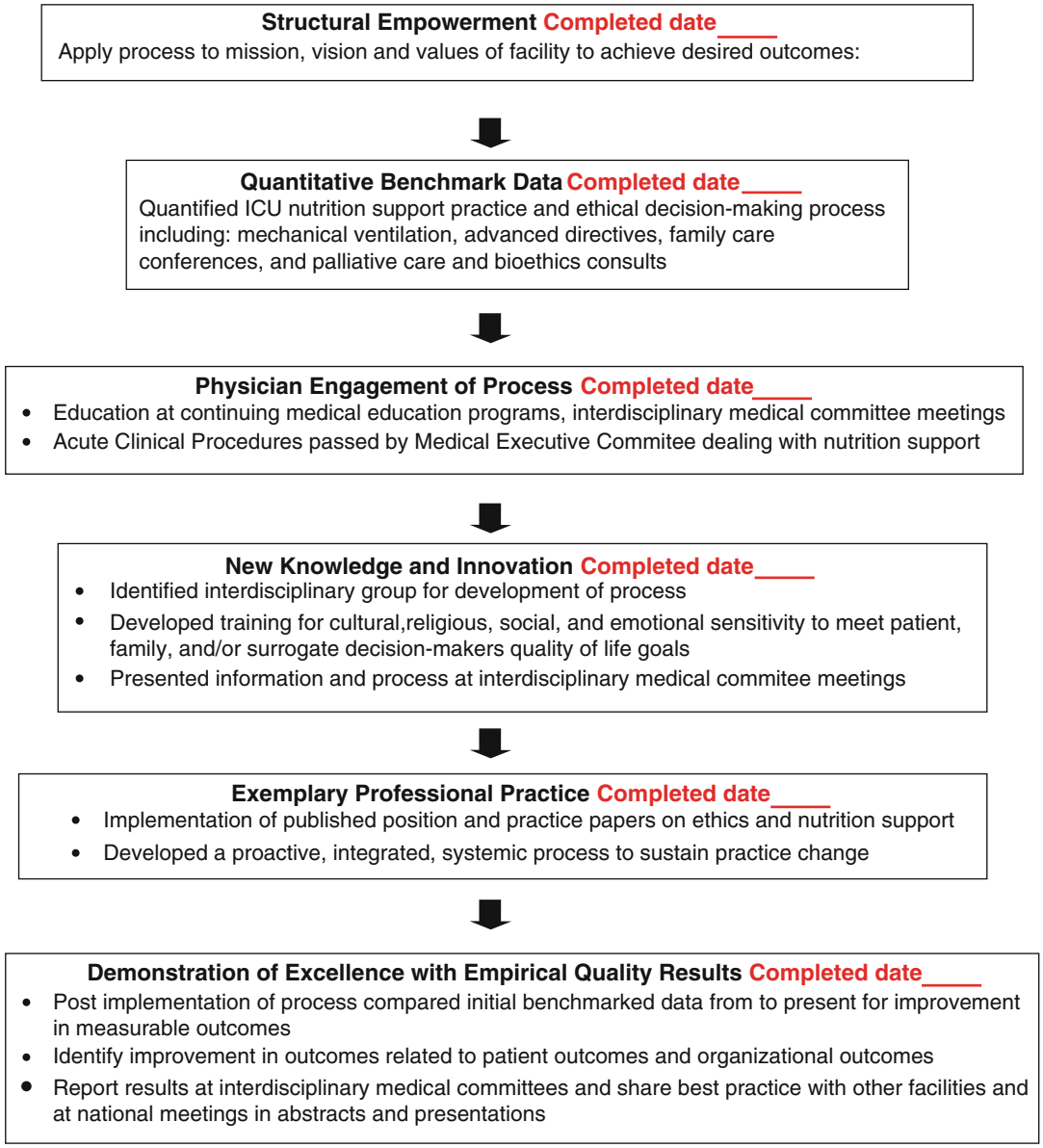


Fig. 12.5 Flowchart implementation of ICU patient-centered health care communication for nutrition support practice

One of the greatest hurdles to overcome in ethics discussion is getting the conversation started. This may be accomplished by a simple discussion about patient-centered care or aspects of ANH therapies, not only by the physician, but other health care professionals. Clinicians from different disciplines may bond with the patient, family or surrogate decision maker, due to commonalities such as culture, faith, ethnicity, age, or even approach, both body and verbal language. The patient, family, or surrogate decision maker may feel an unspoken sense of caring from a clinician, which results in enhanced communication about patient wishes. This should be embraced as a tool to open the conversation about patient wishes for quality of life goals. Communication has to be effective, respectful, and consistent such that the patient/surrogate feels valued and the conversation can flow easily between disciplines and between the care team and the patient/surrogate.

When	What	Who	How
Nutrition support planned/ordered in ICU	Patient, family, and/or surrogate decision-maker education on nutrition support	Nutrition Support Clinician	Review medical record including advance directive and other sources for patient quality of life goals. Engage, empower, and educate patient, family, and/or surrogate decision-maker on nutrition support

Nutrition Support Clinician Focus on Triggers for *Cue-Based Discussion* during nutrition support education with patient, family, and/or surrogate decision-maker, incorporating cultural, religious, social, and emotional sensitivity.

- Patient/person-centered healthcare based on patient wishes
- Family to express what patient would want
- Family and/or surrogate decision-makers role is to represent the patient's wishes and not their own
- Patient, family, and/or surrogate decision-maker are healthcare team members

Nutrition Support Clinician Communicates verbally and in medical record with all appropriate healthcare team members any pertinent concerns/information obtained from patient, family, and/or surrogate decision-maker during nutrition support education.

> Example: During education on a tube feeding to start later that day, family indicates to the nutrition support clinician the patient would not want feeding through tubes and has a document indicating that information, but the document is not on the chart. Nutrition support clinician would then refer the patient, family, and/or surrogate decision-maker to primary care physician for further discussion and notify patient's nurse and social worker, as appropriate for further follow-up and document social worker referral in medical record.

Pertinent Information for Nutrition Support Clinician to be aware of at each facility:

- What is the process for obtaining patient's advance directives, who is involved, where is advance directive located in the patient's chart/electronic medical record?
- Who is responsible for clarification of surrogate decision-maker, what is the process, where is information found?
- Does the facility have a palliative care team and what is the process for palliative care consultation?
- Is there a process for family care conferences, criteria, who sets them up, can nutrition support clinicians be included when needed?
- Is there an Ethics Committee; is a nutrition support clinician on the committee, what is the process for an ethics consult?

Fig. 12.6 Process to optimize ICU clinical ethics and nutrition support communication with health care team and patients, family, and/or surrogate decision maker

Table 12.6 also illustrates the key components in the ability to change the culture of care may include focusing the family and surrogate decision makers on patient-centered care and not themselves, and the awareness of pain being felt by the critically ill patient.

Table 12.6 Sample communication between ICU health care clinician and patient's family member/surrogate decision maker

Health care clinician question	Patient's family member/surrogate decision maker response
Is there anything more the health care team could have done to have helped you during this long hospitalization of your partner?	You could have made me understand that I represented him and not me! (This was said with his fist in the air and strong emotion)
All of the clinicians here focus on patient-centered care. This means we want to do the medical treatments and therapies that the patient would want. Since he is not able to speak for himself at this time, we rely on his spokespersons to tell us exactly what he would want in terms of medical treatments Are you that person?	Yes, I am. He does not want any tubes *Clinician response*: Which tubes are you talking about, since as you can see he has many tubes at this time? *Surrogate*: He does not want a tube coming out of his throat or a tube coming out of his stomach. He talked about this over the years and he made me promise not to have those tubes *Clinician response*: Do you have anything in writing about this? *Surrogate*: No, his mother had these tubes and he never wanted them for himself. My goal is for him to walk out of this room and come home *Clinician response*: That is the same goal that the health care team has too. We are all focused on that goal. I will let the physician and your patient's nurse know what you have just told me. Please tell your partner's physician what you have just told me
Patient's family member/surrogate decision maker response	*Health care clinician question*
Is there any hope that the GI tract will start to work again?	With so many organs not working and the GI tract not working despite several attempts, this remains another system in his body that continues not to work
Do miracles ever happen at this hospital?	Yes, I believe that miracles happen here, but they are not always the ones that you are praying for to happen
Do you think he is in any pain? I would know if he was in pain.	How could he not be in pain, he has two tubes coming out of his lungs, he remains on a ventilator, he has skin breakdown, he has to be turned throughout the day, he requires frequent dialysis He is in the room 24/7 with multiple medical treatments and therapies throughout the day
	A couple of weeks after the conversation above the surrogate decision maker asked: I have a question for you. I had diarrhea this weekend and it really hurt. Did you pray that I would have that pain? *Clinician response*: No, I did not pray that you would have diarrhea and feel the pain

The 12 Cs Approach

One practical approach to dealing with the ethical chaos (troubling trichotomy) of ANH in critical care are the 12 Cs (Fig. 12.7) [86]. Communications is the most important for the reasons previously discussed. Competence encompasses updated evidence-based medicine presented in plain language to the patient and family [87, 88]. Appropriate informed consent can be obtained in a patient-centered environment can be obtained using the EBM/E_3BM approach [89]. Consultation should be sought sooner rather than later when questions arise or there is uncertainty as to the available ('when in doubt, give a shout"). Concern should be inclusive, sensitive to diversity, and appropriate terminology used to facilitate the critical/crucial conversations [90]. Finally, as is the case for all health care professionals, our goals are to cure rarely (e.g., appendectomy), treat often (e.g., pneumonia or hypertension), but comfort always (e.g., being caring and compassionate) (Fig. 12.8).

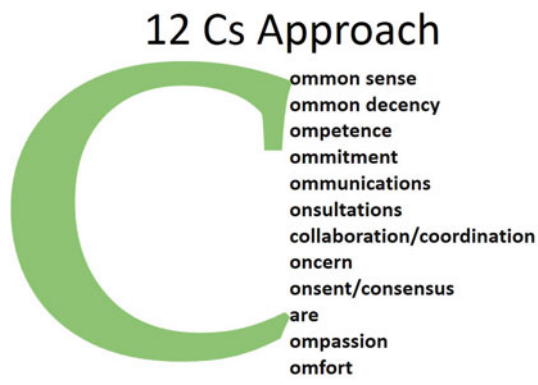


Fig. 12.7 12 Cs in dealing with the troubling trichotomy

Fig. 12.8 Goals of health-care professionals. Reprinted from ref. [3]

Concepts and Tools for Use in Applied Clinical Ethics

Patient-Centered Care

Patient-centered care shifts the focus away from disease and back to patient and family. The care that is provided is respectful of and responsive to individual patient's preferences, needs, and values. Patient values should guide all clinical decisions. Table 12.7 indicates the five steps that clinicians can use to connect with the patient and family. A simplified tip sheet is found in Fig. 12.6 that clinicians can use to incorporate communication tools into their nutrition support practice [46, 52, 73–75].

Incorporating the processes presented in Table 12.7 and Fig. 12.6 could be evaluated and used as part of the organizational performance improvement. The evaluation tool shown in Fig. 12.9 for ICU patient-centered health care communication for nutrition support practice includes both the health care team and patient, family, and/or surrogate decision-maker satisfaction.

Table 12.7 Five steps for nutrition support clinicians to connect with the patient and family

Steps	Process
1. Develop rapport	• Review patients chart for clinical status, including advance directive • Ask the patient, family, and/or surrogate decision maker to be allowed to enter their room • Introduce yourself, including name and reason for visit • Talk slowly, respectively, make eye contact, and sit down, if possible • Determine the connection of the visitors in the room to the patient
2. Determine concerns	• Ask the patient, family, and/or surrogate decision maker if there are any concerns that should be addressed before starting to provide information and education • Resolve these concerns and/or indicate who should be contacted to further discuss these concerns
3. Educate on nutrition therapy	• Determine language preferred for education, obtain approved translation service • Provide simplified language discussion about the patient's nutrition status and nutrition therapies being planned • Use the teach-back method to determine the patient, family, and/or surrogate decision maker's ability to understand, process, and use the information for therapy decisions • Review written information on the therapy if requested, in patient's preferred language for education
4. Focus on patient-centered care	• Introduce the patient-centered care concept to redirect the family and/or surrogate decision maker's role in the therapy decision process • The health care clinician would state, "All of the health care clinicians are focused on patient-centered care. We want to provide all therapies, including nutrition through tubes, based on the patient's wishes. If the patient is not able to tell us what they would want, we rely on the family or designated decision maker to tell us what the patient would want"
5. Communicate care response	• Contact other health care clinicians based on the responses as to the patient, family, and/or surrogate decision maker's concerns • Determine need to expedite communication with health care team members, based on need to modify current therapies being provided or planned for in the future for the patient • Document the information in the electronic medical record

Sensitivity Awareness in the Critically Ill

Sensitivity Awareness in the Critically Ill is a major factor to consider when dealing with individuals from different countries, faiths, and ethnic groups. Table 12.5 identifies aspects of the diversity in relationship to patient-centered versus family-centered focus for end-of-life treatment decision making [28, 57, 71–85].

In actuality everyone should be treated as encompassing a diverse perspective on ethical considerations for decision making, especially for the critically ill. There is no *one model* that is representative of an individual or family dynamics when removed from their normal lives and thrust into a dynamic emotionally charged environment, where life and death decisions are made with and sometimes by strangers. This perspective is incumbent on the health care clinician to approach all patients and family with respect and sensitivity, as we learn collectively what will make the patient and family recognize we have their best interest in the care of the patient as our goal. The knowledge of this information and communication can only be facilitated by the health care clinicians gaining respect and trust of the patient, family, and surrogate decision makers.

Table 12.6 provides sample communication between ICU health care clinicians and patients, family members, and surrogate decision makers. The conversations are unique and demonstrate the need to clarify concepts and deal with simplified language to improve the understanding of the information presented by the health care clinicians. Table 12.8 incorporates the 12 Cs into the crucial conversations that occur between health care clinicians and patients, family members, and surrogate decision makers.

Nutrition support clinician name (print) _____ Date_____ Time_____

Complete Before Patient Visit

Patient demographics:

Place patient sticker (name, MR# age, admit date) here

Cultural Diversity:

Religion _____

Race_____

Ethnicity
and or language _____

Patient Admit to ICU from ER or_____ Reason for Admit from other unit _____

Decision-making Documentation in Chart:

Yes/No (circle) DPAHC and/or POLST (date _____)

Patient wishes_____

Decision-maker (relationship to patient) _____

Patient code status_____

Clinical Status:

Admit diagnosis _____

Was patient able to participate in discussion? Yes/No (circle) If not, why?_____

Complete After Patient Visit

Healthcare Team Member Evaluation of Process:

Family member(s)/surrogate decision-makers name participating in discussion_____

_____

Was this process helpful? Yes/No (circle) (Least 1 2 3 4 5 Most)

Explain_____

_____

How could this process be improved?_____

_____

Patient, Family, and/or Surrogate Decision-Maker Evaluation of Information/Process:

Was patient able to verbalize information provided? Yes/ No (circle)

Was this information helpful? Yes/ No (circle)

Explain_____

_____

How could this information/process be improved?_____

Fig. 12.9 Evaluation tool for ICU patient-centered health-care communication for nutrition support practice

Shared Decision Making

Shared decision making emphasizes the importance that patients are educated on the essential role in participating in selecting medical treatment alternatives and given effective tools to help understand options and consequences of decisions. Patients receive emotional support to express values and preferences and are able to ask questions without censure from clinicians. In the shared decision-making process, clinicians need to relinquish their authoritative role and train to become more effective coaches or partners. Shared decision making is a pinnacle of patient-centered care [91].

Table 12.8 Crucial conversations and the 12 Cs

Twelve Cs	Application to scenario
Common sense	What is important and the key to success is neither the advance directive nor the advance care plan, but rather the critical/crucial conversation(s) that precedes and continues after executing both of them
Common decency	The voice of all stakeholders should be heard and respected
Competence	Sound ethical decisions are founded upon solid science. Nutrition support professionals should bring to such conversations a command of the evidence base for ANH in particular conditions
Commitment	Perhaps the most crucial counsel to all those struggling with ANH decisions is to continue the conversation so that the surrogate, family, and all practitioners involved in the case can keep the focus where it belongs on the values, interests, and welfare of the patient
Communications	These often difficult conversations/communications must be inclusive of all stakeholders, be patient-centered, provide evidence-based facts, arrange for adequate time for questions, and in language understood by all
Consultation	Nutrition support professionals, chaplains, and other specialists relevant to a specific case can provide invaluable assistance as can the involvement of an ethics consultation service
Collaboration	The concept of transdisciplinarity, while not often associated with nutrition support teams, is pivotal to the crucial conversations regarding ANH in the specific disease and states and entities discussed in this chapter. Thus, in addition to the adage that "There is no I in team," each member of the teams needs to realize that "There is no success without 'U'."
Consent/consensus	To be successful, these conversations must incorporate the patient's, family's, and physician's medical goals of care, but also consider the cultural values and religious beliefs of family, patient, and professionals
Concern	It is the conversation that is important as a sign and expression of mutual concern
Care goals	These conversations, to be successful, must incorporate not just the medical goals of patient, family, and team, but also consider the cultural values and religious beliefs of family, patient, and professionals
Compassion	Compassion for the suffering of the patient or even perception of suffering on the part of the family must be the motivating force and remain at the center of these conversations
Comfort	Comfort that can "always be provided" when cure is impossible and treatment is temporary and partial should be the unifying thread running through the discussion

ANH artificial nutrition and hydration

Preventive Ethics

Preventive ethics is based on the premise that ethical conflicts are largely preventable. By identifying common triggers of ethical conflict a proactive approach can be developed to alter the process that results in the ethical dilemma. Preventive ethics results in a dramatic shift from traditional ethics approach, which uses a case-by-case approach to deal with the problem before it occurs [92].

Health Literacy

Health literacy is essential for both health care provider and recipient of the health treatment and information. There is a major problem as to the patient's understanding of what a health care provider says to them. Adequate health literacy involves the capacity to obtain, process, and understand basic health information and services needed to make appropriate decisions. Patient-centered care focuses on improving health literacy [93, 94].

Teach-Back Method

Teach-back method ensures that individuals understand what they have been taught. Providing the education for the patient is not sufficient, teach-back method requires demonstration by the individual taught that they understand the information. Asking the patient to demonstrate what they have been taught or express the information back is used in this process. If patient does not explain correctly, the individual is retaught using a different method and then asked to explain or demonstrate what they have been taught again [94].

Palliative Care Consultation

Palliative care consultation involves an approach that improves the quality of life for the patient and their families facing the problem associated with life-threatening illness. This is accomplished through the prevention and relief by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual [95].

Core members of a palliative care team include a physician, nurse, social worker, and chaplain. Additional health care clinicians are available at different facilities depending on the patient population needs and the expertise of the clinicians. Nutrition support clinicians, pharmacists, recreational therapists, and psychologists could also be involved with the palliative care process [96, 97].

Advance Directives

There is a misconception by the patient, family, and surrogate decision maker about advance directives, concerning how decisions should be made for the critically ill. This is especially true when an advance care directive is present, but neither the patient nor family has recently read the document. Often advance directives are vague and do not provide clear cut information on how to handle various situations that occur in the critical care setting. Examples of documents that include specific reference to nutrition therapies are listed in Table 12.9.

Table 12.9 Examples of nutrition content in advance care forms

Advance care form	Content information dealing with nutrition
Five wishes	I want to be offered food and fluids by mouth, and kept clean and warm Life-support treatment means any medical procedure, device or medication to keep me alive. Life-support treatment includes: medical devices put in me to help me breathe; food and water supplied by medical device (tube feeding); cardiopulmonary resuscitation (CPR); major surgery; blood transfusions; dialysis; antibiotics; and anything else meant to keep me alive
Physician Orders for Life-Sustaining Treatment (POLST)	Artificially administered nutrition: Offer food by mouth if feasible and desired No artificial means of nutrition, including feeding tubes Trial period of artificial nutrition, including feeding tubes Long-term artificial nutrition, including feeding tubes Additional orders:

Resources

Patient-Centered Outcome Research Institute (PCORI)

PCORI helps answer patient-centered care questions such as:

1. What are my options and what are the potential benefits and harms of these options?
2. How can clinicians and the care delivery systems they work in help me make the best decisions about my health and health care?

www.pcori.org/

The Conversation Project

1. A grass-roots effort in collaboration with Institute of Healthcare Improvement (IHI) to normalize the conversation about end-of-life care.
2. Intent to make talks easier, forum for sharing stories, and resources for conversation, starter kit, and guides to help people.

www.theconversationproject.org

Conversation-Ready Health Care Community developing reliable care processes based on the following core principles:

1. Engage with our patients and families to understand what matters most to them at the end-of-life.
2. Steward this information as reliably as we do allergy information.
3. Respect people's wishes for care at the end-of-life by partnering to develop shared goals of care.
4. Exemplify this work in our own lives so that we understand the benefits and challenges.
5. Connect in a manner that is culturally and individually respectful of each patient.

Institute for Healthcare Improvement. Collaborative Conversation Ready Health Care Community. http://www.ihi.org/Engage/collaboratives/ConversationReadyCommunity/Pages/default.aspx

National Healthcare Decisions Day

1. Initiated to inspire, educate, and empower the public and providers about the importance of advance care planning.
2. Focus on importance of documenting an individual's wishes for health care, including nutrition therapies.

www.nhdd.org/

Conclusion

The chapter focused on the Troubling Trichotomy of what can be done technologically, what should be done ethically, and what must be done legally for critically ill patients, with particular emphasis on concerns regarding artificial nutrition and hydration. Application of the principles presented, through

case studies, were then used in the development of a proactive, integrated, systematic process to prevent and deal with ethical dilemmas in the critical care setting. The role of communication via a transdisciplinary approach, with respect for the patient's wishes and dignity, was emphasized as essential in patient-centered care. Resources were provided to enhance continued learning in this evolving field of applied clinical ethics. The chapter provides the nutrition support and/or critical care professional the background and tools to adapt the various recommendations to their own environment.

