Surgical Metabolism

The Metabolic Care of the Surgical Patient

Kimberly A. Davis
Stanley H. Rosenbaum
Editors

Second Edition

Springer

Surgical Metabolism

Kimberly A. Davis
Stanley H. Rosenbaum
Editors

Surgical Metabolism

The Metabolic Care of the Surgical Patient

Second Edition

Springer

Editors
Kimberly A. Davis
Department of Surgery
Yale University School of Medicine
New Haven, CT
USA

Stanley H. Rosenbaum
Department of Anesthesiology
Yale University School of Medicine
New Haven, CT
USA

ISBN 978-3-030-39780-7 ISBN 978-3-030-39781-4 (eBook)
https://doi.org/10.1007/978-3-030-39781-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

We are delighted to have produced the second edition of our text on surgical metabolism. We continue with our belief, as stated in the first edition, that specialists in the treatment of modern surgical disease must also have a strong understanding of normal metabolism and perturbations induced by surgical interventions.

Our approach is not to follow a traditional systems or organ-based approach but rather to encourage our readers to think of the patients as complex biochemical systems. We intend this work to provide information that supplements the more traditional approaches and provides a detailed overview of the metabolic knowledge needed for surgical practice.

We recognize that the biochemical aspects of modern medicine are advancing so rapidly that it is difficult to keep up even with the best efforts. In this book, some chapters have been updated, and several new chapters have been added. We hope this will help our readers keep pace in this race for state-of-the-art knowledge.

We continue to acknowledge the long-ago trailblazing work of Dr. Francis Moore that represented the birth of the field of surgical metabolism. We also thank our many mentors. Our deep gratitude also goes out to the many contributors whose efforts made this volume possible. We also wish to thank the support we received from our academic chairs at Yale School of Medicine, Dr. Nita Ahuja of the Department of Surgery and Dr. Roberta Hines of the Department of Anesthesiology. Once again, this work could not have been produced without the fine efforts of Ms. Elise Paxson and the rest of the Springer publishing team.

New Haven, CT, USA

Kimberly A. Davis
Stanley H. Rosenbaum

Contents

Contributors

Suresh " Mitu" Agarwal, MD, FACS, FCCM Department of Surgery, Duke University Medical Center, Durham, NC, USA

David A. August, MD Rutgers Cancer Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Robert D. Barraco, MD, MPH Department of Surgery, Lehigh Valley Health Network, Allentown, PA, USA

Sneha G. Bhat, MD Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

Bishwajit Bhattacharya, MD Department of Surgery, Yale New Haven Hospital, New Haven, CT, USA

Reagan W. Bollig, MD Division of Trauma and Critical Care UTMC, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

Eric H. Bradburn, MS, DO, FACS Penn Medicine Lancaster General Health, Lancaster, PA, USA

Emily Cantrell, MD Department of Surgery, University of California San Diego, San Diego, CA, USA

Michael Chapek, BS Department of Surgery, Oregon Health and Science University, Portland, OR, USA

Mitchell Jay Cohen, MD FACS Denver Health Medical Center, Denver, CO, USA

Division of Bioinformatics and Personalized Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Bryan Collier, DO, FACS CNSC Surgical Nutrition, Trauma Center, Virginia Tech Carilion School of Medicine, Carilion Roanoke Memorial Hospital, Roanoke, VA, USA

Brian J. Daley, MD, MBA Division of Trauma and Critical Care UTMC, Department of Surgery, University of Tennessee Medical Center, Knoxville, TN, USA

Kimberly A. Davis Department of Surgery, Yale University School of Medicine, New Haven, CT, USA

Roland N. Dickerson, Pharm.D Department of Clinical Pharmacy and Translational Science, College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA

Jay Doucet, MD, FRCSC, FACS, RDMS Department of Surgery, University of California San Diego, San Diego, CA, USA

Victor A. Gall, MD Rutgers-Robert Wood Johnson Medical School and the Rutgers Cancer Institute of New Jersey, Department of Surgery, Division of Surgical Oncology, New Brunswick, NJ, USA

Richard L. Gamelli, MD, FACS Loyola Burn Center, Loyola University Chicago, and Stritch School of Medicine, Maywood, IL, USA

Jared H. Griffard, MD The University of Tennessee Graduate School of Medicine, Knoxville, TN, USA

Timothy J. Harrison, DO, MS, FACS, FACOS Department of Surgery, Lehigh Valley Health Network, Allentown, PA, USA

Rawhi Hashem, MD Department of Anesthesiology and Critical Care Medicine, Hadassah—Hebrew University Medical Center, Hebrew University – Hadassah School of Medicine, Jerusalem, Israel

Elizabeth H. Holt, MD, PhD Section of Endocrinology and Metabolism, Yale Medical School, New Haven, CT, USA

Vadim Koshenkov, MD Rutgers-Robert Wood Johnson Medical School and the Rutgers Cancer Institute of New Jersey, Department of Surgery, Division of Surgical Oncology, New Brunswick, NJ, USA

Rosemary A. Kozar, MD Department of Surgery, University of Maryland School of Medicine, Program in Trauma, Baltimore, MD, USA

Kristina Z. Kramer, MD John H. Stoger, Jr. Department of Trauma and Burn Surgery, Hospital of Cook County, Chicago, IL, USA

Ryan A. Lawless, MD Department of Surgery, Denver Health Medical Center, Denver, CO, USA

Christy M. Lawson, MD Division of Trauma and Critical Care, Department of Surgery, University of Tennessee Medical Center, Knoxville, TN, USA

Amy Liepert, MD Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Daniel I. Lollar, MD Virginia Tech Carilion School of Medicine, Carilion Roanoke Memorial Hospital