References

1. Bone RC. Sir Issac Newton, sepsis, SIRS and CARS. Crit Care Med. 1996;24(7):1125–8.
2. Bone RC, Balk RA, Cerra FB, Dillinger RP, Fein AM, Knaus WA, et al. Definitions of sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP-SCCM Consensus Conference Committee. Chest. 1992;101(6):1644–55.
3. Barrocas A, Yarbrough G, Becnel PA, Nelson JE. Ethical and legal issues in nutrition support of the geriatric patient: the can, should and must of nutrition support. Nutr Clin Pract. 2003;18:37–47.
4. Barrocas A. Nutrition support and the troubling trichotomy: a call to action. Nutr Clin Pract. 2006;21(2):108–12.
5. In re Cruzan. 497 U.S. 261; 1108. Ct.2841; 111L, ED2d 224;1990 U.S. Lexis 3301; 58 U.S.L.W. 4916, 1990.
6. Fine RL. Ethical issues in artificial nutrition and hydration. Nutr Clin Pract. 2006;21(2):118–25.
7. Beauchamp TL, Childress JF. Principles of biomedical ethics. 5th ed. New York, NY: Oxford University Press; 2001.
8. Schloendorff v. Society of New York Hospital, 211 N.Y. 125, 129-130, 105 N.E. 92, 93 (1914)
9. Mueller PS. The Terri Schiavo saga – ethical and legal aspects and implications for clinicians. Arch Med Wewn. 2009;119(9):574–80.
10. Baumrucker SJ. Continuation of feeding tube. Am J Hosp Palliat Care. 2006;23:236–40.
11. Uniform Determination of Death act. National Conference of Commissioners on Uniform State Laws. 1981.
12. Wijdicks EFM, Varelas PN, Greer DM. Evidence-based guideline update: determining brain death in adults. Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2010;74: 1911–8.
13. Wilson J, Christensen. Why brain dead means really dead. http://www.cnn.com/2014/01/06/health/brain-dead-basics/index.html. Accessed 4 June 2014.
14. Ecker JL. Death in pregnancy – an American tragedy. N Engl J Med. 2014;370(10):889–90.
15. Texas Constitution and Statutes. Health and safety codes http://www.statutes.legis.state.tx.us/docs/hs/htm/hs.166.htm#166.049. Accessed 4 June 2014.
16. Magnus DC, Wilfond BS, Caplan AL. Accepting brain death. N Engl J Med. 2014;370(10):891–4.
17. Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). N Engl J Med. 1994; 330:1499–508.
18. Gostin LO. Legal and ethical responsibilities following brain death: the McMath and Muñoz cases. JAMA. 2014;311:902–4.
19. Daily Mail Reporter. Family of 'brain-dead' Jahi McMath say teen is showing signs of life as they blast state's report on hospital's handling of her case as 'BS'. Dailymail.com. March 15, 2014. http://www.dailymail.co.uk/news/article-2581522/Family-brain-dead-Jahi-McMath-say-teen-showing-signs-life-blast-states-report-hospitals-handling-case-BS.html. Accessed 4 June 2014.
20. Gomes Jr CA, Lustosa SA, Matos D, Andriolo RB, Waisberg DR, Waisberg J. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for adults with swallowing disturbances. Cochrane Database Syst Rev. 2012;3, CD008096. doi:10.1002/14651858.CD008096.pub3.
21. Landau E. When 'life support' is really 'death support'. http://www.cnn.com/2013/12/28/health/life-support-ethics/index.html. Accessed 4 June 2014.
22. Szabo I. The ethics of being brain dead: doctors and bioethicists discuss Jahi McMath and Marlese Muñoz. USA Today. 10 Jan 2014
23. The Hippocratic oaths-classical and modern. http://www.pbs.org/wgbh/nova/body/hippocratic-oath-today.html. Accessed 4 June 2014.
24. World Medical Association Declaration of Helsinki. Ethical principles of medical research involving human subjects. JAMA. 2013;310(20):2191–4.
25. Lipman TO. Ethical issues in nutrition support and cancer. Nutrition Week Program Handbook. American Society for Parenteral and Enteral Nutrition. 2004;812–4

26. Keown J. Medical murder by omission? The law and ethics of withholding and withdrawing treatment and tube feeding. Clin Med. 1993;3(5):460–3.
27. Barrocas A, Bivona B, Schwartz DB. Medical and legal aspects, Chapter 46. In: Buchman A, editor. Clinical nutrition in gastrointestinal disease. Throfare, NJ: Slack; 2006.
28. Knox LS. Ethics and nutrition support in the intensive care unit. Crit Care Nurs Clin North Am. 1993;5(1):17–21.
29. Emmanuel LL, von Gunten CF, Ferris FD (Eds). Education for physicians on end-of-life care. Module 9:1-13. Chicago, IL: EPEC Project. The Robert Wood Johnson Foundation; 1999.
30. Braddock 3rd CH, Edwards KA, Hasenberg NM, Laidley TL, Levinson W. Informed decision making in outpatient practice: time to get back to basics. JAMA. 1999;282(4):2313–20.
31. Mitchell SL, Teno JM, Kiely DK, Shaffer ML, Jones RN, Prigerson HG, et al. The clinical course of advanced dementia. N Engl J Med. 2009;361:1529–38.
32. Dooneief G, Marder K, Tang MX, Stern Y. The clinical dementia rating scale: community-based validation of "profound" and "terminal" stages. Neurology. 1996;46:1746–9.
33. Choi SH, Lee BH, Kim S, Hahm DS, Jeong JH, Yoon SJ, et al. Interchanging scores between clinical dementia rating scale and global deterioration scale. Alzheimer Dis Assoc Disord. 2003;17:98–105.
34. Barrocas A, Geppert C, Durfee SM, Maillet JO, Monturo C, Mueller C, et al. A.S.P.E.N. ethics position paper. Nutr Clin Pract. 2010;25(6):672–9.
35. Haddad RY, Thomas DR. Enteral nutrition and enteral tube feeding. Review of the evidence. Clin Geriatr Med. 2002;18(4):867–81.
36. Oyoga S, Schein M, Gardezi S, Wise L. Surgical feeding gastrostomy: are we overdoing it? J Gastrointest Surg. 1999;3(2):152–5.
37. Abuskis G, Mor M, Segal N, Shemesh I, Plout S, Sulkes J, et al. Percutaneous endoscopic gastrostomy: high mortality in hospitalized patients. Am J Gastroenterol. 2000;95(1):128–32.
38. Grant MD, Rudberg MA, Brody JA. Gastrostomy placement among hospitalized Medicare beneficiaries. JAMA. 1998;271(24):1973–6.
39. Finucane TE, Christmas C, Travis K. Tube feedings in patients with advanced dementia: a review of the evidence. JAMA. 1999;282(14):1365–70.
40. Murphy LM, Lipman TO. Percutaneous endoscopic gastrostomy does not prolong survival in patients with dementia. Arch Intern Med. 2003;163(11):1351–3.
41. Cervo FA, Bryan L, Farber S. To PEG or not to PEG: a review of evidence for placing feeding tubes in advanced dementia and the decision making process. Geriatrics. 2006;61(6):30–5.
42. Gillick MR. Rethinking the role of tube feeding in patients with advanced dementia. N Engl J Med. 2000;342(3):206–10.
43. Schwartz DB, Barrocas A, Wesley JR, Kliger G, Pontes-Arruda A, Arenas Márquez H, et al. Gastrostomy tube placement in patients with advanced dementia or near end of life. Nutr Clin Pract. 2014;29:829–40.
44. Meier DE, Ahronheim JC, Morris J, Baskin-Lyons S, Morrison RS. High short-term mortality in hospitalized patients with advanced dementia: lack of benefit of tube feeding. Arch Intern Med. 2001;161(4):594–9.
45. Sampson EL, Candy B, Jones L. Enteral tube feeding for older people with advanced dementia. Cochrane Database Syst Rev. 2009;2, CD007209.
46. O'Sullivan Maillet J, Schwartz DB, Posthauer ME. Position of the American Dietetic Association: ethical and legal issues in feeding and nutrition. J Acad Nutr Diet. 2013;113:828–33.
47. Körner U, Bondolfi A, Bühler E, Macfie J, Meguid MM, Messing B, et al. Introduction part to the ESPEN guidelines on enteral nutrition: ethical and legal aspects of enteral nutrition. Clin Nutr. 2006;25(2):196–202.
48. Ciocon JO, Silverstone FA, Graver LM, Foley CJ. Tube feedings in elderly patients. Indications, benefits and complications. Arch Intern Med. 1988;48(2):429–33.
49. Ellenshaw JE, Sutcliffe JM, Saunders CM. Dehydration and the dying patient. J Pain Symptom Manage. 1995;10(3):192–7.
50. Friederich L. End-of-life nutrition: is tube feeding the solution? Ann Long Term Care. 2013;16:1263–6.
51. McCann RM, Hall WJ, Groth-Juncker A. Comfort care for the terminally ill patients. The appropriate use of nutrition and hydration. JAMA. 1994;272(16):1263–6.
52. Schwartz DB. Integrating patient-centered care and clinical ethics into nutrition practice. Nutr Clin Pract. 2013;28(5):543–55.
53. Murakani JF, Wong WF. The decision to withdraw tube feeding. Hawaii Med J. 1995;54:483–9.
54. Franklin C, Weil MH. When critically ill patients refuse life-sustaining care. Semin Anesth. 1991;10(3):195–202.
55. Braithwaite RS. EBM's six dangerous words. JAMA. 2013;310(20):2149–50.
56. Altman DG, Bland JM. Absence of evidence is no evidence of absence. BMJ. 1995;311(7003):485.
57. Geppert CMA, Barrocas A, Schwartz DB. Ethics and law (chapter 30). In: The A.S.P.E.N. nutrition support core curriculum, 2nd edn. Silver Spring, MD: American Society for Parenteral & Enteral Nutrition; 2012.

58. Jones BM. Nutritional support at the end of life: the relevant ethical issues. Eur J Gastroenterol Hepatol. 2007;19:383–8.
59. Nandiwada DR, Dang-vu C. Transdisciplinary health care education: training team players. J Health Care Poor Underserved. 2010;21:26–34.
60. Catlett C, Halper A. Team approaches: working together to improve quality. In: Frattalie C, editor. Quality improvement digest. Rockville, MD: American Speech-Language-Hearing Association; 1992:1–34.
61. Kubler-Ross E. On death and dying. New York: McMillan; 1969.
62. Barrocas A. The dying patient: a team affair. Surg Team. 1973;2:38–43.
63. Barrocas A. Death and dying – a team approach to care. Postgrad Med. 1981;69(4):175–80.
64. Mendelson D, Ashby M. The medical provision of hydration and nutrition: two very different outcomes in Victoria and Florida. JLM. 2004;11:282–91.
65. Miller TB. "Reading" the body of Teri Schiavo: inscriptions of power in medical and legal discourse. Lit Med. 2009;28(1):33–54.
66. Spencer RA, Palmisano DJ. Specialized nutrition support of patients – a hospital's legal duty? QRB Qual Rev Bull. 1985;11:160–4.
67. Palmisano DJ. Malpractice prophylaxis: overview of the law and definitions. Capsules. 1983;6:2–5.
68. Schneiderman LJ, Gilmer T, Teetzel HD. Impact of ethics consultations in the intensive care setting: a randomized, controlled trial. Crit Care Med. 2000;28(12):3920–4.
69. Schneiderman LJ, Gilmer T, Teetzel HD, Dugan DO, Blustein J, Cranford R, et al. Effect of ethics consultations on non-beneficial life-sustaining treatments in the intensive care setting: a randomized controlled trial. JAMA. 2003;290(9):1166–72.
70. Gilmer T, Schneiderman LJ, Teetzel H, Blustein J, Briggs K, Cohn F, et al. The costs of non-beneficial treatment in the intensive care setting. Health Aff (Millwood). 2005;24(4):961–71.
71. Bayer W, Mallinger JB, Krishnan A, Shields CG. Attitudes toward life-sustaining interventions among ambulatory black and white patients. Ethn Dis. 2006;16:914–9.
72. Phipps E, True G, Harris D, Chong U, Tester W, Chavin SI, et al. Approaching the end of life: attitudes, preferences, and behaviors of African-American and white patients and their family caregivers. J Clin Oncol. 2003; 21:549–54.
73. Torke AM, Garas NS, Sexson W, Branch WT. Medical care at the end of life: views of African American patients in an urban hospital. J Palliat Med. 2005;8:593–602.
74. Volandes AE, Paasche-Orlow M, Gillick MR, Cook EF, Shaykevich S, Abbo ED, et al. Health literacy not race predicts end-of-life care preferences. J Palliat Med. 2008;11:754–62.
75. Searight HR, Gafford J. Cultural diversity at the end of life: issues and guidelines for family physicians. Am Fam Physician. 2005;71:515–22.
76. Preedy VR, editor. Diet and nutrition in palliative care. Boca Raton, FL: CRC; 2011.
77. Ethical and religious directives issued by the United States conference of catholic bishops. 5th edition. 17 Nov 2009.
78. Kelley AS, Wenger NS, Sarkisian CA. Opiniones: end-of-life care preferences and planning. J Am Geriatr Soc. 2010;58:1109–16.
79. Gebara J, Tashjian H. End-of-life practices at a Lebanese hospital: courage or knowledge? J Transcult Nurs. 2006;17:381–8.
80. Schwartz DB. Ethical considerations in the critically ill patient. In: Cresci G, editor. Nutritional therapy for the critically ill patient: a guide to practice. 2nd ed. Boca Raton, FL: Taylor & Francis; 2015.
81. Ferrell BR, Coyle N. Textbook of palliative nursing. New York: Oxford University Press; 2001.
82. Andrews M, Boyle J. Transcultural concepts in nursing care. 3rd ed. Philadelphia, PA: Lippincott & Wilkins; 1999.
83. Galanti G. Caring for patients from different cultures: case studies from American hospitals. 2nd ed. Philadelphia, PA: University of Pennsylvania Press; 1997.
84. Lipson JG, Dibble SL, Minarik PA, editors. Culture and nursing care: a pocket guide. San Francisco, CA: UCSF Nursing Press; 1996.
85. Krishna L. Nasogastric feeding at the end of life: a virtue ethics approach. Nursing Ethics. 2011;18(4):485–94.
86. Barrocas A, Barrocas N, Griver YM. Health care in transition: the physician and the OWAs. J La State Med Soc. 1988;140:37–41.
87. Council on Scientific Affairs and Council on Ethical and Judicial Affairs of the American Medical Association. Persistent vegetative state and the decision to withdraw or withhold life support. JAMA. 1970;263(3):426–30.
88. Position of the American Academy of Neurology on certain aspects of the care and management of the persistent vegetative state patient. Adopted by the Executive Board, American Academy of Neurology, April 21, 1988, Cincinnati, Ohio. Neurology. 1988;38(21):125–6.
89. Jones BJM. Ethics and artificial nutrition towards the end of life. Clin Med. 2010;10(6):607–10.

90. Wick JY, Zani GR. Removing the feeding tube: a procedure with a contentious past. Consult Pharm. 2009; 24(12):894–83.
91. Barry MJ, Edgman-Levitan S. Shared decision making ─ the pinnacle of patient-centered care. N Engl J Med. 2012;366:780–1.
92. Epstein EG. Preventive ethics in the intensive care unit. Am Assoc Crit Care Nurs. 2012;23:217–24.
93. Carbone ET, Zoellner JM. Nutrition and health literacy: a systematic review to inform nutrition research and practice. J Acad Nutr Diet. 2012;112:254–65.
94. Weiss BD. Health literacy and patient safety: help patients understand manual for clinicians. 2nd edition. American Medical Association Foundation; 2007. www.ama-assn.org/ama1/pub/upload/mm/367healthlitclinicians.pdf.
95. Mirel M, Hartjes T. Bringing palliative care to the surgical intensive care unit. Crit Care Nurs. 2013;33:71–4.
96. Schwartz DB. Advancing RD, nutrition support practice with clinical ethics. Support Line. 2014;36:12–21.
97. Schwartz DB. RD role in ethical decision making for enteral and parenteral nutrition. Todays Dietitian. 2013; 15(1):28.

Chapter 13
Safe Practices for Enteral and Parenteral Nutrition

Joseph I. Boullata

Keywords Administration • Competency Documentation • Enteral nutrition • Medication errors • Order review • Parenteral nutrition • Policies and procedures • Prescribing • Quality improvement • Safety • Systems safety

Key Points

- Enteral and parenteral nutrition are associated with inherent clinical complications but are also susceptible to errors based on the system within which they are being used.
- The nutrition support therapy process includes patient assessments and plans, prescribing of the regimen, order review, order preparation (including labeling and dispensing), administration to the patient, and documentation.
- Each step in the nutrition support therapy process is fraught with the potential for errors which will impact patient safety.
- Incorporation of all available guidelines and recommendations into policies, procedures, and practices is a valuable risk mitigation strategy.

Introduction

Acutely ill patients often require nutrition support when managed in a critical care setting. This can take the form of enteral nutrition (EN) or parenteral nutrition (PN) when a diet cannot be tolerated or is impractical. Although many nutrition support textbooks include a chapter on safety, these often focus on the clinical complications of EN and PN. This chapter steps beyond those important complications to discuss not only the therapies but the systems within which they are used. Safe practices in EN and PN involve a broader interplay of healthcare providers, departments, and administrative structures, interacting with the numerous steps in the nutrition support therapy process. Concepts underpinning these practices are broadly applicable in all of clinical care. Maintaining a safety culture

J.I. Boullata, PharmD, RPh, BCNSP (✉)
Pharmacology and Therapeutics, University of Pennsylvania, Philadelphia, PA, USA

Clinical Nutrition Support Services, Hospital of the University of Pennsylvania,
418 Curie Boulevard, Fagin Hall, Philadelphia, PA 19104, USA

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_13,

around patients receiving EN/PN depends on continuous surveillance, recognizing potential areas for patient harm at each step in the process, and systematic reporting of all errors (including near misses) with subsequent system improvements made upon review. All members of the critical care team and the supporting organizational structures must accept the priority of maintaining no less a safety focus for EN and PN than for any other medication or medical procedure.

Safety Culture in the Intensive Care Unit

A safety climate or culture is critical for identifying safety issues and reducing error rates in the intensive care unit (ICU). Patients in the ICU are far from immune to errors that have plagued patients in other settings. In general, medication errors occur at a rate of about 6 per 100 orders. However in the ICU, medication error rates may approach 33 %, depending on methods, perspectives, and categories included, with rates reported as high as 2344 errors per 1000 patient-days [1, 2]. As sparse as the data are on medication errors, even less is documented specifically on nutrition support therapy in the ICU. The limited reporting often stems from a perception that EN and PN are merely a meal replacement and as such are not included in error reporting systems.

Although specific error rates for EN and PN are not readily available, they can be viewed through the same lens as other medication errors [3–5]. When systematically evaluated, errors can occur at each step of the medication-use process, which results in potential and actual adverse events [1]. For example, higher error rates in the ICU correlate both to workload and difficulties implementing a safety climate. Of course, a medication error need not reach a patient or cause an adverse outcome to still be considered an error (Fig. 13.1) [6].

Communication is a valuable component of a safety culture including open and nonpunitive disclosure of errors. This assumes adequate staffing and incorporation of expertise on the ICU team. Interprofessional patient care teams in the ICU are an approach that promotes patient safety [1]. Human factors play a large role in patient safety that may be addressed with improving processes and systems. System and practice improvements have improved medication safety in the ICU [7–9]. However, the patient is not helped if inadequate reporting and investigation cannot respond to ongoing errors.

Errors are not necessarily the fault of the provider most proximal to the incident, and are often related to faulty systems within which the provider operates. A nonpunitive approach has been adopted

Category	Definition	Harm
A	Circumstances or events that have the capacity to cause error	No
	An error occurred, …	
B	But did not reach patient	No
C	Reached patient, but did not cause patient harm†	No
D	Reached patient, required monitoring and/or intervention to preclude harm	No
	An error occurred, …	
E	May have contributed to or resulted in patient harm, required intervention	Yes
F	May have contributed to or resulted in patient harm, required hospitalization‡	Yes
G	May have contributed to or resulted in permanent patient harm	Yes
H	Required intervention necessary to sustain life	Yes
I	May have contributed to or resulted in patient's death	Death

†Impairment of physical, emotional, or psychological function or structure of the body and/or resulting pain
‡Initial or prolonged hospitalization

Fig. 13.1 Medication error categories. Adapted from [6]

by most healthcare settings in reporting medication errors; with the exception of reckless or criminal behavior. Anonymous and fact-based reporting can dramatically increase recorded errors over the flawed and out of date incident-reporting systems, making the system part of an institution's ongoing quality improvement efforts and clinical effectiveness measures [10]. The management of medication errors presupposes a system of identifying those errors within a health system.

The newer systems for maintaining safety management in healthcare draw from experiences and techniques from the aviation industry, and from human factors experts. Rather than merely interpreting a medication error incident as a regulatory violation or non-adherence to best practice guidelines or recommendations, a systems focus is more constructive. Although investigations via root cause analysis and failure mode and event analysis can allow adequate responses to isolated medication errors, they may not be inclusive enough to allow for a systematic systems review. Conducting a systematic (i.e., methodical) systems (i.e., including all parts and steps) review has been well described [11]. Errors reviewed in context enhance learning and the subsequent remedies and systems improvements put in place to create a safer environment. No different from clinical recommendations, the recommendations to address errors need to be specific, measureable, assignable, realistic, and timely [12].

Designing systems to support the clinicians' physical/cognitive efforts allows for improvements in safety. Evidence from human factors engineering science suggests that improvements in patient safety in systems as complex as the ICU requires optimal interaction between people and the system [13]. This can involve better tools, technologies, environments, tasks, policies, standards, and guidelines that should be matched to the tasks and environment of the teams and fully supported by administrators. For example, checklists serve as a tool to support human memory limitations, pressures on time, and frequency of interruptions. Errors and lapses in rule adherence are inevitable despite education and policy reinforcement, especially if the rules are not congruent with the care delivery system.

Although education is a good start, followed by rules and policies with related checklists, standardization and automation and some forcing functions are often required for more permanent fixes. Patient safety organizations have advocated information technologies that reduce adverse events throughout the medication-use process [14]. Of note, electronic order entry by itself does not necessarily reduce medication errors. Introduction of electronic order entry systems with decision support tools are expected to reduce errors and improve patient care when approached systematically and comprehensively by an organization [15].

Standardization refers to development and implementation of technical and practice standards into a process so that all health care providers deliver the same level of safe care. Standardization does not refer to—and should not lead to—a one-size-fits-all strategy. Process standardization including independent double-checks and automation with forcing functions may better suit improvements in medication safety.

All providers are active partners in the care of critically ill patients. This is just as important for neonates as older children, young adults and older adults [16, 17]. The team members need to share the same model and mission while understanding each other's roles and expectations. Practically, improvements start with mapping the process along with careful observation and interviews to analyze the system of care. This is an iterative process of gathering and sorting data at the level of the patient, personnel, environment/equipment, organization, and even regulatory controls [11]. Then the data are analyzed systematically. This can include mapping against quality assurance targets to answer the "why" (i.e., structure), "how" (i.e., process), and "what" (i.e., outcome) of a specific incident or group of similar errors [11]. Finally specific recommendations are made for improvements to the system. System redesign will then help improve performance.

A safety climate can contribute to reduction in medication error rates in the ICU [18]. Implementation of new interventions requires adequate education, revision, and time to make a significant impact. A significant reduction in medication preparation errors was reported in a prospective study of a multifaceted education intervention, which used direct observation [8]. Another prospective, multicenter, observational study addressed issues of staffing levels and number of patient access devices both of which are critical to nutrition support therapy interventions—showing that reduced staffing and

increased access devices were both strong predictors of error [18]. A systematic review of interventions aimed at medication errors in the ICU setting revealed that changes in work schedules, modes of education, medication reconciliation or protocols/guidelines could reduce medication errors, but the available data are not conclusive and did not examine nutrition support therapy specifically [9].

It is clear that the complexity of care in the ICU increases risk for harm. This care includes a large number of medical interventions not least of which are EN and PN. Errors can occur at each stage of the nutrition support therapy process; from prescribing through to patient monitoring and reassessment (Fig. 13.2). The complexity of EN and PN means that the order review and preparation process is at least as important as prescribing and administration. Sentinel events involving EN and PN are rarely captured. Even when difficult to implement improvements to the nutrition support therapy process or when outcomes are not easily documented these advancements have been important to describe [19, 20].

The Nutrition Support Therapy Process

The nutrition support therapy process, modeled after the medication-use process, describes the system within which EN and PN preparations are used. This process includes a number of critical patient-focused steps (see Fig. 13.2); from the initial patient assessment, to a prescriber's order for a nutrition support regimen, the clinical pharmacist review of the orders, the preparation, labeling, and dispensing of the regimen, the administration of the nutrition support therapy to the patient, and finally subsequent monitoring of the patient with reassessment by the nutrition support service to complete the loop. A great deal of documentation is expected in each of the steps. This includes the nutrition support service or dietitian's assessment and plan, the prescribers order, the pharmacists review with all clarifications and interventions, the nurse's assessment and administration to the patient, documentation of independent double-checks at any point of transcription or verification with the original prescriber's orders. All the documentation should be readily retrievable from the patient's medical record or associated information system(s) [21–23].

With appreciation of the complexity and multidisciplinary nature of the nutrition support therapy process comes the recognition that errors may occur at each step in the process. EN- and PN-related

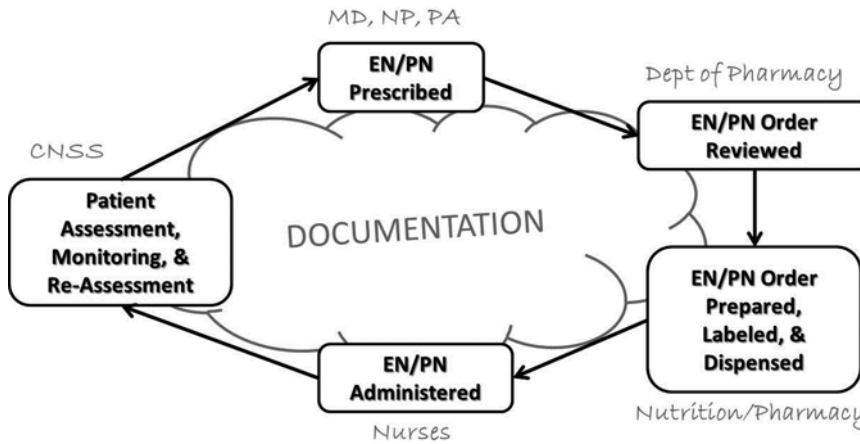


Fig. 13.2 The nutrition support therapy process

errors occur at every step in the process, including documentation, and need to be routinely captured and reported regardless of whether or not they reach the patient. Each of these errors must then be available for regular review by the institution's oversight structure.

The nutrition support therapy process involves a number of clinicians from different departments working in concert to provide safe nutrition care, where good communication and standardization across all steps is a risk management strategy [20]. Given these requirements for interprofessional communication and interdepartmental responsibilities, the nutrition support therapy process is more complex than that for most drugs. For example, the classification of PN as a high-alert medication is justified because significant patient harm may occur when it is provided in error or outside accepted best practices [24–26]. EN is a therapeutic intervention with similar risk for error in the system within which it is used. Safety concerns are broader than the EN or PN preparation itself, and are best addressed by individuals with nutrition support competency. The availability of clinical specialists in nutrition support (dietitians, nurses, pharmacists, physicians) who work with critically ill patients on a routine basis is the recommended model. Ideally nutrition support specialists provide the care necessary at each step within accepted guidelines and standards of practice. Institutions are required to develop and maintain policies, procedures, and best practices related to nutrition support including validation of the competencies of those involved at each step in the process [23,26a]. National guidelines for these have been published by professional organizations [23, 25–28]. Clearly written policies and procedures that address all roles and responsibilities in the nutrition support therapy process are necessary within a safety framework. Those individuals recommending, prescribing, reviewing orders, preparing, or administering nutrition support therapy shall meet institutional criteria (i.e., training, credentialing, competency certification) for their roles and responsibilities. A periodic review of those individuals against institution-specific criteria will also be described in the policies.

Therefore the nutrition support therapy process requires an institutional system of oversight (e.g., committee) that would ensure consistency of policies, procedures, and practices across all departments involved in the process, as well as consistency with published standards and guidelines. Additionally this oversight structure would allow for the systematic review of all EN- and PN-related errors, and identify deviations from best practices or standards of care, towards further improving the safety of the institution's nutrition support therapy process. Each of these steps and the specific roles and responsibilities within a standardized process is expected to reduce the risk of harm to the patient.

Patient Assessment

Patient assessment is best kept in the hands of clinical nutrition specialists as defined by education, training, and board certification. The process and practice of nutrition assessment should be clearly defined in ICU policies and procedures to be consistent with those held by the participating departments. The process of nutrition screening and assessment is reviewed in depth in Chap. 3. Nutrition assessment is most often performed by dietitians, but physicians, nurses, and pharmacists may also be involved. Given the acuity of critically ill patients, and the high prevalence of malnutrition risk, an initial assessment is performed within 24 h with reassessments on a regular (often daily) basis. The initial clinical assessment of the patient, by the dietitian or nutrition support service, is based on available subjective and objective data to determine an appropriate indication for nutrition support therapy and the ensuing plan of care. After reviewing the history and diagnoses, the clinician evaluates clinical signs and performs a physical examination including anthropometric data collection. Then, together with laboratory markers and any functional indicators, the clinician uses all the available data to make an assessment of the patient's nutrition status [29]. This standardized approach allows for documenting malnutrition risk and developing an appropriate nutrition care plan for the patient [30, 31]. Each assessment is clearly documented in the electronic medical record along with an accompanying nutrition care plan that accounts for risk-benefit. This plan is then communicated with the physician or designee who orders the EN or PN by prescription.

Prescribing

Prescribing should take place in a medication safety zone: an ergonomically sound, well lit area without interruptions or distractions [23]. A complete description of the ordering process should be included in the ICU policies and procedures to be consistent with those of participating departments (Table 13.1). Including clinical decision support in the prescribing process embeds control in limiting errors. Handwritten orders are to be avoided, as are verbal/telephone orders, for preparations as complex as EN and PN, in favor of standardized order sets. Detailed order templates are available that can be modified to suit a clinical setting's electronic order entry system [23, 27]. These templates describe each required element of the prescription order from patient identifiers, to the access device, administration method and rate (see Table 13.1). Human breast milk used for infants has been included within the EN safe practice guidelines but will not be discussed further in this chapter [27]. The parenteral nutrients are ordered in amount per day (or amount per kg

Table 13.1 Safe practices in prescribing nutrition support therapy [20, 23, 27, 28]

Minimum	Optimum
Use standardized order templates for:	Policy/procedure exists for prescribing EN and PN orders
• Adult regimens	Electronic access to institution/unit-specific ordering policy/procedure
• Pediatric regimens	Electronic order entry with built-in clinical decision support tools
• Neonatal regimens	
Include:	
An order entry deadline	Patient allergies and adverse effects with manifestations
Patient demographics, height, weight, and indication	Nutrient dosing limits (clinical and stability/compatibility implications)
Each nutrient ingredient	List the content of any fixed dose multicomponent ingredients
• In a standardized sequence	All related orders for monitoring and nutrition support consult
• Using standard units of measure	
Route of administration and location of access device	
Duration of infusion or	
• Timing of intermittent administration	
• Timing of cycling regimen	
Prescriber contact information	
Nutrition support resource contact information	
PN-specific:	
• Electrolytes and other minerals ordered as elemental dose by available salts	
EN-specific:	
• Formula type (descriptive generic term)	
• Delivery site and access device	
• Administration method and rate	
• Supplementary orders (e.g., advancement, flushing, HOB elevation, monitoring)	
Reordering requires completion in its entirety	
Avoid:	
Trailing zeroes	Any handwritten paper order forms[a]
Percent concentrations	Any transcription steps
Use of "mL" as an ingredient unit of measure	
An abbreviated reordering process	

[a]When computerized order entry system is down, an editable electronic document should be available, and a paper order template is available as a last resort

per day for pediatric patients), with electrolytes/minerals ordered as the elemental dose by salt. EN orders should also include the amount of macronutrients per day in the selected formula. The EN and PN regimens are not intended to be routinely used as a drug delivery vehicle [27, 28]. Although best avoided, any transcription step requires an independent double-check process that will be documented and auditable.

Order Review

A knowledgeable clinical pharmacist, in an environment without distractions, will verify that the nutrition support therapy order is complete and that the patient has the appropriate access including site confirmation of the distal end of the catheter or enteral feeding tube (EFT). This stage in the process will be clearly described in ICU policies and procedures to be consistent with those of the pharmacy department (Table 13.2). Complete orders will include all required elements (e.g., patient identifiers, dosing weight, nutrient ingredients with doses, route of administration, access device, and administration method) [23]. The pharmacist will then review the order further to confirm an indication and appropriate dosing of each ingredient based on the patient's allergies, nutritional needs, metabolic status, organ function, and other medical interventions [23]. The reviewing pharmacist will need full access to the patient medical records including the most recent nutrition assessment and plan. The contents of the PN are reviewed for compatibility of the dozens of ingredients with each other, as well as the stability of the final admixture [23]. Any other medication being administered through the same enteral or parenteral access device will also be closely reviewed for compatibility. Although not often dispensed by the pharmacy, EN orders placed on the patient's pharmacy profile allows an EN review process to take place. In addition to the process described above, the pharmacist will evaluate all ordered medication for appropriateness of EFT administration and whether the drug and its formulation are appropriate for the distal end of the feeding tube, or whether the patient's EN needs to be held to avoid an interaction with one or more of their concurrent drugs [32].

Preparation, Labeling, and Dispensing

The preparation and administration steps are of particularly high risk. Lack of knowledge and experience, as well as deviations from guidelines, play a large role in creating errors at these steps [8]. Clearly defined policies and procedures describing each step in preparing nutrition support therapy regimens for ICU patients should exist and be consistent with participating departments.

Table 13.2 Safe practices in reviewing the nutrition support therapy order [20, 23, 28, 32]

Minimum	Optimum
Each order is verified by a clinical pharmacist	Policy/procedure exists for reviewing EN and PN orders
Review components for appropriateness of: • Dosing • Compatibility • Stability	Include a description of: • The responsible individual(s) • Independent double-check for any transcription step Document any clarifications and interventions required before order can be prepared/dispensed
Clarify any issues with the prescriber	
Review administration of all concurrent medications for: • Safety • Stability • Compatibility	

Closed EN feeding systems are commonly in place, which obviates any preparation step that could otherwise introduce contaminants into the sterile formula. However, there are many potential points of contamination when an open feeding system is used [26, 27]. Decanting commercial EN formula into the infusion container requires strict aseptic technique in a clean environment (i.e., not at the bedside). The connection to the administration set should also be performed using aseptic technique. Using the sterile closed EN feeding systems allows hanging for up to 36–48 h depending on the product if the system is not violated beyond the initial insertion of the enteral administration set. This is contrasted with a limited hang time of 4–8 h for the formula and container when using an open feeding system, even if prepared aseptically in the pharmacy [27]. Aseptic technique is critical for the preparation steps of both EN and PN given that they are such excellent growth media.

Once the PN order is deemed appropriate, it will be prepared (i.e., compounded, labeled, and dispensed) in a pharmacy adhering to stringent guidelines for compounded sterile preparation [21–23, 28, 33, 34]. These guiding and regulatory documents are intended to reduce the risk for contamination as well as the many errors in dosing and interactions. PN can also be prepared by activating commercially available multichambered bags and adding micronutrients as necessary for each patient. This preparation step still takes place in the pharmacy and the product is labeled no differently than a compounded PN admixture prior to dispensing [23, 28]. However, most of the currently available multichambered products cannot meet the needs of most critically ill patients without excessive fluid and/or caloric loads given their low amino acid concentrations and fixed proportions of macronutrients.

There are a number of EN and PN label templates available for adoption [23, 27]. Standardized patient-specific labels should be affixed to all EN and PN infusion containers, which can be cumbersome with the small volume containers used for neonates. These labels will include all the elements of the original order in the same sequence and units of measure for nutrient content. Organizations should define whether the patient-specific EN labels will include all nutrients or only the macronutrients and select micronutrients therein. Commercial EN formula content labeling and health claims are to be interpreted with caution until more specific regulations are in place [27].

Administration

All practices for administering EN/PN should be clearly defined in ICU policies and procedures (Table 13.3). Strict aseptic technique is necessary in preparing to administer EN and PN. Another source of contamination is the water supply used for flushing EFTs and diluting medications for enteral administration [36, 37]. Purified water (i.e., sterile water for irrigation, USP) will be free of

Table 13.3 Safe practices in administering nutrition support therapy [20, 23, 27, 28, 35]

Minimum	Optimum
Identify a standardized start time for administration	Policy/procedure exists for administering EN and PN
Compare the patient-specific label with the original order	Include a system of independent double-check to confirm:
Complete appropriate patient identification	• Nutrition support preparation matches original order
Set up infusion pump and administration set (including the appropriate filter for PN)	• Infusion pump settings
	• Line tracing
Trace administration set/lines to verify correct access connection	Include EN/PN in bar-code medication administration initiatives
Complete the infusion within the EN/PN beyond-use date/time	Document all clarifications/interventions required, as well as double-checks performed, before the EN or PN preparation can be administered

both infectious and chemical contaminants and should be used in place of other sources (i.e., tap water) [26, 27, 35]. The EN and PN preparations can be visually inspected, with labels verified against the original order to confirm all ingredients, the beyond-use date, and directions for administration for the right patient. The tubing is then traced to point of origin. Tubing and catheter misconnection errors are always of concern in the critically ill patient. For patients who may be receiving EN and PN concurrently during transition periods there is the very real possibility, until the new enteral connectors are adopted in practice, that the EN formula may be inadvertently administered intravenously with potentially catastrophic outcomes [38–40]. For this reason, there should be very clear protocols in place that include an independent double-check of the route, line tracing and labeling, and pump infusion rate by another nurse prior to initiating the pump. Use administration pumps whose function and accuracy have been verified by clinical engineering. It is important to train non-clinical staff (and visitors) not to reconnect any lines. Avoid making adaptations to any enteral or parenteral device. All connections (and reconnections) require tracing the lines back to their origins, ideally labeling both ends, and having these double-checked before initiating (or reinitiating) any infusion pump. This should also be performed with every change in shift. Any EN or PN preparations brought from a patient's home or another institution are not to be administered given the impossibility of assuring content safety.

Additional safety measures for EN administration include elevation of the head of the bed to 45° (30° minimum), when practical and not contraindicated, with the intention of reducing aspiration, as well as flushing of the EFT routinely with sterile water to maintain access patency, within limits of patient volume status (i.e., using the lowest volume to clear the tube of residual feeding formula or medication) [27].

Administering medication through an EFT is fraught with potential errors if the correct drug formulation, preparation and administration techniques are not employed. Nurses are most often charged with preparation of the drug product for EFT administration, although in some institutions the pharmacists may be given the responsibility of preparing dosage forms within compatibility and stability parameters. Only the rare drug has FDA-approved labeling for administration through EFTs. All precautions are to be taken to double-check the drug and its appropriateness for administration to avoid errors that could be costly (Table 13.4). A prospective observational study indicated that medication errors of preparation/administration via EFT involved about 60 % of all doses [41]. A retrospective study revealed that only 55 of 532 doses administered into a small bowel EFT were considered appropriate [42]. The consequences of inappropriate drug preparation and administration include therapeutic failure, toxicity, and feeding tube obstruction requiring replacement. Many patients are prescribed medications which may result in these complications [43]. Having established interdisciplinary policies, procedures and practices can improve this challenging aspect of patient care including a reduction in errors [44].

Table 13.4 Ten safe practices for drug administration via enteral feeding tubes [27, 35]

1. Requires an order specifying the route (i.e., enteral) and site (e.g., jejunostomy tube) of administration
2. Do not add medication to the enteral nutrition formula
3. Do not mix medications together
4. Use only immediate-release drug dosage forms (solid or liquid)
5. Dilute each medication with purified water (i.e., sterile water for irrigation, USP) before administration
6. Administer each medication separately through an appropriate access site
7. Use a clean enteral syringe to accurately measure, prepare, and administer medication
8. Flush feeding tube with purified water before and after medication administration (between each drug when possible)
9. Flush feeding tube with water, and restart feeding in a timely manner
10. Consult with a pharmacist with specific expertise as needed

Table 13.5 Safe practices in monitoring and documenting nutrition support therapy [20, 23, 27, 28, 32, 35]

Minimum	Optimum
Monitor all patients receiving EN or PN	Policy/procedure exists for
Develop institution/unit-specific evidence-based practice guidelines that support patient monitoring and reassessment	• Monitoring EN and PN therapy
The EN/PN order, its review, preparation, and administration are each clearly documented in the permanent medical record	• Documenting all related activities in the eMR
	• Documenting errors at each step in the nutrition support therapy process
	Evaluate effectiveness of all clinicians involved
	All EN/PN order clarifications, activities and errors (including near misses) are easily retrievable for routine review
	Systematic systems reviews are performed as needed

eMR electronic medical record, *EN* enteral nutrition, *PN* parenteral nutrition

Documentation

Policies and procedures should exist for not only clinical monitoring of the patients receiving EN/PN, but for documentation of all related activities and of any errors in the nutrition support therapy process (Table 13.5). Unless the culture already exists within an organization to consider, document, and report all errors with EN and PN, most institutions assume that there are no safety issues or errors. EN and PN are therapies that are prescribed, prepared, dispensed, administered, and monitored similar to other medications. Their administration also involves the use of infusion devices that may be used in error. In fact, in systems that do capture these errors well, nutrition support therapy ranks among the top causes of all medication errors. Internal reporting to the medication safety committee or other appropriate pharmacy and therapeutics-type committee should be routine. Any errors that are identified at any step along the nutrition support therapy process should be reported externally to the Institute for Safe Medication Practices as well via https://www.ismp.org/orderforms/reporterrortoISMP.asp.

Making the Nutrition Support Therapy Process Safer

Clinicians with expertise in nutrition support therapy should be included in designing and implementing improvements to the process. The involvement of a nutrition support team or clinical nutrition service with the entire process can improve patient care and reduce overall costs [45]. Unfortunately such a team is not always available despite best intentions of an organization. At the very least a standing nutrition committee including ICU and institutional administrator representation should be charged with oversight. This group will be involved with examining the institution's nutrition support therapy process. Interprofessional collaboration (including clinical engineering, information technology, and purchasing departments) is necessary for evaluations and strategic planning. Comparisons with best practices, based on the many regulatory guidelines and recommendations cited in previous sections, will allow a clear description of gaps in practice. This should occur within an oversight structure so that all deviations from best practices or standards of care and any EN/PN-related errors receive full attention and adequate response within the organization. Although EN- and PN-related errors are known to occur, very few organizations capture these; or when they do are less likely to share them in the literature [4–6].

Improved communication amongst healthcare providers, and standardization of each step in the nutrition support therapy process, are valuable risk management strategies. Implementing the safe practice guidelines and maintaining competency of those involved in the process has been described before [20, 46]. An electronic order entry and information system can improve the safety of PN and may be cost-effective while reducing the rate of medication errors [47–50]. Approaches to improving safety often face significant organizational challenges but can be successful when based on published practice guidelines and standards [19, 23, 46].

Every step of the nutrition support therapy (especially PN) process can be adversely influenced by the ongoing crisis of product shortages in the USA which in turn lead to suboptimal and in some cases fatal patient outcomes [51]. An interprofessional group is likewise valuable in responsiveness and contingency planning around product shortages [20].

There is an expectation of healthcare organizations to use a standardized approach to EN and PN including clinicians with nutrition support expertise, policies and procedures for all steps in the process, a comprehensive educational program, and a competency assessment for all those involved in the nutrition support process [23]. A.S.P.E.N. has several documents providing clinical guidelines and best practice recommendations for EN and PN totaling over 250 specific recommendations [23, 27, 28]. A new document on safe practices for EN therapy is expected in 2016.

Conclusion

PN is a high-alert medication and EN is a product with similar risk for error in the system within which they are used. EN and PN require detailed and safety-focused policies, procedures, practices and systems. For the safety of the critically ill patient, institutions should incorporate all appropriate clinical guidelines, recommendations, and other regulatory documents into their system of care and support a culture of safety. This includes the expectation of ongoing surveillance and that errors at any step in the nutrition support therapy process be collected and reported for evaluation with subsequent corrective actions implemented. Health care providers can become more directly involved in enhancing patient safety by following best practices and documenting their activities at each step in the nutrition support therapy process.

References

1. Kane-Gill SL, Jacobi J, Rothschild JM. Adverse drug events in intensive care units: risk factors, impact, and the role of team care. Crit Care Med. 2010;38:S83–9.
2. Wilmer A, Louie K, Dodek P, Wong H, Ayas N. Incidence of medication errors and adverse drug events in the ICU: a systematic review. Qual Saf Health Care. 2010;19:e7.
3. Sacks GS, Rough S, Kudsk KA. Frequency and severity of harm of medication errors related to the parenteral nutrition process in a large university teaching hospital. Pharmacotherapy. 2009;29:966–74.
4. Guenter P, Boullata J. Drug administration by enteral feeding tube. Nursing. 2013;43(12):26–33.
5. Boullata JI, Guenter P, Mirtallo JM. A parenteral nutrition use survey with gap analysis. JPEN J Parenter Enteral Nutr. 2013;37:212–22.
6. National Coordinating Council for Medication Error Reporting and Prevention. About medication errors. 2001. Available from: www.nccmerp.org/medErrorCatIndex.html. Accessed Mar 2014.
7. Benoit E, Eckert P, Theytaz C, Joris-Frasseren M, Faouzi M, Beney J. Streamlining the medication process improves safety in the intensive care unit. Acta Anaesthesiol Scand. 2012;56:966–75.
8. Chedoe I, Molendijk H, Hospes W, Van den Heuvel ER, Taxis K. The effect of a multifaceted educational intervention on medication preparation and administration errors in neonatal intensive care. Arch Dis Child Fetal Neonatal Ed. 2012;97:F449–55.

9. Manias E, Williams A, Liew D. Interventions to reduce medication errors in adult intensive care: a systematic review. Br J Clin Pharmacol. 2012;74:411–23.
10. Stump LS. Re-engineering the medication error reporting process: removing the blame and improving the system. Am J Health Syst Pharm. 2000;57 suppl 4:S10–7.
11. Duchscherer C, Davies JM. Systematic systems analysis: a practical approach to patient safety reviews. Calgary: Health Quality Council of Alberta; 2012.
12. Doran GT. There's a S.M.A.R.T. way to write management's goals and objectives. Manag Rev. 1981;70(11):35–9.
13. Scanlon MC, Karsh B-T. Value of human factors to medication and patient safety in the intensive care unit. Crit Care Med. 2010;38:S90–6.
14. Cheng CM. Hospital systems for the detection and prevention of adverse drug events. Clin Pharmacol Ther. 2011;89:779–81.
15. Cotter CM. Computerized physician order entry from a Chief Information Officer perspective. J Crit Care. 2004;19:283–9.
16. Dabliz R, Levine S. Medication safety in neonates. Am J Perinatol. 2012;29:49–56.
17. Mansour M, James V, Edgley A. Investigating the safety of medication administration in adult critical care settings. Nurs Crit Care. 2012;17:189–97.
18. Valentin A, Schiffinger M, Steyrer J, Huber C, Strunk G. Safety climate reduces medication and dislodgement errors in routine intensive care practice. Intensive Care Med. 2013;39:391–8.
19. Boitano M, Bojak S, McCloskey S, McCaul DS, McDonough M. Improving the safety and effectiveness of parenteral nutrition: results of a quality improvement collaboration. Nutr Clin Pract. 2010;25:663–71.
20. Hudson LM, Boullata JI. A quality improvement case report: an institution's experience in pursuing excellence in parenteral nutrition safety. JPEN J Parenter Enteral Nutr. 2014;38:378–84.
21. Rich DS, Fricker MP, Cohen MR, Levine SR. Guidelines for the safe preparation of sterile compounds: results of the ISMP sterile preparation compounding safety summit of October 2011. Hosp Pharm. 2013;48:282–294,301.
22. American Society of Health-System Pharmacists. ASHP guidelines on compounding sterile preparations. Am J Health Syst Pharm. 2014;71:145–66.
23. Ayers P, Adams S, Boullata J, Gervasio J, Holcombe B, Kraft MD, et al. A.S.P.E.N. parenteral nutrition safety consensus recommendations. JPEN J Parenter Enteral Nutr. 2014;38:296–333.
24. Institute for Safe Medication Practices. List of high-alert medications, 2012. Available from: http://ismp.org/Tolls/institutionalhighAlert.asp. Accessed Mar 2014.
25. Boullata JI. Overview of the parenteral nutrition use process. JPEN J Parenter Enteral Nutr. 2012;36:10S–3.
26. Padula CA, Kenny A, Planchon C, Lamoureux C. Enteral feedings: what the evidence says. Am J Nurs. 2004;104:62–9.
26a. Guenter P, Boullata JI, Ayers P, et al. Standardized competencies for parenteral nutrition prescribing: the American Society for Parenteral and Enteral Nutrition model. Nutr Clin Pract. 2015; doi:10.1177/0884533615591167.
27. Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, et al. Enteral nutrition practice recommendations. JPEN J Parenter Enteral Nutr. 2009;33:122–67.
28. Boullata JI, Gilbert K, Sacks G, Labossiere RJ, Crill C, Goday P, et al. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling and dispensing. JPEN J Parenter Enteral Nutr. 2014;38:334–77.
29. Jensen GL, Hsiao PY, Wheeler D. Adult nutrition assessment tutorial. JPEN J Parenter Enteral Nutr. 2012;36:267–74.
30. White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus statement: Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition – Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN J Parenter Enteral Nutr. 2012;36:275–83.
31. Mehta NM, Corkins ME, Lyman B, Malone A, Goday PS, Carney LN, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. JPEN J Parenter Enteral Nutr. 2013;37:460–81.
32. Boullata JI. Pharmaceutical issues in patients receiving enteral nutrition. Pharm Pract News. 2011;1–4.
33. American Society for Health-System Pharmacists. ASHP guidance on the safe use of automated compounding devices for the preparation of parenteral nutrition admixtures. Am J Health Syst Pharm. 2000;57:1343–8.
34. United States Pharmacopeia. USP chapter <797>: pharmaceutical compounding – sterile preparations. U.S. Pharmacopeia/National Formulary, edition 36/31. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2013.
35. Boullata JI. Drug administration through an enteral feeding tube. Am J Nurs. 2009;109(10):34–42.
36. Anaissie EJ, Penzak SR, Dignani MC. The hospital water supply as a source of nosocomial infections: a plea for action. Arch Intern Med. 2002;162:1483–92.
37. Rogues AM, Boulesreau H, Lashéras A, Boyer A, Gruson D, Merle C, et al. Contribution of tap water to patient colonization with Pseudomonas aeruginosa in a medical intensive care unit. J Hosp Infect. 2007;67:72–8.
38. Ulicny KS, Korelitz JL. Multiorgan failure from the inadvertent intravenous administration of enteral feeding. JPEN J Parenter Enteral Nutr. 1989;13:658–60.

39. Huddleston K, Creekmore P, Wood B. Administration of infant formula through the intravenous route: consequences and prevention. Am J Matern Child Nurs. 1994;19:40–2.
40. Kennelly C, Barnes S. Inadvertent IV administration of enteral formula (letter). Am J Crit Care. 1998;7:80.
41. Bertsche T, Niemann D, Mayer Y, Ingram K, Hoppe-Tichy T, Haefeli WE. Prioritising the prevention of medication handling errors. Pharm World Sci. 2008;30:907–15.
42. Boullata J, Aloupis M, Fodero K, et al. Appropriateness of drug administration in enterally fed patients. Crit Care Med. 2009;37(Suppl):A122.
43. Lonergan MT, Coughlan T, Collins R, O'Neill D. A majority of tube-fed patients are on medications that require special precautions. Age Ageing. 2010;39:495–6.
44. van den Bemt PMLA, Cusell MBI, Overbeeke PW, Trommelen M, van Dooren D, Ophorst WR, et al. Quality improvement of oral medication administration in patients with enteral feeding tubes. Qual Saf Health Care. 2006;15:44–7.
45. DeLegge MH, Kelley AT. State of nutrition support teams. Nutr Clin Pract. 2013;28:691–7.
46. Kumpf VJ. Implementation of safe practices for parenteral nutrition formulations. Am J Health Syst Pharm. 1999;56:815–7.
47. Hilmas E, Peoples JD. Parenteral nutrition prescribing processes using computerized prescriber order entry: opportunities to improve safety. JPEN J Parenter Enteral Nutr. 2012;36 Suppl 2:32S–5.
48. Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA. 1998;280:1311–6.
49. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med. 2003;163:1409–16.
50. Kaushal R, Jha AK, Franz C, Glaser J, Shetty KD, Jaggi T, et al. Return on investment for a computerized physician order entry system. J Am Med Inform Assoc. 2006;13:261–6.
51. Holcombe B. Parenteral nutrition product shortages: impact on safety. JPEN J Parenter Enteral Nutr. 2012;36:44S–7.

Chapter 14
The Economic Impact of Nutrition Support, and the Multidisciplinary Approach

Robert DeChicco and Ezra Steiger

Keywords Multidisciplinary • Nutrition support team • Cost-effectiveness analysis • Cost savings • Cost avoidance • Malnutrition • Nutrition intervention • Care paths • Physician nutrition experts • Nutrition screen • Nutrition assessment

Key Points

- Medical interventions should be evaluated from both clinical and economic perspectives.
- Cost-effectiveness of an intervention is the change in clinical outcome compared to the cost of the intervention.
- Hospitalized patients with malnutrition require more health care resources compared to their counterparts without malnutrition.
- Nutrition intervention is cost effective.
- Malnutrition is under-reported and under-reimbursed in the USA.
- A multidisciplinary approach to providing nutrition is associated with improved clinical and economic outcomes.
- Limiting inappropriate use of PN is cost effective primarily because it avoids potential PN-related complications.
- The lack of physician nutrition experts and reimbursement for nutrition-related services adversely affect the viability of existing nutrition support teams and the creation of new teams.

R. DeChicco, MS (✉)
Nutrition Support Team, Center for Human Nutrition, Cleveland Clinic,
9500 Euclid Avenue, Cleveland, OH 44195, USA

27020 Sleepy Hollow Drive, Westlake, OH 44145, USA
e-mail: dechicb@ccf.org

E. Steiger, MD
Department of General Surgery, Cleveland Clinic Lerner College of Medicine,
Desk A100, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: steigee@ccf.org

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_14,

Introduction

Increasing health care costs and current trends away from the traditional fee-for-service model of medical care towards reimbursement for patient outcomes both make necessary a reexamination of medical interventions, not only from the clinical perspective, but also from an economic standpoint. One method to examine the economic impact of an intervention is cost effectiveness analysis, or change in outcome compared to the cost of the intervention (Appendix 15.1). This allows the comparison of multiple similar interventions used to prevent or treat a disease or condition to determine which intervention has the lowest cost per unit of outcome, such as episodes of a disease prevented, or years of quality life gained.

The cost-effectiveness of a medical intervention can be measured in a variety of ways. Reducing health care expenditures while maintaining health care outcomes is considered cost savings; increasing health care expenditures in the short term that results in a reduction in expenditures or health benefit in the long term is considered cost avoidance. Neither cost savings nor cost avoidance is synonymous with cost-effectiveness. Routine screening for cancer, for example, requires additional health care expenditures to perform the screening procedures. In this case, the intervention may still be considered worthwhile if it confers a substantial health benefit relative to the cost, such as reducing mortality rates. On the other hand, an intervention can increase health care expenditures while worsening clinical outcomes, such as performing surgery compared to ongoing monitoring in an elderly man with newly diagnosed prostate cancer.

Nutrition is not exempt from causing increases in costs and deserves financial scrutiny. While nutrition intervention can improve clinical outcomes, and delaying or withholding nutrition is not clinically beneficial in most cases, the economic impact of all possible nutrition interventions must still be considered when determining which intervention will provide the greatest benefit at the lowest cost. This is often challenging because there are often multiple options for the type, timing, and mechanism of delivering nutrition, each having its unique set of costs, risks, and benefits. Additionally, the economic benefits of nutrition interventions are difficult to measure because they are usually described in terms of clinical outcomes such as shortened hospital length of stay or reduced complications rather than financial outcomes such as a reduction in expenditures or increase in revenues. To further complicate matters, nutrition is only one of many potential factors that can affect clinical outcomes, so there is not always a clearly demonstrable cause-and-effect relationship. The goal of this chapter is to examine the evidence for an economic impact of providing nutrition to hospitalized patients to allow clinicians to make a more informed decision when choosing the most appropriate intervention. The benefits and shortcomings of using a multidisciplinary team approach to providing nutrition are discussed, as well. Finally, suggestions for practice that can improve cost effectiveness of providing nutrition are listed.

Impact of Malnutrition

Malnutrition is pervasive in hospitalized patients. The prevalence of malnutrition in hospitalized patients varies, in part due to a lack of uniformity of definition, but is generally reported at 30 % or more in most studies [1–4]. This has not changed since the first studies were published 40 years ago [5]. In addition, malnutrition tends to worsen in hospitalized patients with increasing length of stay [1], and the elderly are more likely to have more malnutrition compared to their younger counterparts [2]. This is particularly concerning when the number of people 65 years or older will double in the USA in the next 25 years, and elderly people will make up 20 % of the population by 2030 [6].

Malnutrition in hospitalized patients is associated with negative clinical and economic outcomes. It can be a contributing cause, or a consequence, of many disease conditions. Studies have

demonstrated increased complications [1, 7–10], increased length of stay [7, 8, 11], increased readmissions [3, 11], and increased risk of mortality [3, 7, 9] for patients with malnutrition. In addition, such patients require more health care resources compared to their counterparts without malnutrition [1, 3, 12, 13]. While most studies examine the cost of malnutrition for subgroups of patients in single institutions, extrapolating the results to an entire health care system may be more meaningful. The British Association for Parenteral and Enteral Nutrition estimated £7.3 billion ($11 billion) was spent on disease-related malnutrition in 2003, representing approximately 10 % of the country's total health care expenditures [14].

The first step in treating hospitalized patients with malnutrition is identifying those individuals at risk. This can be accomplished by performing a nutrition screen to determine those who need a more thorough evaluation. Nutrition screening results in increased recognition of malnutrition and more frequent consults to dietitians [15], and increased nutrition intervention [16]. The Joint Commission on Hospital Accreditation requires acute care facilities to perform nutrition screening within 24 h of admission [17]. Most hospitals in the USA have a nutrition screening program in place which is typically performed by the nursing staff by imbedding nutrition questions within the nursing admission assessment [18]. Unfortunately, there is no consensus on what constitutes nutrition risk, and screening practices vary from institution to institution. As a result, many dietitians perform secondary nutrition screens because they feel screening by the nursing staff at their institution is inconsistent or inadequate, or they are not being notified on all patients who are deemed to be at nutrition risk [18].

Expert guidelines recommend that patients identified to be at nutrition risk should undergo a detailed nutrition assessment to determine the presence, etiology, and degree of malnutrition [19]. This should include a combination of the following: medical, nutrition, and medication histories; physical exams; anthropometric measurements; and laboratory data [20]. A detailed nutrition assessment also establishes a benchmark against which future nutritional progress can be measured and is an integral component of the nutrition care plan.

Reimbursement for hospitalization paid for under diagnosis-related group (DRG) reimbursement is increased, sometimes quite significantly, when the patient has qualifying diagnoses. Certain types of malnutrition qualify, and once identified should be documented appropriately in the medical record. Multiple International Classification of Diseases (ICD) codes are available to document malnutrition but they are not interchangeable. Recently, the Centers for Medicare and Medicaid Services increased the severity of diagnostic codes for 263.0 (malnutrition of moderate degree) and 263.1 (malnutrition of mild degree) from non-complicating condition status to a complication or comorbid condition (CC) while maintaining 262 (severe protein-calorie malnutrition) as a major complication or comorbid condition (MCC) in recognition of the impact of disease-related malnutrition [21]. Codes such as 261 (nutritional marasmus) and 260 (kwashiorkor) are inappropriate for adult patients because they are defined by ICD as pediatric conditions, and are considered predominantly tropical. If these codes are used for adult patients, the provider may receive lower reimbursement or outright rejection of the claim because the diagnosis does not match the age or clinical condition of the patient. Outdated or inappropriate terms can also result in an inaccurate calculation of an institution's patient case mix index, and underestimate severity of illness, risk of mortality, and expected length of stay, all of which impact on reimbursement rates.

Malnutrition has historically been under-reported and under-reimbursed in hospitalized patients. In 2010, only 3.2 % of US hospital discharges included a diagnosis of malnutrition [22]. The reasons for this shortfall are not clear, but likely due to a combination of factors including inadequate nutrition screening and assessment along with inappropriate or under-documentation of malnutrition in the medical record. Regardless, this inadequate attention to malnutrition also results in delays in timely and appropriate nutrition intervention for patients, and under-allocation of health care resources for malnutrition for institutions.

Recognition of and reimbursement for malnutrition in hospitalized patients is a multi-step process that requires collaboration among nurses, registered dietitians (RD), physicians and other licensed independent practitioners (LIPs, e.g., nurse practitioners), medical coders, and revenue cycle

professionals [23]. As stated, the process usually begins when patients undergo nutrition screening at the time of admission, usually by nursing. Those deemed to be at nutrition risk undergo a detailed nutrition assessment by an RD who, when appropriate, recommends a diagnosis of malnutrition, documents it in the medical record, and communicates it to the other disciplines involved in the patient's care. Physicians/LIPs, if in agreement with the dietitian's recommended diagnosis, document malnutrition in their history and physical, progress notes, and/or discharge notes. From there, medical coders review physician/LIP documentation and convert it into the appropriate ICD code. This is transmitted to the payer who reimburses the institution. Any deviation or omission along this process can prevent appropriate recognition of malnutrition and reimbursement to the institution. Revenue cycle and finance professionals can help track the impact malnutrition diagnosis provides.

Cost-Effectiveness of Nutrition Intervention

Considering malnutrition is pervasive in hospitalized patients, is either a cause or consequence of many disease conditions, and is a major contributor to health care expenditures, it is reasonable to assume treating malnutrition would be cost effective. Unfortunately, proving the cost-effectiveness of nutrition intervention is difficult for a number of reasons. The actual cost to each hospital to provide nutrition intervention, and how much each institution charges patients for these goods and services is unknown and is proprietary information. Further, the cost of a day in the intensive care unit or regular nursing floor, or to treat a malnutrition-related complication, can vary widely from hospital to hospital.

The cost of nutrition intervention in patients who are able to eat depends upon the frequency and type of diet counseling and the use of oral nutrition supplements (ONS).Nutrition support is more costly than diet and/or ONS, especially when the costs of placing and maintaining and access device and monitoring of therapy are included. But the cost of nutrition intervention, even parenteral nutrition (PN), is modest compared to the cost of having to treat a preventable nutrition-related complication or of extending the length of stay. Among complications associated with malnutrition, the cost of treating an acute respiratory infection, for example, is estimated at $13,350 to $19,530 per episode, adjusted to 2009 dollars, in the USA [24]. Likewise, the average cost of a day in a US hospital in 2010 was $1629 and $2025 for for-profit and nonprofit hospitals, respectively [25].

The difference between the cost of nutrition intervention and cost of care is even larger in the critically ill. This occurs because the cost of nutrition intervention remains the same regardless of level of care, while the daily cost of care in an intensive care unit (ICU) is considerably higher compared to a regular nursing floor. A 2005 study examined the mean daily cost of an ICU stay in medical, surgical, and trauma units with and without mechanical ventilation from 250 US hospitals. The average daily cost of an ICU day was $10,794 with mechanical ventilation and $6667 without mechanical ventilation for day 1. The costs dropped to $4796 and $3496 on day 2, and remained at $3968 and $3184 from day 3 forward [26].

Nutrition intervention improves clinical and nutritional outcomes in selected patients with malnutrition. Nutrition intervention is associated with improved physical function [27], quality of life [27], nutrition status [28], nutrition intake [29], reduced length of stay [15], and reduced readmission frequency [27, 28]. But these studies further illustrate the difficulty proving cost effectiveness. Outcomes resulting from nutrition intervention are usually described in terms of improved clinical outcomes rather than decreased expenditures. And some of these, such as nutrition status and intake, are not meaningful outcomes. Determining savings by avoidance of a complication, such as an episode of hospital-acquired pneumonia or catheter-related bloodstream infection, is more theoretical than actual. In addition, nutrition intervention is one of perhaps many factors influencing the occurrence of these episodes.

In spite of these challenges, studies specifically designed to examine the cost effectiveness of nutrition intervention in patients able to eat have demonstrated positive results. The use of ONS in patients with malnutrition has been shown to be cost effective in a variety of settings [30, 31]. It is unclear how much effect the use of ONScan have in the acute care setting, given that the average length of hospital stay in the USA is only 4.8 days [32]. It is more likely the benefits of ONS are realized post-discharge given the chronic nature of malnutrition. A systematic review and meta-analysis of randomized controlled trials reported a significant reduction in hospital readmissions over 2–12 months with the consumption of ONS post-hospitalization for 6 weeks to 1 year [33]. This illustrates the potential benefit for continuing to implement, monitor, and adjust the nutrition care plan across the different levels of care within the acute care setting, and post-discharge, either in long-term care facilities or the community. Failure to coordinate care can increase the likelihood of complications, hospital readmissions, declines in functional status, and increased dependency and has been estimated to cost the USA between $25 and $45 billion in excess health care spending in 2011 [34].

The use of enteral nutrition (EN) is cost effective, particularly when it is used in place of PN in patients with a functional gastrointestinal tract. Enteral nutrition is less costly to administer compared to PN [35], but more importantly, EN avoids the risk of PN-related complications. This was demonstrated in a meta-analysis of studies comparing the economic benefit of EN to PN in critically ill patients. The authors concluded that EN reduces the risk of both major infectious and noninfectious complications, and reduces hospital and ICU length of stay and length of nutritional treatment [36]. How many patients on PN could receive EN is unknown. But, if only 10 % of patients receiving PN could be fed enterally, savings from reduced adverse events by using EN would be $1500 per patient; and $2500 per patient from reduced hospital length of stay. Nationally, this would result in a savings of $35 million and $57 million, respectively. These cost differences may decrease as the incidence of such complications of PN as central line-associated bloodstream infection are better prevented as part of overall improvements in hospital care, but it is highly unlikely that costs will ever become equal. Appropriate timing of EN in the critically ill can also prove to be cost effective. An economic analysis from the perspective of the US acute care hospital system demonstrated early EN provided to critically ill patients can reduce total costs by an average of $14,462 per patient compared to standard care [37].

The cost-effectiveness of nutrition support requires the availability of appropriate products and adherence to best-practice protocols. National standards and guidelines exist for ordering, preparing, delivering, and monitoring EN [38] and PN [39]. Institutions should use these to establish enteral and parenteral formularies with products designed to meet the needs of their patient populations, as well as clear protocols for when and how to administer each product. Establishing an enteral formulary with well-defined categories and eliminating clinically equivalent products may be cost effective by reducing inventory and encouraging competitive bidding [40]. But the greatest economic benefit of the availability and appropriate use of an enteral formula is the reduction in health care expenditures due to improved clinical outcomes. In one study, the impact of immunonutrition formulas on hospital costs in patients undergoing elective surgery for gastrointestinal cancer was examined using a database of nationally representative inpatient discharge data. Results demonstrated a savings of $3300 per patient based on a reduction in complication rates, and $6000 per patient based on shortened hospital length of stay [41]. The therapeutic effect of these specialized EN formulas, however, has been poorly proven. These are reviewed in Chap. 10.

A PN formulary should address to what extent to incorporate standardized PN formulas. Standardized formulas may be less costly to prepare compared to custom formulas, especially when compounding is performed in-house and in smaller hospitals, and evidence suggests that their use may result in fewer episodes of central venous catheter-related bloodstream infections compared to custom formulas [42]. However, standardized formulas are less able to meet the nutrition requirements of individual patients [43]. Whether this affects clinical outcomes has yet to be determined. But patients receiving standardized formulas may also require more frequent separate intravenous electrolyte replacements compared to patients receiving custom formulas, which may negate their cost

advantage [44]. And in theory, the cost and increased risk of infection in customized formulas may be mitigated when a central compounding pharmacy, for example one that services multiple hospitals and a large number of patients in a geographical region, is used.

Multidisciplinary Approach to Nutrition Delivery

Nutrition delivery can be successfully managed by a variety of approaches. These include individual clinicians, groups of clinicians of the same discipline organized into a section or department, patient care teams comprised of individuals from different disciplines often from different departments organized around caring for a specific patient population, and formal multidisciplinary nutrition support teams (NSTs). Each approach to nutrition delivery has its own distinct advantages and shortcomings based on the type and number of patients, and overall duties and responsibilities of the caregivers.

Individual clinicians or groups of clinicians from the same discipline can successfully manage nutrition delivery for a wide variety of patient populations provided that they have the necessary knowledge and experience. The advantage of this type of approach is that decisions can be made and implemented quickly without the complexity of a team. But the quality of care in this scenario is highly dependent upon the knowledge, experience, and skill of individual practitioner(s). This may vary and be difficult to assess. The Academy of Nutrition and Dietetics offers a Dietetics Career Development Guide illustrating how practitioners can attain increasing levels of knowledge and skills throughout their career, which leads to increased levels of practice from novice to expert [45]. Specialty certification in a focused area, such as nutrition support, is one method to demonstrate knowledge. But knowledge does not equate to expertise, or even competence. Becoming a Certified Nutrition Support Clinician, for example, simply acknowledges the clinician has the core knowledge necessary to be able to provide safe and efficacious nutrition support, not that the clinician is an expert.

Expert clinical guidelines help standardize nutrition care independent of approach. Adherence to these guidelines through the use of algorithms or clinical care paths can improve clinical and nutritional outcomes by improving the quality and standardization of practice. Nutrition support algorithms used in critically ill patients, for example, improve calorie and protein delivery [46–48].

An important advantage of multidisciplinary NSTs is the diverse scope of practice and combined knowledge, experience, and skills of members. Conversely, it is difficult for an individual practitioner to match the scope and level of care provided by a multidisciplinary team. And without an organized framework that encourages input from multiple disciplines, there is the potential for individual disciplines to make decisions independently that do not consider aspects of the patient's care that might be better understood by another discipline.

Historically, NSTs were established to manage the complexities of PN, and specifically to correct the unacceptably high incidence of central venous catheter-related septic and mechanical complications [49]. Providing PN under the care of NSTs has been demonstrated to decrease catheter infection rates [50], and their role has expanded over the years to include management of patients in a variety of settings, receiving both PN and EN, educating fellow health care colleagues, performing outcomes-based research, and developing policies and best practices. Roles of NST members at Cleveland Clinic are listed in Appendix 15.2. While members from each discipline contribute their own specialized knowledge, there is common core knowledge across all nutrition support disciplines required for competent practice. This core knowledge was recognized by ASPEN and led to the development of the Certified Nutrition Support Clinician certification.

The clinical and nutritional benefits and cost-effectiveness of the multidisciplinary approach to the delivery of nutrition has been studied in a variety of settings and patient populations with mixed results. There are many examples demonstrating intervention by a NST improving clinical and

nutritional outcomes (Appendix 15.3). And at least one study was able to demonstrate economic benefits of a NST after accounting for the cost of the team itself [51]. In this study, a benefit of $4.20 was realized for every $1.00 invested in NST management in patients receiving enteral nutrition support. Among the challenges in interpreting the results of these studies are differences in study design, subjects, composition of the team, outcome measures, and frequency and length of follow-up. Most are small and lack sufficient power to detect differences between the control and intervention groups.

Overprescribing PN is more likely to occur when there isn't a governing body or system in place to evaluate appropriateness. Many physicians fail to appreciate the risks associated with PN and view it as an easy, low-risk method to provide nutrition for patients unable to eat adequately despite a functional gastrointestinal tract. The rates of inappropriate PN use have been reported as high as 56 % in institutions with limited or no oversight [52]. On the other hand, inappropriate PN use decreases in the presence of oversight by NSTs [52–55]. This is most likely to occur when NSTs have final prescriptive authority to approve or deny the use of PN [54, 56, 57].

When a formal NST is not possible, empowering different disciplines to oversee the ordering of PN may also have a positive impact. In a single before and after study, decreased inappropriate PN has been reported after PN order writing privileges were granted to RDs with master's degrees, certification in nutrition support, and appropriate training [58].

The savings attributed to decreasing inappropriate PN is not only due to cost of the formula itself. Additional expenses include placement and maintenance of venous access, imaging studies, and additional monitoring with capillary blood glucose measurements or electrolyte panels. Cost savings aside, the real benefit of reducing inappropriate PN is clinical. Avoiding inappropriate PN decreases the patient's risk of developing PN-related complications [35, 59].

The primary financial shortcoming of a formal multidisciplinary NST is the overhead cost of the team combined with limited ability to generate revenue. In addition to salaries and benefits of individual members, expenses associated with management of the team include administrative costs, office space, and supplies. In comparison, most members of the NST, other than physicians, have limited ability to bill for their services. The primary revenue-related value of dietitians and nurses to the NST is as physician extenders. In this way, physicians can care for, and bill on, more patients than they could normally do on their own. In spite of this, NSTs are generally not considered self-supporting services. And because justifying expenditures by hospitals based on theoretical cost savings is difficult, keeping NSTs economically viable is challenging when NST involvement in patient care is not mandated and reimbursement for nutrition-related activities is limited. As a result, disbanding of existing NSTs is outpacing the creation of new NSTs in the USA [60].

A significant challenge to delivering nutrition in a multidisciplinary approach is the lack of physician nutrition experts. A white paper was published by the National Academy of Science 30 years ago, noting the lack of nutrition education in US medical schools, and making specific recommendations [61]. Unfortunately, little has changed since then. The lack of nutrition education in medical schools is compounded by the lack of formal nutrition education in residency programs [62, 63], and the lack of opportunities for advanced training in nutrition compared to other subspecialties. Currently, there are only 11 nutrition fellowship programs in the USA [64]. Other postgraduate training programs in nutrition exist, but they are limited in number and scope. Symptomatic of the lack of physician nutrition experts is the decreasing physician membership in national nutrition societies and number of physicians taking nutrition board certification exams [65]. Physician membership in the American Society for Parenteral and Enteral Nutrition (ASPEN), established in 1974, decreased from a peak of 1752 in 1990 to 634 in 2009 while dietitian membership increased from 2638 to 3149 during that same time period [65].

The lack of physician nutrition experts and reimbursement for nutrition-related services adversely affect the viability of existing NSTs, and the creation of new teams. Physician nutrition experts are facing increasing pressure from their institutions to perform procedures with higher reimbursement rates,

making it less likely they can focus on nutrition. Based on a survey of ASPEN members, physician members spent <25 % of their time performing activities related to nutrition support on average, and only 5.6 % were full-time nutrition support physicians [60]. And there is little financial incentive for new physicians to choose nutrition as a subspecialty as reimbursement rates are low compared to procedural specialties. Members from institutions with disbanded NSTs cited lack of physician support as one of the leading reasons for the NST being disbanded. Members from institutions without NSTs similarly cited lack of physician support as a roadblock to establishing an NST [60].

The lack of nutrition training for health care professionals is not isolated to physicians. Bedside nurses, in particular, are well positioned to affect their patients' nutritional intake but receive little formal nutrition education. Studies have demonstrated that adherence to nutrition algorithms and allowing nurses autonomy to deliver tube feedings result in increased delivery of nutrients [66]. But nurses may lack knowledge of enteral nutrition [67] and often view nutrition as low priority [68].

Conclusion: Suggestions for Practice

- *Ensure early recognition of malnutrition*. Perform nutrition screening of all hospitalized patients within 24 h of admission to determine those at nutrition risk. Refer patients deemed to be at nutrition risk to a RD for a more thorough evaluation.
- *Diagnose and document malnutrition appropriately*. Perform and a detailed nutrition assessment for all patients deemed to be at nutrition risk and document malnutrition by physicians and LIPs in the medical record.
- *Ensure early and appropriate nutrition intervention*. Develop a nutrition care plan for all patients who are malnourished, or at risk of being malnourished and implement it on a timely basis. Develop a plan for monitoring response to nutrition therapy and adjust the nutrition care plan as needed.
- *Consider cost-effectiveness when determining nutrition intervention*. Develop an evidence-based enteral and parenteral nutrition formulary which avoids clinically equivalent or unproven and expensive products and considers cost-effectiveness.
- *Establish evidence-based pathways for administration of oral*, *enteral*, *and parenteral nutrition*. Develop clear indications and contraindications for each oral, enteral, and parenteral product including the timing of therapy.
- *Ensure continuity of nutrition care*. Document the nutrition care plan and communicate it to the next caregiver as the patient transfers from different levels of medical care within the acute care setting as well as when the patient is discharged to home or a long-term care facility.
- *Decrease inappropriate use of PN*. Establish a system that requires prior approval for the use of PN by a group who is knowledgeable about indications for PN and can also recommend alternative therapies. Preferably, this group would be led by one or more physician nutrition experts, with expertise in maximizing EN, who would have final authority from the hospital's medical board to approve or deny PN use. In the absence of final authority, require providers to consult experienced and qualified clinicians who can provide non-binding recommendations. Minimally, establish or adopt policies and procedures, such as nutrition support algorithms, to help determine the most appropriate nutrition intervention.
- *Remove barriers to providing nutrition*. Establish guidelines to minimize interruptions in nutrition due to procedures or tests, and delays in placement of enteral or intravenous access devices used for nutrition. Provide bedside RNs autonomy under strict protocol to administer tube feedings. Minimize bedside RNs and house staff autonomy for holding tube feedings unnecessarily. Maximize the role of RDs, and incorporate them into all care teams.

- *Create multidisciplinary culture of treating/preventing malnutrition*. Create multidisciplinary patient care teams or formal NSTs for patients at greatest need. Require other clinical services to document nutrition status and nutrition intervention in their daily notes by incorporating it into their electronic note templates and by creating a quality or documentation improvement process. Require providers to address nutrition as part of daily bedside rounds, especially in the ICU.
- *Increase nutrition training*. Incorporate and require nutrition education for residency and fellowship programs. Mandate nutrition education be a part of the continuing education program for permanent staff including physicians, physician assistants, pharmacists, and nurses. Include discussions on the cost-effectiveness of nutrition. Dedicate time for continuing education of NST members.

Appendix 15.1: Definitions

Cost-effectiveness analysis (CEA) is a type of economic evaluation that examines both the costs and health outcomes of alternative intervention strategies. CEA compares the cost of an intervention to its effectiveness as measured in natural health outcomes (e.g., "cases prevented" or "years of life saved"). CEA results are presented in a cost-effectiveness ratio, which expresses cost per health outcome (e.g., cost per case prevented and cost per life year gained). CEA is generally used to either: compare alternative programs with a common health outcome, or assess the consequences of expanding an existing program [69].

Cost savings—An action that will result in fulfillment of the objectives of a purchase, at a cost lower than the historical cost or the projected cost [70].

Cost avoidance—Action taken to reduce future costs, such as replacing parts before they fail and cause damage to other parts. Cost avoidance may incur higher (or additional) costs in the short run but the final or life cycle cost would be lower [70].

Licensed independent practitioner—Any practitioner permitted by law and by the organization to provide care and services, without direction or supervision, within the scope of the practitioner license and consistent with individually assigned clinical responsibilities [71].

Appendix 15.2: Specialists on Cleveland Clinic Nutrition Support Team (NST) and Their Roles [72]

Director, Center for Human Nutrition

- Oversee activities of the Center for Human Nutrition encompassing the NST, Center for Gut Rehabilitation and Transplant (CGRT), Home Nutrition Support Service (HNSS), and Nutrition Therapy Department.
- Perform duties as an NST staff physician
- Direct the physician nutrition fellowship program

NST/HNSS Staff Physicians

- Oversee the PN approval process and overall delivery of nutrition support to patients evaluated and managed by the NST, including both hospitalized and home parenteral nutrition (HPN) patients.

- Oversee collaborative interventions by the NST and CGRT to decrease reliance on PN by optimizing enteral nutrition (EN) and evaluating for bowel transplantation, if appropriate.
- Conduct daily bedside rounds.
- Supervise educational and research activities of the NST.

Director, Nutrition

- Direct and manage overall operations of the NST, HNSS, CGRT, and Nutrition Therapy Department.
- Develop and implement policies, procedures, and guidelines promoting the safe and appropriate use of nutrition.
- Direct quality assurance and research activities of the Center for Human Nutrition.

NST Manager/Nutrition Education Coordinator

- Manage activities of the NST.
- Direct education and training of all newly hired NST clinicians as well as residents, fellows, dietetic interns, and pharmacists-in-training rotating with the NST.
- Coordinate continuing education activities.
- Provide nutrition care to patients followed by the NST (below).

NST Dietitians

- Assess patients for the appropriate use of EN and PN.
- Perform comprehensive nutrition assessment for patients followed by the NST.
- Provide nutrition care to patients followed by the NST under the direction of an NST physician.
- Evaluate and manage fluid, electrolyte, acid–base, blood glucose, macro- and micronutrient status using physical assessment as well as a review of laboratory, radiology, pathology, microbiology, and clinical reports.
- Develop, document, and implement nutrition care plans.
- Participate in bedside rounds with NST physician and prepare daily PN orders.
- Evaluate and prepare patients for HPN, including stabilizing and cycling the PN formula.
- Communicate the nutrition care plan with the patient, primary service, other pertinent consult services, pharmacy, case manager, and social worker as indicated.

NST Nurses

- Participate in the care and evaluation of patients requiring HPN.
- Assume responsibility for the care, maintenance, selection, and troubleshooting of long-term central venous access devices (CVADs) used for PN.
- Identify and mark appropriate catheter exit sites for patients prior to the insertion of permanent tunneled catheters.
- Obtain quantitative blood cultures on patients with long-term CVADs and suspected catheter-related bloodstream infections

- Educate HPN patients and caregivers on catheter care, infusion therapy, and home self-monitoring.
- Coordinate HPN patient discharge planning with the patient, primary service, other pertinent consult services, social worker, and case manager.
- Serve as a resource to hospital and homecare nurses through inservices regarding catheters and catheter care.

Enteral Access Nurses

- Evaluate the need for and place small bowel feeding tubes.
- Act as advocate for EN by educating healthcare professionals, patients, and families about the benefits of EN and the need for feeding tube placement.

HNSS Manager

- Manage activities of the HNSS.
- Perform duties of a HNSS clinician (below).

HNSS Clinicians

- Collaborate with the patient, primary service, other pertinent consult services, and the case manager in the discharge planning process for HPN patients.
- Review and optimize final PN formulas for patients discharged with HPN and communicate these prescriptions to appropriate home care providers.
- Maintain a database on all patients followed by the HNSS.
- Manage HNSS outpatients under the direction of the staff physician by monitoring labs and other pertinent information and modifying the HPN prescription accordingly.
- Communicate formula changes to the patient, home care provider, and infusion provider.
- Provide 24-h pager coverage for urgent problems and advise patients and caregivers on the most appropriate plan of action.
- Evaluate patients in the outpatient clinic.

Pharmacist

- Monitor drug therapy for dosing and drug-nutrient interactions.
- Serve as a resource for PN-related issues, especially involving compounding, compatibility, and stability.
- Serve as a liaison between the NST and the Pharmacy Department.

CGRT Manager

- Manage activities of the CGRT including program development and marketing, hiring and training, development and maintenance of policies, procedures, and quality assurance mechanisms.

- Perform duties of an CGRT dietitian (below).

CGRT Dietitians

- Conduct detailed evaluation of diet, medication, surgical history, and anatomy of intestinal failure patients.
- Develop comprehensive treatment plans for intestinal failure and pre- and post-intestinal transplant patients in the hospital, home, and ambulatory clinic setting.
- Monitor and assess effectiveness of CGRT interventions.
- Maintain a clinical database for all patients followed by CGRT.
- Prepare and present relevant clinical information to facilitate the evaluation process for intestinal and multivisceral transplantation.

Social Worker

- Assess all patients requiring HPN for cognitive and functional capacity, psychosocial stability, and family or caregiver support.
- Counsel and assist patients with socioeconomic and psychological issues and refer patients to the Psychiatry Department as needed.
- Collaborate with the NST, primary service, and pertinent services regarding the disposition of patients being discharged with HPN.
- Coordinate hospital-to-hospital transfers for patients receiving PN.

Case Managers

- Investigate and verify insurance benefits for HPN coverage of patients being discharged to home, rehabilitation, skilled nursing, or long-term acute care facilities.
- Establish all HPN discharge needs and services including transportation, home nursing visits, HPN training, home care and infusion providers, or placement in a rehabilitation, skilled nursing, or long-term acute care facility.
- Collaborate with the NST, primary service, and other pertinent services regarding the disposition of patients being discharged on HPN.

Appendix 15.3: Improved Clinical, Nutritional, and Financial Outcomes Associated with NSTs

- Reduce/avoid PN episodes [73]
- Less short-term use of PN [52]
- Increase energy intake [50, 74–76]
- More days meeting estimated energy needs [74]
- Increase protein intake [74, 77]
- More days meeting estimated protein needs [74]

- Reduce duration of PN therapy [78]
- Reduce absence of oral intake [78]
- Shorten length of stay [51, 78]
- Reduce mortality rate [51, 73]
- Reduce readmission rate [51]
- Reduce total cost of hospitalization [78]
- Decrease catheter-related sepsis [73, 78, 79]
- Reduce episodes of hyperglycemia [76, 78]
- Reduce electrolyte and metabolic complications [80]
- Reduce total complications [77]
- Reduce metabolic complications [52]
- Reduce episodes of abnormal liver enzymes [78]

References

1. Braunschweig C, Gomez S, Sheean P. Impact of declines in nutritional status on outcomes in adult patients hospitalized for more than 7 days. J Am Diet Assoc. 2000;100:1316–22.
2. Kyle U, Unger P, Mensi N, Genton L, Pichard C. Nutrition status in patients younger and older than 60 y at hospital admission: a controlled population study in 995 subjects. Nutrition. 2002;18:463–9.
3. Lim S, Ong K, Chan Y, Loke W, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr. 2012;31:345–50.
4. Study Group of Hyperglycemia in Parenteral Nutrition, Nutrition Area of the Spanish Society of Endocrinology and Nutrition (SEEN). The subjective global assessment predicts in-hospital mortality better than other nutrition-related risk indexes in noncritically ill inpatients who receive total parenteral nutrition in Spain (prospective multicenter study). J Acad Nutr Diet. 2013;113:1209–18.
5. Bistrian B, Blackburn G, Vitale J, Cochran D, Naylor J. Prevalence of malnutrition in general medical patients. JAMA. 1976;235:1567–70.
6. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health, Centers for Disease Control and Prevention. The state of aging and health in America. Accessed on January 18, 2014, from: http://www.cdc.gov/aging/pdf/state-aging-health-in-america-2013.pdf
7. Scheisser M, Muller S, Kirchhoff P, Breitenstein S, Schafer M, Clavien P. Assessment of a novel screening score for nutrition risk in predicting complications in gastrointestinal surgery. Clin Nutr. 2008;27:565–70.
8. Amaral TF, Antunes A, Cabral S, Alves P, Kent-Smith L. An evaluation of three nutrition screening tools in a Portuguese oncology center. J Hum Nutr Diet. 2008;21:575–83.
9. Ozkalkanili MY, Ozkalkanli DT, Katircioglu K, Savaci S. Comparison of tools for nutrition assessment and screening for predicting the development of complications from orthopedic surgery. Nutr Clin Pract. 2009;24:274–80.
10. Fry DE, Pine M, Jones BL, Meimban RJ. Patient characteristics and the occurrence of never events. Arch Surg. 2010;145:148–51.
11. Thomas DR, Zdrowski CD, Wilson MM, Conright KC, Lewis C, Tariq S, et al. Malnutrition in subacute care. Am J Clin Nutr. 2002;75:308–13.
12. Chima CS, Barco K, Dewitt ML, Maeda M, Teran JC, Mullen KD. Relationship of nutritional status to length of stay, hospital costs, and discharge status of patients hospitalized in the medicine service. J Am Diet Assoc. 1997;97:975–8.
13. Correia M, Waitzberg D. The impact of malnutrition on morbidity, mortality, length of hospital stay, and costs evaluated through a multivariate model analysis. Clin Nutr. 2003;22:235–9.
14. Elia M. Nutrition and health outcomes. Nutrition. 2006;22:576–8.
15. Kruizenga H, Van Tulder M, Seidell J, Thijs A, Ader H, Van Bokhorst-de van der Schueren M. Effectiveness and cost-effectiveness of early screening and treatment of malnourished patients. Am J Clin Nutr. 2005;82:1082–9.
16. Schindler K, Pernicka E, Laviano A, Howard P, Schutz T, Bauer P, et al. How nutritional risk is assessed and managed in European hospitals: a survey of 21,007 patients findings from the 2007-2008 cross-sectional nutrition day survey. Clin Nutr. 2010;29:552–9.
17. The Joint Commission. Provision of Care, Treatment, and Services. Accessed on February 16, 2014, from: http://www.jointcommission.org/mobile/standards_information/jcfaqdetails.aspx?StandardsFAQId=471&StandardsFAQChapterId=78

18. Chima C, Dietz-Seher C, Kushner-Benson S. Nutrition risk screening in acute care: a survey of practice. Nutr Clin Pract. 2008;23:417–23.
19. White J, Guenter P, Jensen G, Malone A, Schofield M. 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;36:275–83.
20. American Society for Parenteral and Enteral Nutrition (ASPEN) Board of Directors and Clinical Practice Committee. Definition of terms, styles, and conventions used in ASPEN Board of Directors-Approved Documents. Accessed on January 19, 2014, from: http://www.nutritioncare.org/Professional_Resources/Guidelines_and_Standards/Guidelines/2012_Definitions_of_Terms,_Style,_and_Conventions_Used_in_A_S_P_E_N__Board_of_Directors-Approved_Documents/
21. Rosen B, Maddox P, Ray N. A position paper on how cost and quality reforms are changing healthcare in America: focus on nutrition. JPEN J Parenter Enteral Nutr. 2013;37:796–801.
22. Corkins M, Guenter P, Dimaria-Ghalili R, Jensen G, Malone A, Miller S, et al. Malnutrition diagnoses in hospitalized patients: United States, 2010. JPEN J Parenter Enteral Nutr. 2014;38(2):186–95.
23. Giannopoulos G, Merriman L, Rumsey A, Zwiebel D. Malnutrition coding 101: financial impact and more. Nutr Clin Pract. 2013;28:698–709.
24. Cangelosi M, Rodday A, Saunders T, Cohen J. Evaluation of the economic burden of diseases associated with poor nutrition status. JPEN J Parenter Enteral Nutr. 2014;38:35S. doi:10.1177/0148607113514612.
25. Becker's Hospital Review. Average cost per inpatient day across 50 states in 2010. Accessed on February 2, 2014, from: http://www.beckershospitalreview.com/lists/average-cost-per-inpatient-day-across-50-states-in-2010.html
26. Dasta J, McLaughlin T, Mody S, Piech C. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med. 2005;33:1266–71.
27. Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease – a randomized controlled trial. Clin Nutr. 2008;27:48–56.
28. Odelli C, Burgess D, Bateman L, et al. Nutrition support improves patient outcomes, treatment tolerance, and admission characteristics in oesophageal cancer. Clin Oncol (R Coll Radiol). 2005;17:639–45.
29. Babineau J, Villalon L, Laporte M, Payette H. Outcomes of screening and nutritional intervention among older adults in healthcare facilities. Can J Diet Pract Res. 2008;69:89–94.
30. Norman K, Pirlich M, Smoliner C, Kilbert A, Schulzke J, Ockenga J, Lochs H, Reinhold T. Cost-effectiveness of a 3-month intervention with oral nutritional supplements in disease-related malnutrition: a randomized controlled pilot study. Eur J Clin Nutr. 2011;65:735–42.
31. Freijer K, Nuijten M, Schols J. The budget impact of oral nutritional supplements for disease related malnutrition in elderly in the community setting. Front Pharmacol. 2012;3:1–8.
32. Centers for Disease Control and Prevention. Discharges, days of care, and average length of stay in nonfederal short-stay hospitals, by selected characteristics. Accessed on January 23, 2014, from: http://www.cdc.gov/nchs/data/hus/hus12.pdf#094
33. Stratton R, Hebuterne X, Elia M. A systematic review and meta-analysis of the impact of oral nutrition supplements on hospital readmissions. Ageing Res Rev. 2013;12:884–97.
34. Berwick D, Hackbarth A. Eliminating waste in US health care. JAMA. 2012;2307:1513–6.
35. Pritchard C, Duffy S, Edington J, Pang F. Enteral nutrition and oral nutrition supplements: a review of the economics literature. JPEN J Parenter Enteral Nutr. 2006;30:52–9.
36. Cangelosi M, Auerbach H, Cohen J. A clinical and economic evaluation of enteral nutrition. Curr Med Res Opin. 2011;27:413–22.
37. Doig GS, Chevrou-Severac H, Simpson F. Early enteral nutrition in critical illness: a full economic analysis using US costs. Clinicoecon Outcomes Res. 2013;5:429–36.
38. Bankhead R, Boullatta J, Brantley S, Corkins M, Guenter P, Krenitsky J, et al. Enteral nutrition practice recommendations. JPEN J Parenter Enteral Nutr. 2009;33:122–67.
39. Boullata J, Gilbert K, Sacks G, Labossiere R, Crill C, Goday R, et al. ASPEN Clinical Guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. JPEN J Parenter Enteral Nutr. 2014;38:334. doi:10.1177/0148607114521833.
40. Wildish D. Enteral formulary management: a cost-effective approach. Can J Diet Pract Rec. 2006;67:193–8.
41. Mauskopf J, Candrilli S, Chevrou-Severac H, Ochoa B. Immunonutrition for patients undergoing elective surgery for gastrointestinal cancer: impact on hospital costs. W J Surg Oncol. 2012;10:1–7.
42. Turpin RS, Canada T, Liu X, Mercaldi C, Pontes-Arruda A, Wischmeyer P. Nutrition therapy cost analysis in the US: pre-mixed multi-chamber bag versus compounded parenteral nutrition. Appl Health Econ Health Policy. 2011;9:281–92.
43. Blanchette L, Huiras P, Papadopoulos S. Standardized versus custom parenteral nutrition: impact on clinical and cost-related outcomes. Am J Health Syst Pharm. 2014;71:114–21.

44. Busch R, Curtis C, Leverson G, Kudsk K. Use of piggyback electrolytes for patients receiving individually prescribed vs premixed parenteral nutrition. JPEN J Parenter Enteral Nutr. 2015;39:586. doi:10.1177/0148607113518583.
45. Academy of Nutrition and Dietetics. Dietetics Career Development Guide. Accessed on February 2, 2014 from: http://www.eatright.org/Members/content.aspx?id=7665
46. Martin CM, Doig GS, Heyland D, Morrison T, Sibbald WJ. Multicentre cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). CMAJ. 2004;170:197–204.
47. Kiss C, Byham-Gray L, Denmark R, Loetscher R, Brody R. The impact of implementation of a nutrition support algorithm on nutrition care outcomes in an intensive care unit. Nutr Clin Pract. 2012;27:793–801.
48. Heyland D, Murch L, Cahill N, MCall M, Muscedere J, Stelfox H, et al. Enhanced protein-energy provision via the enteral route feeding protocol in critically ill patients: results of a cluster randomized trial. Crit Care Med. 2013;41:2743–53.
49. Wesley J. Nutrition support teams: past, present, and future. Nutr Clin Pract. 1995;10:219–28.
50. Fischer G, Opper F. An interdisciplinary nutrition support team improves quality of care in a teaching hospital. J Am Dietet Assoc. 1996;96:176–8.
51. Hassell J, Games A, Saffer B, Harkins L. Nutrition support team management of enterally fed patients in a community hospital is cost-beneficial. J Am Dietet Assoc. 1994;94:993–8.
52. 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;23:109–13.
53. Ochoa JB, Magnuson B, Swintowsky M, Loan T, Boulanger B, McClain C, Kearney P. Long-term reduction in the cost of nutritional intervention achieved by a nutrition support service. Nutr Clin Pract. 2000;15:174–80.
54. Newton R, Timmis L, Bowling TE. Changes in parenteral nutrition supply when the nutrition support team controls prescribing. Nutrition. 2001;17:347–8.
55. Martin K, DeLegge M, Nichols M, Chapman E, Sollid R, Grych C. Assessing appropriate parenteral nutrition ordering practices in tertiary care medical centers. JPEN J Parenter Enteral Nutr. 2011;35:122–30.
56. Maurer J, Weinbaum F, Turner J, Brady T, Postone B, D'Addario V, et al. Reducing the inappropriate use of parenteral nutrition in an acute care teaching hospital. JPEN J Parenter Enteral Nutr. 1996;20:272–4.
57. Saalwachter AR, Evans HL, Willcutts KF, O'Donnell K, Radigan A, McElearney S, et al. A nutrition support team led by general surgeons decreases inappropriate use of total parenteral nutrition on a surgical service. Am Surg. 2004;70:1107–11.
58. Peterson SJ, Chen Y, Sullivan CA, Kinnare K, Tupesis N, Gourang P, et al. Assessing the influence of registered dietitian order-writing privileges on parenteral nutrition use. J Am Diet Assoc. 2010;110:1703–11.
59. Vanderheyden S, Casaer M, Kesteloot K, Simoens S, De Rijdt T, Peers G, et al. Early versus late parenteral nutrition in ICU patients: cost analysis of the EPaNIC trial. Crit Care. 2012;16:R96.
60. DeLegge M, Wooley J, Guenter P, Wright S, Brill J, Andris D, et al. The state of nutrition support teams and update on current models for providing nutrition support therapy to patients. Nutr Clin Pract. 2010;25:76–84.
61. National Academy of Sciences. Nutrition education in U. S. Medical Schools. Washington, DC: National Academies Press; 1985.
62. Deen D, Spencer E, Kolasa K. Nutrition education in family practice residency programs. Fam Med. 2003;35:105–11.
63. Adams KM, Lindell KC, Kohlmeier M, Zeisel SH. Status of nutrition education in medical schools. Am J Clin Nutr. 2006;83:941S–4.
64. National Board of Physician Nutrition Specialists. Fellowship Programs. Accessed on February 8, 2014 from: http://www.nutritioncare.org/NBPNS/index.aspx?id=6437
65. McClave S, Mechanick J, Bistrian B, Graham T, Hegazi R, Jensen G, et al. What is the significance of a physician shortage in nutrition medicine? JPEN J Parenter Enteral Nutr. 2010;34:7S–20.
66. Heyland D, Cahill N, Dhaliwal R, Wang M, Day A, Alenzi A, et al. Enhanced protein-energy provision via the enteral route in critically ill patients: a single center feasibility trial of the PEP uP protocol. Crit Care. 2010;14:R78. doi:10.1186/cc8991.
67. Bourgault A, Ipe L, Weaver J, Swartz S, O'dea P. Development of evidence-based guidelines and nurses' knowledge of enteral feedings. Crit Care Nurse. 2007;27:17–22.
68. Marshall AP, Cahill NE, Gramlich L, MacDonald G, Alberda C, Heyland DK. Optimizing nutrition in intensive care units: empowering critical care nurses to be effective agents of change. Am J Crit Care. 2012;21:186–94.
69. Centers for Disease Control. Cost effectiveness analysis: introduction. Accessed on February 14, 2014 from: http://www.cdc.gov/owcd/eet/costeffect2/fixed/1.html
70. BusinessDictionary.com. Accessed on February 14, 2014 from: http://www.businessdictionary.com/definition/cost-saving.html
71. Licensed Independent Practitioner Delegation of Tasks to Physician Assistants and Advance Practice Registered Nurses. Accessed on March 11, 2014, from: http://www.apna.org/files/public/LIPClarification.pdf

72. Coughlin K, DeChicco R, Hamilton C, editors. Cleveland Clinic nutrition support handbook. Cleveland, OH: Cleveland Clinic; 2011.
73. Kennedy J, Nightingale J. Cost savings of an adult hospital nutrition support team. Nutrition. 2005;21:1127–33.
74. Gales B, Riley D. Improved total parenteral nutrition therapy management by a nutritional support team. Hosp Pharm. 1994;29:469–75.
75. ChrisAnderson D, Heimburger DC, Morgan SL, Geels WJ, Henry KL, Conner W, et al. Metabolic complications of total parenteral nutrition: effect of a nutrition support service. JPEN J Parenter Enteral Nutr. 1996;20:206–10.
76. Fettes SB, Lough M. An audit of the provision of parenteral nutrition in two acute hospitals: team versus nonteam. Scott Med J. 2000;45:121–5.
77. Traeger SM, Williams GB, Milliren G, Young DS, Fisher M, Haug MT. TPN by a nutrition support team: improved quality of care. JPEN J Parenter Enteral Nutr. 1986;10:408–12.
78. Hagiwara S, Mori T, Tuchiya H, Sato S, Higa M, Watahiki M, et al. Multidisciplinary nutritional support for autologous hematopoietic stem cell transplantation: a cost-benefit analysis. Nutrition. 2011;27:1112–7.
79. Jacobs D, Melnik G, Forlaw L, Gebhardt C, Settle G, DiSipio M, Rombeau J. Impact of a nutritional support service on VA surgical patients. J Am Coll Nutr. 1984;3:311–5.
80. Dalton MJ, Schepers G, Gee JP, Alberts CC, Eckhauser FE, Kirking DM. Consultative TPN teams: the effect on the incidence of TPN-related complications. JPEN J Parenter Enteral Nutr. 1984;8:146–52.

Chapter 15
Microbiome in the Critically Ill

Meredith Barrett and Daniel H. Teitelbaum

Keywords Microbiome • Parenteral nutrition (PN) • Obesity • Probiotics • Breast cancer • Malnourishment • Symbiosis • Human host • Probiotics • Short-chain fatty acids • Gnotobiotic • Toll-like receptors (TLRs) • Nucleotide-binding domain and leucine-rich repeat containing receptors (NLRs)

Key Points

- The human microbiome is composed of 10^{14} bacteria, which are a key component in health and disease.
- The intestine, particularly the colon, houses the largest percentage of bacteria.
- A functional microbiome is beneficial to its host in states of health with derangements in the microbial population being seen in states of disease.
- Studies performed on germ-free animals have provided information on the effects of the microbiome.
- The microbiome is key in the developing immune system as well as inflammatory signaling cascades.
- Utilizing the microbiome, including probiotic administration, is a promising subject for study for the development of future therapeutics in the critically ill.
- Parenteral nutrition (PN) and enteral nutrition deprivation promotes a more virulent microbial population.
- Recent research has shown the microbiome to play a role in the development of obesity.

Introduction

An exciting field of study with therapeutic promise in treatment of the critically ill patient is that of modulating the intestinal microbiome. With national research funding from the NIH and other interested private funding agencies, as well as dramatic advancements in our ability to classify and

M. Barrett, MD
Department of Pediatric Surgery, Mott Children's Hospital, University of Michigan,
1540 East Hospital Center Drive, Ann Arbor, MI 48104, USA
e-mail: mebarret@med.umich.edu

D.H. Teitelbaum, MD (✉)
Department of Surgery, University of Michigan, 1540 East Hospital Center Drive, Ann Arbor, MI 48104, USA
e-mail: dttlmb@med.umich.edu

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_15,

study microbes, our fund of knowledge regarding the intestinal microbiome has expanded greatly over the past decade [1]. With this data has come an appreciation for the importance of the intestinal microbiome in both health and disease as well as its vast potential for therapeutic intervention. The following chapter provides an introduction to the intestinal microbiome as it relates to the provision of enteral and parenteral nutrition in the critically ill, including a discussion of current data, as well as areas for future study and intervention.

Historical Background

The importance of the human-bacterial relationship has been well documented throughout the modern study of medicine. Starting with the dramatic impact resulting from the implementation of hygienic measures on the reduction of postpartum infections [2], some of the greatest achievements of medical history have been the control of diseases mediated by bacteria [3, 4]. More recently, focus has been placed on the importance of commensal bacteria (i.e., normal flora) and their impact in states of health and disease. The term microbiome has been used to describe the billions of bacteria which inhabit the human body. It has been described by Lederberg as "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space" [5]. With the advent of laboratory techniques, such as 16s rRNA pyrosequencing, investigators have been able to broaden their study and definition of this important symbiotic community. The National Institute of Health (NIH) has recognized the significant therapeutic potential by funding the Human Microbiome Project (HMP). Its objectives are standardizing data resources, characterizing the microbiome, and determining changes in health and disease, with the ultimate goal of improving health through microbiome manipulation [1]. This multimillion dollar research endeavor has already produced exciting results that point to the therapeutic potential of manipulating the microbial environment within us.

An Introduction to the Microbiome: Colonization and Stabilization

The human fetus resides in a sterile environment within the uterus. Initial bacterial acquisition is from the mother via childbirth [6]. Initially presumed to be primarily due to passage through the vaginal tract, acquisition through interaction with maternal feces is now thought to be the initial method of colonization [7, 8]. Further colonization of the newborn occurs through environmental interactions early in life via environmental contact, and microbial populations eventually inhabit the skin, vagina, and respiratory and gastrointestinal tracts. It is estimated that the human microbiota contains 10^{14} bacterial cells, with the most heavily colonized organ being the gastrointestinal tract [9]. Importantly, the microbial population of the gastrointestinal tract is heterogeneously distributed. The colon houses 70 % of the total mammalian microbiome whereas the stomach and small bowel, each with its own unique populations of organisms, are far less populated [10]. Despite the mode of acquisition of a bacterium varying based on environment and diet, the phyla which ultimately inhabit the gut in health have been found to be relatively stable. This is likely due to the overall symbiotic relationship between bacteria and host. Two phyla have evolved to become the most populous inhabitants of the GI tract—gram-positive Firmicutes and gram-negative Bacteroidetes [11]. Alterations in these two populations are seen in states of infection and disease, and in some instances may actually drive the pathogenesis of the disorder [12].

Natural Benefits of Microbiome

The intestinal microbiome, despite its vast numbers and variability, is relatively well-conserved among healthy humans. Both bacteria and host receive benefit secondary to this inhabitance, as detailed in the sections below. This has been proven experimentally, via use of axenic, or germ-free, mice [13]. These mice, maintained in a germ-free environment, have provided important data on the benefits of the microbiome as well as physiologic changes in its absence [14, 15].

When compared to their wild-type, conventionalized counterparts, germ-free mice have a noticeably distinct and immature immune system. Abnormal immune cells, immature lymphoid structures, and hypoplastic Peyer's patches are seen [16]. With reinstitution of bacteria, a rapid maturation and normalization of the immune system occurs.

Beyond immune modulation, the commensal bacteria of the GI tract provide protection against pathologic organisms encountered on a daily basis. The term "competitive exclusion" has been used to describe their ability to block potential pathogens from invading their host [17]. Utilization of nutrients and physical occupation of potential bacterial attachment sites prevents colonization by other pathogens [18].

The microbiome can modulate the host's immune system via interaction with receptors. Toll-like receptors (TLR) are located on the cell surface of epithelial cells and immune cell populations, particularly in the lamina propria (LP). Nod-like receptors (NLR) are located within the cytoplasm of immunocytes [19]. TLRs are a component of the innate)immune system which are able to sense bacterial, fungal, or viral invasion via interaction with microbes particularly via recognition of pathogen-associated molecular patterns (PAMPs)—or non-self patterns [20, 21]. These PAMPs are presented to the TLR, which recognizes the foreign bacteria, frequently via interaction with bacterial lipopolysaccharides (LPS) or other bacterial products. Upon recognition, a complex intracellular cascade occurs, leading to release of inflammatory cytokines. Two important pathways associated with the TLR signaling cascade are the MyD88-dependent and -independent cellular cascades [22].

Myeloid differentiation primary response gene (MyD88) is an intracellular membrane-associated molecule. When associated with interleukin-1 (IL-1) receptor-associated kinase (IRAK), it leads to phosphorylation and activation of tumor necrosis factor alpha (TNF-α) [21]. This transcription factor induces the immunocyte cell to create and release inflammatory cytokines, IL-6, and IL-1, via the MyD88-dependent pathway. Immunocytes have also demonstrated the ability to induce an inflammatory response independent of MyD88. Similarly initiated via stimulation through TLR activation, the end product of this independent pathway is interferon-gamma instead of TNF-α.

Identification of bacteria can also occur within the enterocyte via activation of NLRs. Similar in action to TLRs, NLRs are able to activate an immune response by sensing foreign bacterial components within the cell itself. This interaction, like that of TLRs, activates a series of reactions through which cytokines are released [21].

Aside from preventing local invasion, recognition of pathogenic bacteria by the microbiota can also signal a systemic response. Dendritic cells located within Peyer's patches present antigens to B-cells, which secrete IgA and antibodies through the lamina propria [23, 24]. This interaction allows for further maturation of the immune system. As Clark et al. described, host bacterial recognition of potentially invasive pathogens leads to a systemic response and antibody production [25]. Recognition of microbiota via interaction with NLR1 allows the bone marrow to produce "primed" neutrophils. These neutrophils are released into the circulation and are able to identify pathogens distant from the gastrointestinal tract [25].

The gut microbiome is essential for the production of certain short-chain fatty acids (SCFAs) and certain vitamins, including vitamin B12. Fermentation of insoluble starches by colonic bacteria leads to production of SCFAs, acetate, propionate, and butyrate, each with its unique function in vivo [26].

The proportion of these three SCFAs within the colon is 60:20:20, with acetate being most populous [27]. Acetate is the primary substrate for cholesterol synthesis. Propionate is intimately involved in the Krebs cycle as a substrate for energy production. Butyrate is the preferred fuel for colonocytes, with 70–90 % of butyrate being metabolized in the colon [28]. Butyrate is also anti-inflammatory via its ability to up-regulate IL-10 leading to an inhibition of inflammatory cytokine expression [29]. The health of the colon is responsive to SCFAs and derangements in their production and population is seen in disease. Beyond production of essential nutritional elements, bacteria are crucial in the breakdown of metabolites of amino acids that would otherwise be toxic to the human host [30].

Microbiome and Diet

A major source of nutrients for the commensal GI population is the daily ingestion of nutrients. Strikingly, many of the nutrients consumed have no nutritional value for the host, but rather provide nutrition to the microbial community. This begins with the consumption of human milk by the neonate. Some of the most prevalent metabolomic components in breast milk are complex oligosaccharides that have no nutritional value for the infant, but provide a rich nutritional environment for Firmicutes-dominant microbes [31]. Studies of formula versus breastfed newborns provide evidence that from birth the intestinal microbiome is affected by diet [32]. In fecal studies by Pop et al., bacterial diversity was greater in infants exclusively breastfed compared to those who were formula fed. Interestingly, these additional bacteria are of a more virulent variety than those that inhabit the formula-fed intestine [33]. Given that the newborn period is a time of immune maturation, these more virulent bacteria may aid in immune enrichment and growth for the newborn.

Diet variance continues to mold the microbiome beyond the fetal period. There were significant differences in intestinal bacterial composition in African-fed compared with European-fed children [34]. The African diet is much lower in animal protein and fat compared to the European diet. Although both groups had Bacteroidetes and Firmicutes predominant bacteriology, European children were found to have a much higher percentage of Bacteroidetes. African children were also found to have more microbial richness and biodiversity. The authors were able to determine that diet was strongly associated with microbial diversity, beyond differences in environment alone, suggesting that "diet has a dominant role over other possible variables such as ethnicity, sanitation, hygiene, geography, and climate in shaping the gut microbiome" [34]. Though conclusions on health outcomes could not be made from this particular study, a depleted microbial complement, as seen in children receiving a Western diet, has been associated with worse health outcomes [35].

Despite differences in microbial diversity and depth among different populations, maturation of the intestinal microbiome from infancy to adulthood consistently produces a microbiome housing primarily Bacteroidetes and Firmicutes. Interestingly, diet continues to affect these microbial populations beyond the adolescence—with population changes and adjustments being seen with changes in food consumption [36, 37].

Studies relating the makeup of the microbiome to the development of disease are, thus far, observational or indirect. With these findings, however, investigations regarding the effect of diet have gained greater interest, in particular because certain diseases and cancers are far more common in Western countries [36]. Inflammatory bowel disease, autism, and breast cancer are a few of the diseases which display a Western propensity. The presence of an impact of environmental factors is further corroborated by the epidemiologic studies of women with breast cancer. Women in Western countries are significantly more likely to develop breast cancer than similarly matched women in Africa and Asia [38]. First-generation Americans gain the same risk of developing breast cancer as other Western females if raised in these countries. Such a rapid epidemiologic change cannot be

explained by evolutionary changes. Western diets, high in fat, result in proteobacteria growth within the microbiome [39]. This microbial population is known to deplete the circulating lymphocyte population. Multiple studies have shown depleted lymphocyte function to be associated with a more aggressive subtype of breast cancer and increased recurrence rate [40, 41]. Given these findings, environmental influences, including diet, are interesting targets for investigating modulators of these changes.

Microbiome in the Critically Ill

Disruption of the intestinal epithelial barrier leading to bacterial translocation has long been associated with infection leading to systemic disease [42–44]. More recent studies of the microbiome in states of illness have revealed the importance of preserving the commensal microbial communities in improving outcomes in the critically ill [45, 46]. In his study of microbial diversity in the critically ill, Shimizu obtained fecal specimens to determine microbiome composition. The feces of patients with severe systemic inflammatory response syndrome (SIRS) was collected and studied. Classification as diverse, depleted, or single was determined via visual analysis of gram stain bacterial isolates from stool [47]. Further analysis of the bacteria was pursued via culture [46, 47]. Infectious complications including enteritis, bacteremia, and mortality were then assessed. Data revealed a higher mortality rate in the patients with diminished and depleted gram stain compared to the diverse. These groups also suffered from enteritis more frequently than those diversely populated. Finally, these patients were also found to have lower levels of SCFAs, important in metabolism and inflammation as discussed earlier.

We demonstrated similar results in our study of microbial diversity and perioperative outcomes [35]. In a group of surgical patients, enteral deprivation led to lack of microbial diversity and worse perioperative outcomes. Complications, including anastomotic leak, wound infection, and bacteremia, were more commonly seen in the parentally fed patients who had a low intestinal microbial diversity. As previously mentioned, decreased microbial diversity in some studies has been associated with worse outcomes, particularly in the critically ill. Although the mechanisms driving this are unknown, PN depletes enteral nutrition to gut bacteria, potentially leading to this loss of diversity. Increased infectious complications seen in this patient population is likely secondary to loss of diversity secondary to enteral deprivation [35, 48].

The cause and effect relationship between worse outcomes seen with decreased diversity is not established, and may be due to multiple causes. With decreased diversity, virulent bacteria may predominate. This leads to a proinflammatory state in which cytokines such as TNF-α cause a breakdown of epithelial tight junctions [42, 49]. Certain bacteria increase this response by producing virulence factors, which contribute to the breakdown of tight junctions, compounding the problem [50]. This breakdown allows for bacterial translocation and systemic infection [51].

With the known complications associated with decreased bacterial diversity, one must be prudent with delivery of antibiotics. A study by Vincent in 2009 found that 71 % of patients in the ICU receive antibiotics for various infections, primarily respiratory [52]. These antibiotics can also deplete the gastrointestinal microbiome. Such depletion is associated with a secondary expansion of opportunistic infections, particularly Clostridium difficile (C. diff) and vancomycin-resistant enterococcus (VRE). This response occurs rapidly and lasts long after the antibiotic is discontinued. DNA pyrosequencing performed on three healthy individuals who were given a short course of antibiotics showed disruption of the microbial population months after antibiotic withdrawal [53]. These findings have prompted increased awareness and an interest in more prudent delivery of antimicrobials in the critically ill.

Probiotics and the Microbiome as a Therapeutic Target

With growing knowledge of the detrimental effects of bacterial eradication, the potential for the intestinal microbiome as a therapeutic target has been confirmed by early studies. For example, fecal transfer from a healthy donor to an ill patient has proven beneficial in patients with C. difficile colitis [54]. Given these findings, focus on bolstering the microbial armamentarium with probiotic treatment along with prudent antibiotic use has been an area of therapeutic interest. Probiotics are defined by the World Health Organization (WHO) as "live microorganisms which when consumed in appropriate amounts confer health benefits." The most commonly utilized include lactobacillus and bifidobacterium [55]. It is theorized that these bacteria provide "competitive inhibition" to pathologic invasion and in the setting of critical illness allow for repopulation of depleted and sick microbial populations. Probiotics have been found to induce an anti-inflammatory response via interaction with dendritic cells in vitro [56]. This interaction releases IL-10 and transforming growth factor beta (TGF-β), two anti-inflammatory cytokines of the innate immune system [57].

With regard to the intensive care unit (ICU) population, recent studies have shown mixed results. In their study of critically ill patients, Forestier et al. found a statistically significant decrease in pseudomonas colonization and respiratory infection in patients undergoing probiotic therapy versus the non-treated control group [58]. In a recent meta-analysis, Barraud et al. found lower levels of ICU-acquired pneumonia and shorter ICU length of stay, but no change in overall mortality [59]. In the neonatal population, a 2013 Cochrane review found decreased rates of necrotizing enterocolitis (NEC) in low birth rate babies (<1500 g) [60]. However, the overall quality of controls in these latter NEC studies have been called into question, including the dosing and type of probiotic used and delivered to these infants.

Despite these potentially exciting results, the PROPATRIA trial did not exhibit such promising findings. This 2008 study in patients with severe pancreatitis resulted in increased mortality and bowel ischemia in patients receiving probiotics compared to placebo [61, 62]. Questions of potential shortcomings in design and methodology have since been raised, yet these findings have resulted in recommendations for a more hesitant approach toward indiscriminate administration of probiotics in the critically ill population [63]. Further study must take place prior to final judgment on probiotics in the critical care setting can be made. This therapeutic option is likely to remain in the discussion of optimal critical care until more definitive data is available.

Microbiome in Parenteral Nutrition Supported Patients

Parenteral nutrition feeds the patient globally, but places the intestinal microbiota in a state of nutrient withdrawal. With such deprivation, the microbiota undergoes a drastic population change to a more virulent makeup. The normally predominant Firmicutes are exchanged for a gram-negative Proteobacteria population [12]. This shift creates a proinflammatory state via TLR signaling. Increased proinflammatory cytokines, with a down regulation in T-regulatory cells, is seen in mouse models of PN, accompanied by eventual epithelial barrier breakdown [51]. With increased permeability of gut epithelium, bacteria enter the bloodstream. This is one potential mechanism to explain the observed increased infection rates and septic complications observed in patients undergoing PN therapy [64].

In experimental mouse models of PN, the microbial population not only shifts to a proteobacteria-dominant population, but also becomes much more homogenous [35], whereby the microbial population of the small and large bowel become similar. Gram-negative bacteria overpopulate the commensal gram-positive Firmicutes. This more homogenous and virulent gram-negative microbial population drives TLR-4 signaling, and a proinflammatory response These results further confirm that initiation of PN may have potential deleterious impact, and should not be lightly undertaken.

Microbiome in Obesity

The obesity epidemic is a growing health problem in America and other Western countries, with half the American population predicted to be obese by 2030 [65]. Given obesity's obvious detrimental health effects, as well as strain on the overall health care system, studies further elucidating its cause and modifiable risk factors are at the forefront of scientific study. One hopeful area of investigation is manipulation of the gut microbiome.

The survival of the intestinal microbiome depends on its extraction of essential nutrients and energy from food. In their study of genetically obese mice, Ley et al. discovered a higher proportion of Bacteroidetes to Firmicutes in the obese mouse population [66]. Backhed et al. found bacteria-free mice to be 40 % leaner despite greater food consumption than wild-type mice [67]. Perhaps even more interesting, the introduction of bacteria to these rodents resulted in an increased body weight. Further, the instillation of bacteria isolated from obese mice resulted in an even more significant weight gain. These findings all suggest that certain bacterial populations help harvest greater energy from the diet than others, allowing for easier weight gain by the host.

Obesity and the metabolic syndrome are associated with a low-grade inflammatory state, which may also be driven by gut microbiota. High-fat diets increase TLR receptors which in turn lead to increased permeability of intestinal epithelial tight junctions [68]. This allows for an increase in LPS in the bloodstream. A component of the gram negative bacterial cell wall, LPS puts the body into a state of inflammation. This inflammatory state has been associated with the development of diabetes, atherosclerosis, and nonalcoholic fatty liver disease [69]. The role of TLR has also been shown in a group of TLR-5 knockout mice who demonstrate significant obesity compared to matched wild-type strains [70].

With such compelling preliminary data there is strong hope for therapeutic promise in manipulation of the microbiome to prevent both obesity and metabolic syndrome. Modulation of the microbiome via diet, probiotics, or even fecal transplantation of a more favorable microbial population presents therapeutic potential for this growing epidemic [71].

Microbe Foraging for Nutrients

Another exciting area of study, particularly regarding the critically ill, is that of microbial nutrient deprivation. To survive and thrive, pathogenic bacteria must compete with resident flora for nutrition. Beyond competing with resident flora for nutrition, these bacteria also have to evade host immune defenses. To effect this, bacteria produce a number of antimicrobial resistance and virulence factors such as flagella and encapsulation. Further, these pathogens have developed is the ability to manipulate their acquisition of host nutrition [72, 73].

An example of such a pathogen that has developed the ability to utilize host nutrition is Salmonella enterica [74]. Via horizontal transfer, S. enterica has gained the ability to consume host tetrathionate and nitrate, two nutrients usually unable to be utilized by the organism [75]. This mode of adaption is also seen in *Escherichia coli* where gene acquisition has allowed for nitrate utilization in anaerobic metabolism [76]. Legionella, through interaction with host cells and endoplasmic reticulum, is able to utilize host proteases for amino acid production [77]. Pathogens have also evolved to utilize an immune defense, autophagy, for nutritional gain via induction of cell destruction to release nutritious cell components.

With these findings come the potential for future antimicrobials which limit pathogen nutritional access [72]. By altering metabolic pathways utilized by pathogens, antimicrobials could prevent further bacterial growth. Obviously, such alterations pose dangers to commensal, beneficial bacteria, and any metabolic changes induced by such antimicrobials must be done judiciously. Preliminary research in mice suggests that such changes can be induced without leading to complete microbial depletion.

Conclusion

The intestinal microbiome harbors more than 10^{14} bacteria. These commensal microbes contribute to the health of the host. With improvements in microbial sequencing and identification, the knowledge of the importance of the microbiome has grown. Studies have also demonstrated the potential for therapeutic manipulation of the microbiome. Continued research as to how best utilize this ecosystem within us promises to provide health discoveries in the future.

References

1. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486(7402):207–14.
2. Loudon I. Ignaz Phillip Semmelweis' studies of death in childbirth. J R Soc Med. 2013;106(11):461–3.
3. Wishnow RM. The conquest of the major infectious diseases in the United States: a bicentennial retrospect. Annu Rev Microbiol. 1976;30:427–50.
4. Aylward B, Hennessey KA, Zagaria N, Olive JM, Cochi S. When is a disease eradicable? 100 years of lessons learned. Am J Public Health. 2000;90(10):1515–20.
5. Lederberg J, Mccray T. 'Ome sweet' omics--a genalogic treasury of words. Scientist. 2001;15:8–10.
6. Dethlefsen L, Eckburg PB, Bik EM, Relman DA. Assembly of the human intestinal microbiota. Trends Ecol Evol. 2006;21(9):517–23.
7. Grönlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. J Pediatr Gastroenterol Nutr. 1999;28(1): 19–25.
8. Mändar R, Mikelsaar M. Transmission of mother's microflora to the newborn at birth. Biol Neonate. 1996;69(1): 30–5.
9. Savage DC. Microbial ecology of the gastrointestinal tract. Annu Rev Microbiol. 1977;31:107–33.
10. 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.
11. Tyakht AV, Kostryukova ES, Popenko AS, Belenikin MS, Pavlenko AV, Larin AK, et al. Human gut microbiota community structures in urban and rural populations in Russia. Nat Commun. 2013;4:2469.
12. Miyasaka EA, Feng Y, Poroyko V, Falkowski NR, Erb-Downward J, Gillilland MG, et al. Total parenteral nutrition-associated lamina propria inflammation in mice is mediated by a MyD88-dependent mechanism. J Immunol. 2013;190(12):6607–15.
13. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med. 2009;1(6):6ra14.
14. Tlaskalova-Hogenova H, Stepankova R, Kozakova H, Hudcovic T, Vannucci L, Tuckova L, et al. The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: contribution of germ-free and gnotobiotic animal models of human diseases. Cell Mol Immunol. 2011;8(2):110–20.
15. Tlaskalová H, Kamarýtová V, Mandel L, Prokesová L, Kruml J, Lanc A, et al. The immune response of germ-free piglets after peroral monocontamination with living Escherichia coli strain 086. I. The fate of antigen, dynamics and site of antibody formation, nature of antibodies and formation of heterohaemagglutinins. Folia Biol (Praha). 1970;16(3):177–87.
16. Schuijt TJ, van der Poll T, de Vos WM, Wiersinga WJ. The intestinal microbiota and host immune interactions in the critically ill. Trends Microbiol. 2013;21(5):221–9.
17. Walter J, Ley R. The human gut microbiome: ecology and recent evolutionary changes. Annu Rev Microbiol. 2011; 65:411–29.
18. Smith VH, Holt RD. Resource competition and within-host disease dynamics. Trends Ecol Evol. 1996;11(9): 386–9.
19. Janeway CA. Approaching the asymptote? Evolution and revolution in immunology. Cold Spring Harb Symp Quant Biol. 1989;54(Pt 1):1–13.
20. Hoffmann JA. The immune response of Drosophila. Nature. 2003;426(6962):33–8.
21. Kawai T, Akira S. The roles of TLRs, RLRs and NLRs in pathogen recognition. Int Immunol. 2009;21(4):317–37.
22. Takeda K, Akira S. TLR signaling pathways. Semin Immunol. 2004;16(1):3–9.
23. Brandtzaeg P. Secretory IgA: designed for anti-microbial defense. Front Immunol. 2013;4:222.

24. Wells JM, Rossi O, Meijerink M, van Baarlen P. Epithelial crosstalk at the microbiota-mucosal interface. Proc Natl Acad Sci U S A. 2011;108 Suppl 1:4607–14.
25. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. Shock. 2007;28(4):384–93.
26. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol. 2006;40(3):235–43.
27. Hijova E, Chmelarova A. Short chain fatty acids and colonic health. Bratisl Lek Listy. 2007;108(8):354–8.
28. Cook SI, Sellin JH. Review article: short chain fatty acids in health and disease. Aliment Pharmacol Ther. 1998;12(6):499–507.
29. Säemann MD, Böhmig GA, Zlabinger GJ. Short-chain fatty acids: bacterial mediators of a balanced host-microbial relationship in the human gut. Wien Klin Wochenschr. 2002;114(8-9):289–300.
30. Zedelius J, Rabus R, Grundmann O, Werner I, Brodkorb D, Schreiber F, et al. Alkane degradation under anoxic conditions by a nitrate-reducing bacterium with possible involvement of the electron acceptor in substrate activation. Environ Microbiol Rep. 2011;3(1):125–35.
31. Ben XM, Li J, Feng ZT, Shi SY, Lu YD, Chen R, et al. Low level of galacto-oligosaccharide in infant formula stimulates growth of intestinal Bifidobacteria and Lactobacilli. World J Gastroenterol. 2008;14(42):6564–8.
32. Pop M. We are what we eat: how the diet of infants affects their gut microbiome. Genome Biol. 2012;13(4):152.
33. Schwartz S, Friedberg I, Ivanov IV, Davidson LA, Goldsby JS, Dahl DB, et al. A metagenomic study of diet-dependent interaction between gut microbiota and host in infants reveals differences in immune response. Genome Biol. 2012;13(4):r32.
34. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010;107(33):14691–6.
35. Ralls MW, Miyasaka E, Teitelbaum DH. Intestinal microbial diversity and perioperative complications. JPEN J Parenter Enteral Nutr. 2014;38:392.
36. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559–63.
37. Ohland CL, Kish L, Bell H, Thiesen A, Hotte N, Pankiv E, et al. Effects of Lactobacillus helveticus on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. Psychoneuroendocrinology. 2013;38(9):1738–47.
38. Shapira I, Sultan K, Lee A, Taioli E. Evolving concepts: how diet and the intestinal microbiome act as modulators of breast malignancy. ISRN Oncol. 2013;2013:693920.
39. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, et al. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology. 2009;137(5): 1716-24.e1–2.
40. Noh H, Eomm M, Han A. Usefulness of pretreatment neutrophil to lymphocyte ratio in predicting disease-specific survival in breast cancer patients. J Breast Cancer. 2013;16(1):55–9.
41. Azab B, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol. 2013; 30(1):432.
42. Sun X, Yang H, Nose K, Nose S, Haxhija EQ, Koga H, et al. Decline in intestinal mucosal IL-10 expression and decreased intestinal barrier function in a mouse model of total parenteral nutrition. Am J Physiol Gastrointest Liver Physiol. 2008;294(1):G139–47.
43. Feng Y, Teitelbaum DH. Tumour necrosis factor--induced loss of intestinal barrier function requires TNFR1 and TNFR2 signalling in a mouse model of total parenteral nutrition. J Physiol. 2013;591(Pt 15):3709–23.
44. Alverdy JC, Spitz J, Hecht G, Ghandi S. Causes and consequences of bacterial adherence to mucosal epithelia during critical illness. New Horiz. 1994;2(2):264–72.
45. Shimizu K, Ogura H, Goto M, Asahara T, Nomoto K, Morotomi M, et al. Altered gut flora and environment in patients with severe SIRS. J Trauma. 2006;60(1):126–33.
46. Shimizu K, Ogura H, Hamasaki T, Goto M, Tasaki O, Asahara T, et al. Altered gut flora are associated with septic complications and death in critically ill patients with systemic inflammatory response syndrome. Dig Dis Sci. 2011;56(4):1171–7.
47. Shimizu K, Ogura H, Tomono K, Tasaki O, Asahara T, Nomoto K, et al. Patterns of Gram-stained fecal flora as a quick diagnostic marker in patients with severe SIRS. Dig Dis Sci. 2011;56(6):1782–8.
48. Demehri FR, Barrett M, Ralls MW, Miyasaka EA, Feng Y, Teitelbaum DH. Intestinal epithelial cell apoptosis and loss of barrier function in the setting of altered microbiota with enteral nutrient deprivation. Front Cell Infect Microbiol. 2013;3:105.
49. Alverdy J, Gilbert J, Defazio JR, Sadowsky MJ, Chang EB, Morowitz MJ, et al. Proceedings of the A.S.P.E.N.-sponsored workshop: the interface between nutrition and the gut microbiome: implications and applications for human health. JPEN J Parenter Enteral Nutr. 2014;38:167.

50. Weflen AW, Alto NM, Viswanathan VK, Hecht G. E. coli secreted protein F promotes EPEC invasion of intestinal epithelial cells via an SNX9-dependent mechanism. Cell Microbiol. 2010;12(7):919–29.
51. 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.
52. Vincent JL, Jacobs F. Effect of selective decontamination on antibiotic resistance. Lancet Infect Dis. 2011;11(5):337–8.
53. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci U S A. 2011;108 Suppl 1:4554–61.
54. Bakken JS. Fecal bacteriotherapy for recurrent Clostridium difficile infection. Anaerobe. 2009;15(6):285–9.
55. FAO/WHO. Joint FAO/WHO expert consultation of health and nutritional properties of probiotics in food including powder milk and live lactic acid bacteria. Rome: FAO; 2001.
56. Baba N, Samson S, Bourdet-Sicard R, Rubio M, Sarfati M. Commensal bacteria trigger a full dendritic cell maturation program that promotes the expansion of non-Tr1 suppressor T cells. J Leukoc Biol. 2008;84(2):468–76.
57. Preidis GA, Versalovic J. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: gastroenterology enters the metagenomics era. Gastroenterology. 2009;136(6):2015–31.
58. Forestier C, Guelon D, Cluytens V, Gillart T, Sirot J, De Champs C. Oral probiotic and prevention of Pseudomonas aeruginosa infections: a randomized, double-blind, placebo-controlled pilot study in intensive care unit patients. Crit Care. 2008;12(3):R69.
59. Barraud D, Bollaert PE, Gibot S. Impact of the administration of probiotics on mortality in critically ill adult patients: a meta-analysis of randomized controlled trials. Chest. 2013;143(3):646–55.
60. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2014;(4):CD005496.
61. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371(9613):651–9.
62. Besselink MG, Timmerman HM, Buskens E, Nieuwenhuijs VB, Akkermans LM, Gooszen HG, et al. Probiotic prophylaxis in patients with predicted severe acute pancreatitis (PROPATRIA): design and rationale of a double-blind, placebo-controlled randomised multicenter trial [ISRCTN38327949]. BMC Surg. 2004;4:12.
63. Expression of concern--probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375(9718):875–6.
64. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg. 1992;216(2):172–83.
65. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet. 2011;378(9793):815–25.
66. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 2005;102(31):11070–5.
67. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci U S A. 2007;104(3):979–84.
68. Hotamisligil GS. Endoplasmic reticulum stress and inflammation in obesity and type 2 diabetes. Novartis Found Symp. 2007;286:86–94. discussion 8, 162–3, 96–203.
69. Cani PD, Osto M, Geurts L, Everard A. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. Gut Microbes. 2012;3(4):279–88.
70. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010;328(5975):228–31.
71. Arora T, Singh S, Sharma RK. Probiotics: interaction with gut microbiome and antiobesity potential. Nutrition. 2013;29(4):591–6.
72. Abu Kwaik Y, Bumann D. Microbial quest for food in vivo: 'nutritional virulence' as an emerging paradigm. Cell Microbiol. 2013;15(6):882–90.
73. Rohmer L, Hocquet D, Miller SI. Are pathogenic bacteria just looking for food? Metabolism and microbial pathogenesis. Trends Microbiol. 2011;19(7):341–8.
74. Santos RL, Raffatellu M, Bevins CL, Adams LG, Tükel C, Tsolis RM, et al. Life in the inflamed intestine, Salmonella style. Trends Microbiol. 2009;17(11):498–506.
75. Raffatellu M, George MD, Akiyama Y, Hornsby MJ, Nuccio SP, Paixao TA, et al. Lipocalin-2 resistance confers an advantage to Salmonella enterica serotype Typhimurium for growth and survival in the inflamed intestine. Cell Host Microbe. 2009;5(5):476–86.
76. Winter SE, Winter MG, Xavier MN, Thiennimitr P, Poon V, Keestra AM, et al. Host-derived nitrate boosts growth of E. coli in the inflamed gut. Science. 2013;339(6120):708–11.
77. Price CT, Al-Quadan T, Santic M, Rosenshine I, Abu Kwaik Y. Host proteasomal degradation generates amino acids essential for intracellular bacterial growth. Science. 2011;334(6062):1553–7.

Chapter 16
Future Research

David S. Seres and Charles W. Van Way III

Keywords Enteral nutrition • Parenteral nutrition • Nutrition support • Malnutrition • Immunity • Inflammatory response • Gastrointestinal access • Parenteral access • Gut microbiome

Key Points

- Empiric decision making has guided nutrition for thousands of years. But as a guide to enteral and parenteral nutrition therapy, it is no longer adequate. There are too many gaps in our knowledge base.
- Malnutrition is being redefined with disease-related malnutrition. New work is needed in three areas: biomarkers of nutrition/malnutrition, interaction of nutrition with specific diseases, and the effect of malnutrition/starvation on the body systems.
- The interaction between nutrition and the immune system remains poorly understood.
- Timing of nutrition support remains an area of controversy, and causes great clinical uncertainty.
- Enteral nutrition, now widely used, is still poorly understood in many areas, such as optimal delivery, effects on the gastrointestinal tract, and immune-enhancing nutritional formulas.
- The effect of parenteral nutrition is less well understood than it should be. Does it affect the gut microbiome? Why does it have adverse effects on the liver? How do intravenous fats affect the immune system?
- Hypermetabolism and catabolism, and their relationship to nutrition support, need considerably more research.

D.S. Seres, MD, ScM, PNS (✉)
Department of Medicine, Institute of Human Nutrition, Columbia University Medical Center,
650 W 168th Street, P&S 9-501, New York, NY 10032, USA
e-mail: dseres@columbia.edu

C.W. Van Way, III, MD, FACS, FCCM, FCCP, FASPEN
Department of Surgery, Truman Medical Center, School of Medicine,
University of Missouri, Kansas City,
2301 Holmes Street, Kansas City, MO 64108, USA

5745 Cherokee Drive, Fairway, KS 66205, USA
e-mail: cvanway@kc.rr.com

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1_16,

- Obese patients and aged patients are increasing in numbers and importance. These two categories are often difficult to treat, for a variety of reasons. They should be treated with considerably more precision than we are presently able to do.

Introduction

> "Prediction is difficult, especially about the future."
>
> Neils Bohr, Physicist

People have been feeding each other for many thousand years, guided only by empiric decision making. However, our present use of enteral and parenteral nutrition therapy should be guided by more than the common-sense approach of past centuries. A constant theme of the preceding chapters is the need for more and better data to support clinical decision making. This chapter attempts to summarize the authors' and the editors' best estimates of just where research should be going in the next 20–40 years. We have identified many of the major gaps in our knowledge, and urge that they be filled.

As a guide to clinical practice, nutritional research efforts have been incomplete. It is true that we know a great deal about how the body absorbs, transports, utilizes, and excretes macronutrients, micronutrients, and trace elements. But entirely too much of our clinical practice is based empirically, without good data to inform our therapy. Even worse, there is very little data on the outcomes of different nutritional strategies. The authors of chapters in this book have been encouraged to identify areas in which our knowledge is incomplete. We, in this chapter, identify questions about which, the editors feel, further studies should be done.

The latest release of the widely used guidelines for nutritional care of critically ill patients has been issued jointly by the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition [1]. In many areas, these guidelines provide the evidence-based basis for clinical practice. In many other areas, the authors have been forced back on insufficient evidence, and even on expert opinion. We have learned over the past decades that expert opinion is a very shaky substitute for hard evidence.

The hard fact is that nutritional practice can be very difficult to study. Nutrition is not just medical therapy. Rather, it is part of taking care of patients. Starvation for a few days is often unavoidable, and appears not to be harmful. But prolonged starvation cannot be used as a therapeutic alternative, being neither ethical nor practical. It is very difficult to justify to an Institutional Review Board. Carrying out studies in the nutritional field often means working without scientifically rigorous control groups. Of course, there are other situations with the same sort of restrictions. As has been pointed out by Smith and Pell, expert opinion has been perfectly unanimous on the effectiveness of parachutes, with no high-quality controlled studies at all [2].

We have attempted to provide a roadmap for clinical nutritional research for the next several decades. Succeeding in this effort is clearly impossible. Who would have predicted, 20 years ago, that our deeper understanding of the microflora of the gastrointestinal tract would begin to greatly inform our understanding of nutrient processing and absorption? Chapter 15 is, in itself, a road map to the future of research in this area.

But to the best of our poor abilities, we offer the following thoughts.

Malnutrition and Nutritional Assessment

While the new paradigm of disease-related malnutrition has been of great help conceptually, we still lack both a generally accepted definition and usable diagnostic criteria for malnutrition. Our diagnostic categories (ICD-9 and ICD-10) have not changed. Clinical observation lacks precision, yet is

demonstrably better than available laboratory studies or physical measurements. As a result, many clinical studies are flawed by an inability to properly stratify patients in terms of their nutritional deficits. Moreover, most definitions of malnutrition are self-referential, and while predictive of poor clinical outcomes, do not predict conditions in which nourishment will impact outcome.

It is to be hoped that time will permit incorporation of disease-related malnutrition into diagnostic coding, and into clinical thinking. But for the clinician, this will only be a first step. There needs to be considerably more work in at least three areas. First, biomarkers for nutritional status are needed. This is not a simple problem. As an example, recent studies show that vitamin D levels in the general population are low. But the significance of this finding has not been established. There has been a public debate over whether this means anything at all. Is it a marker for more general malnutrition? Is it a deficit which should be corrected? Is it just an abnormal value of no significance? The search for biomarkers has been going on for a century, and has not produced results that are useful enough to answer these kinds of questions.

Second, the interaction of malnutrition with specific diseases is just beginning to be understood. Nutrition and disease have been at the heart of medicine for millennia. But we still understand little of just how they are related. In the early days of parenteral nutrition, it was thought that nutritional support could reverse, by overfeeding, the wasting caused by cancer and other diseases. Hence, the term "hyperalimentation." That was wrong. We still don't know, for example, why 1 or 2 kg of tumor will cause a 70-kg human to waste away and die. But we do know that overfeeding will not reverse the process, at least without effective anti-tumor therapy. The relationship between cancer chemotherapy and nutrition remains inadequately studied. More broadly, there is a large body work on using specific nutritional therapy to manage disease. The use of branched chain amino acids to ameliorate the encephalopathy of chronic liver disease and the use of glutamine to enhance immune function are examples. But successes have been few.

Third, the effect of starvation on body systems is understood only at the level of prolonged starvation. What is the effect of, say, 10 days of starvation on wound healing? On resistance to infection? Is protein malnutrition different from simple caloric deprivation, as might be seen in a weight loss program? Is protein supplementation of the severely ill, as currently practiced, beneficial or detrimental? These are all undetermined, but opinions about these questions remain firmly embedded in our thinking about how we should treat our patients.

These three areas of study and practice are all interrelated. Without biomarkers, it is difficult to determine the effect of a brief period of malnutrition, or the effect of malnutrition on a particular disease. But all of these can be studied within the ethical guidelines of today. Increased understanding would greatly benefit our abilities to provide nutritional therapy to patients.

Effect of Nutrition on the Immune System

The interaction between nutrition and the immune system has been known since antiquity. Indeed, Famine and Disease are two of the Four Horseman of the Apocalypse, an insight that dates back two millennia. As outlined earlier, there is a great deal of evidence that links nutrition, the gut, and both immunity and inflammation. The superior results of enteral as compared with parenteral nutrition seems to be due in large part to the role of the gastrointestinal tract. But we know only in a general way how this is mediated. We have few if any biomarkers for immune system status which can be used to guide clinical therapy or to inform research efforts. Clinical surrogates for the inflammatory response, on the other hand, are much better defined. Indeed, the use of fever, tachycardia, and tachypnea for this purpose is ancient. More modern end points, such as white blood cell count, C-reactive protein, and albumin allow us to track the inflammatory response relatively well, at least from a clinical standpoint. Given these tools, we should know considerably more about the relationship between nutrition and inflammation than we actually do. Research in this area should be pursued.

The most exciting new research in the functioning of the immune system comes from the relationship between the body and the microbiological flora of the gut. As noted in Chap. 2, understanding this relationship is important to the understanding of both of the immune system and the functioning of the gut. These characteristics are just beginning to be understood. The microbiome is also important to the body's processing of nutrients, and the signals that are sent from the gut to the rest of the body. These signals include those related to satiety, and to the rest of the immune system—vitally important to the ill, specifically. The gut-associated lymphatic system may be in fact the most important organ in the immune system. As we further understand how nutrients interact both with the gut and the microflora, many of our therapeutic and dietary regimens will be changed, and for the better.

Timing of Nutrition Support

This is one of the most significant areas of controversy in the whole nutritional field. For example, even within this text, there is disagreement on the timing and indications for enteral nutrition. Notably, the editors and the authors of Chap. 4 do not agree on the strength of the recommendations made in the chapter. A healthy person can tolerate a surprisingly long period of starvation without apparent ill effects other than weight loss and a general loss of energy. But the key word is "apparent." Studies of prolonged fasting have been carried out for a century or more. As a result, we know a great deal about metabolic consequences in healthy patients. But in the realm of critically ill patients, we know relatively little about just how long we may safely withhold nutrition, nor can we measure the adverse effects of doing so. We lack biomarkers, and IRBs will not generally allow us to withhold feeding for significant periods of time. We do know that most patients survive operations, injuries, and illnesses without nutrition support. And so a great deal of our clinical debate revolves around timing, or when to begin nutrition support after a period of medically induced starvation. Some studies have been done, but more are needed.

Complicating this question is two issues. First, the modes of nutrition support available to us are not equal in their risk of complications, nor in their therapeutic benefits. This will be discussed further in section "Enteral Nutrition versus Parenteral Nutrition." Second, we have only very poor ways of measuring the outcome of either nutrition or starvation. We have, over the last 50 years, tried and discarded "precise" measures of assessment, from skin fold thickness and muscle circumference, to serum levels of transport proteins, to acute phase reactants, and now to measurements of muscle mass with new imaging techniques. None of these appear to be particularly useful for this purpose in critically ill patients, and we are only able to study using the outcomes of mortality, complications, and quality of life. While these are certainly the gold standards on which studies should be based, we badly need surrogate markers that can be applied in the clinical setting to start exploring these questions.

Enteral Nutrition Questions

Because enteral nutrition is so widely used, we often tend to think that we understand it, or that it is equivalent to a normal oral diet. But the use of tube feedings is still very much a work in progress. To be sure, we have established that enteral nutrition is, if the gastrointestinal tract works, the preferred method of delivering nutrients. We have come a long way from the early days, when one could order a "blended regular" diet. If you don't know what that is, you're probably better off, not to mention being much younger than the editors. We now have a wide variety of enteral products for our use. And yet, the undeniable progress we've made in this area has simply led us to more questions.

Consider the setting. Bypassing the mouth, esophagus, and all of the sensory organs, a liquid diet is delivered directly into the stomach or proximal small intestine. Nasoenteric tubes are widely used, but even here, there are questions. Larger nasogastric tubes, often used for gastric emptying initially, are continuing to be used for feeding. We are fairly sure that these tubes increase the complications of sinusitis, and are less comfortable, and we think that they may increase the incidence of aspiration. But what is the importance of aspiration when the incidence of aspiration is 50 % in the normal population? The new tube connection standards will prevent catastrophic enteral-to-intravenous errors, but will also tend to mandate the use of smaller tubes. But we don't have direct evidence that the use of smaller tubes will be better for patients. And with the many studies of gastric versus small bowel feedings, we still are somewhat unsure about which should be used in a given patient. Gastric feeding remains the preferred choice overwhelmingly, if only because placement in the small bowel is difficult to accomplish.

Then, consider what happens when the stomach is filled up with tube feeding. Many patients have difficulty with gastric emptying. True, the stomach is adapted to hold 500 ml or more, but it must empty sometime for the nutrition to be effective. Does the formula itself affect this? Does a high-fat, low-carbohydrate enteral formula with fiber impair gastric emptying? Is there anything which can be done to improve gastric emptying? A formula which would enhance gastric emptying would, one would imagine, be very useful. Is this even possible? We do not know.

Diabetic patients raise a whole new set of concerns. Especially in the intensive care unit, diabetic patients may require insulin, and often require an insulin infusion. One of the few disadvantages of enteral nutrition is that insulin cannot be added to the formula. So should such patients receive a different formula? For example, we know from years of study that a high fat, low carbohydrate enteral formula for patients with diabetes has no impact on glycemic control. This makes sense in that glycemic index is only relevant in bolus feeding or meals. But, in patients receiving these glycemic control feeds, is the additional fat metabolized appropriately? Can enteral fat be immunosuppressive, as parenteral omega-6 fats are thought to be? There is a tendency to avoid the use of intravenous fats in patients with the systemic inflammatory response. Does one of these offset the other?

Then there are the questions revolving around just what type of fat that should be used. Does the use of an enteral formula with omega-3 fat impact weight loss? Does providing an enteral formula with omega-3 fat, gamma linolenic acid, and antioxidants within 24 h of the identification of the adult respiratory distress syndrome (ARDS) improve clinical outcomes? These formulas have only been studied against formulas with excess omega-6 fat, or in seriously flawed randomized studies.

The use of "immune-enhancing" formulas remains an active subject for research. There is just enough evidence to possibly justify their use. But there is not enough data available to guide that use. Just as an example, if one starts an immune formula when the patient is admitted to the ICU, what is the endpoint at which it should be stopped? Fever? WBC count? Or something else?

Enteral Nutrition Versus Parenteral Nutrition

The "EN vs. PN" question is one of those perennial subjects of great interest to clinicians. As with many new advances, the initial enthusiasm for parenteral nutrition exceeded the reality. Some of us even thought, during the exciting days of the 1960s and 1970s, that parenteral nutrition would prove to be the answer to such wasting diseases as cancer. The term "hyperalimentation" dates to those early days. By over-feeding patients parenterally, we would deliver nutrition directly to the cells, and bypass all of the clumsy methods worked out by the slow processes of evolution. Not surprisingly, we found that the body's mechanisms worked best. By the mid-1970s, it was obvious that enteral nutrition was superior. Assuming, it should be pointed out, that the patient can tolerate enteral nutrition. As noted in some detail in Chaps. 2 and 6, if the gut works, we should use it.

And yet, we continue to see studies done and published which take patients who can receive enteral nutrition, and subject them to a randomized allocation to enteral versus parenteral. As they say in politics, "no horse is too dead to beat." Patients who cannot take enteral nutrition, are of course excluded from such studies, as they cannot be randomized. But those are the very patients who are receiving parenteral nutrition. In short, most studies select two groups of patients who don't need to receive parenteral nutrition, then feed one group enterally and the other parenterally. We can take it as fully proven that such patients should be fed enterally. Really, such studies may be no longer ethical, unless the technology has changed to such a degree that the safety profile of one or the other therapy has changed dramatically. Unfortunately, the message is sometimes communicated that if patients cannot take enteral nutrition, they shouldn't be fed at all.

Is parenteral nutrition in fact better than no nutrition at all? Most clinicians think that it is, and there is a great deal of evidence to support that. Starvation is, in the long run, lethal. Patients have been maintained on parenteral nutrition for many years, with no oral intake at all. But when the question gets down to the short term, such as feeding patients in the intensive care unit, the answer is far less clear. Studies are very hard to carry out. Since patients receiving parenteral nutrition are a disparate group who tend to be rather more ill than most, studying them is difficult in the first place. The ethical limitations with starvation as a control therapy greatly constrain our ability to study patients who can only be fed parenterally. The important practical question for clinical research is, how little nutrition can one ethically feed a control group, when comparing it to a group fully nourished parenterally? And for how long?

The second question is the effect on the gut of parenteral nutrition. This is something of particular interest to surgeons, who may have to deal surgically with patients whose intestines have atrophied after long-term parenteral nutrition. But it should be of interest to all of us. Does intestinal atrophy, for example, change the intestinal flora? Is the effect of parenteral nutrition different from starvation? Is the atrophy due solely to the lack of use of the intestine, due to an unknown effect of a component of parenteral nutrition, or not related at all and due to the systemic inflammation that is so often part and parcel of the clinical condition which caused the need for parenteral nutrition in the first place? What is the effect on the gut mucosal barrier? Can glutamine, given parenterally, prevent some of the atrophy? What about gastrointestinal growth factors? A number of these questions have been assessed in animal models, but there is much more to do. The effects on clinical outcomes of the parenteral nutrition associated changes in the gut have barely been observed. Certainly, some patients have been kept on home parenteral nutrition for many years, but how do we know that they are free of ill effects? We know about parenteral nutrition-associated liver disease, but we're still trying to find the mechanisms and best way to treat it. About other consequences, we know little.

Hypermetabolism and Catabolism and Their Treatment

Many, if not most, patients in the intensive care unit are hypermetabolic when they arrive. But most have exquisite control of their calorie burn once they are stabilized. Proper ventilation and sedation, as well as control of pain, temperature and anxiety, which all should occur rapidly, drive calorie consumption down to close to that of a normal person at bed rest. No such control exists, however, for nitrogen loss, and while hyperalimentation is no longer practiced where calories is concerned, it is most certainly practiced in how we prescribe protein.

Certainly, for patients who are injured, or who have had major operations, increased metabolic rate is a normal physiologic adaptation (see Chap. 8). But our usual clinical methods are not well adapted to this. The one area in which clinicians routinely adjust therapy for hypermetabolism is trauma. Burned patients, for example, are often treated using a specific burn formula to calculate their needs. For most other patients, we calculate needs by using one of a dozen or so formulas, chosen more

according to taste than to evidence. Then we throw in an additional factor of 20 % or so for stress, infection, sepsis, or injury, and prescribe on that basis. While suitable instruments for indirect calorimetry has been around for decades, we rarely use them. On top of that, studies have routinely shown that patients receive only 60–80 % of the amount prescribed. In essence, we make an educated guess as to nutritional requirements, and then administer two-thirds of that amount. That our patients get better despite this shows more of the toughness of the human body than of the quality of our nutritional practice.

For prescribing protein, we are dependent on even more rudimentary technology. All of our guidelines and practice are based on studies which have measured the amount of nitrogen in the urine. We religiously adhere to the notion that the sicker one is, the more protein they "need." But does feeding that amount of protein make a positive difference in outcomes? Do we have the potential for harming patients by practicing this way? And given that we only achieve a fraction of what we think patients need, is the expense and trouble warranted to get protein supplementation into enterally fed patients?

But are we, actually, practicing in the wrong way? Perhaps patients don't really need all of their nutritional requirements met. Perhaps half or two-thirds is indeed the correct amount. Studies to address this question are almost entirely lacking. This area would seem to be relatively open to clinical research. In the very wide gap between "trickle feeding" and full-dose nutritional support provided by both enteral and "top-up" parenteral nutrition, there could be a lot of good research that would inform clinical practice.

Obesity and Aging

Those who spend their days planning for the future assure us that obesity, in the Western world, will be increasingly important. Indeed, a society of obese citizens tended by robots has been the basis for a popular movie [3]. This prediction is no doubt exaggerated. We hope. Nonetheless, demographic factors predict that we will be caring for a progressively greater number of elderly patients as time goes on. The nutritional community is actually fairly well equipped to deal with both of these. Diet and exercise are well understood in treating obese patients. It may often be ineffective, but they're understood. The nutritional requirements of healthy elderly patients are likewise reasonably well known. But when both of the subgroups end up in the ICU, we are much less equipped with knowledge about what to do.

Critically ill obese patients are a particular problem. Most of the methods by which we judge how much to feed patients are based on weight. Of course, one can just throw up one's hands, and feed the thin patient residing inside the obese patient. That is known as the ideal body weight method. Before dismissing it out of hand, it does seem to work. More or less. In fact, looking at the actual amount fed to obese patients, many of the recommendations and guidelines boil down to just feeding obese patients as if they were of normal weight. We are fairly sure that the actual consumption of calories in obese patients can be measured accurately with indirect calorimetry, but few hospitals actually use this method. We are also sure that the formulas provide only an imprecise, and probably low, estimate of the nutritional needs of the obese patient. But, we have no clue as to whether feeding what is measured results in better outcomes in these patients. We know that over-feeding is a bad idea, but it is very difficult to determine when such patients are being overfed. Without outcomes data, calorie consumption and urea nitrogen losses are all we have to guide us, and they are inadequate to produce the answers we need.

In short, our therapy in this group of patients is both uninformed by data, and inconsistent. We are fairly sure that a critically ill patient is not a good candidate for beginning a weight reduction program. Yet, in effect, that is what we usually do. Hypocaloric feeding combined with over-feeding of protein has been advocated, and is probably the method about which there is most consensus. But this is based

on only a few studies, and has not been compared with other possible regimens for improvement in survival or other important health outcomes. We need studies of different types of diets, ranging from full replacement down to hypocaloric high-protein feeding, and based at least on indirect calorimetry and urinary nitrogen excretion studies. Such studies are not being done.

Aging patients present a different set of problems. We know that body composition changes with age, with decreased muscle mass among other changes, but we are not entirely sure how to translate that knowledge into therapy for the critically ill. Older patients have lower tolerance for critical illness, and tend to be over-represented in the critically ill population. In many critical care units, the average age of patients is in the 60s, reflecting both the increasing average age of the population and the tendency of older patients to be placed in the ICU when ill. Assuming that an elderly patient is simply a young patient grown older is not as large an error as assuming that an obese patient is simply a thin patient trapped in a fat body. But they are both errors, nonetheless.

Conclusion

Nutritional practice is in many ways the stepchild of medicine. The major advances over the last 50 years have been the introduction of parenteral nutrition and the widespread use of enteral nutrition. Both of these modalities have helped medical practice in general. Very few patients today starve to death. The fact that we must say "very few" rather than "zero" is an indictment of our health system, but that's an issue which cannot be resolved with more research. In many of the areas of our daily practice of nutrition support, especially in the intensive care unit, we are forced to say, "Well, I think that's the best way to do it," rather than being sure. Granted, few medical therapies of any sort are either totally understood or completely defined. But the uncertainty quotient in nutrition is somewhat higher than most of us would prefer.

We have attempted to create a road map to help those among us who wish to resolve uncertainty, even if only in a small area of practice. It is our hope that this may make a difference in how well our patients are after ICU care is required.

References

1. McClave SA, et al. 2009. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (S.C.C.M.) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316.
2. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ. 2003;327:1459–61.
3. WALL-E. Pixar Studios, 2008.

Index

D.S. Seres, C.W. Van Way, III (eds.), *Nutrition Support for the Critically Ill*, Nutrition and Health,
DOI 10.1007/978-3-319-21831-1, © Springer International Publishing Switzerland 2016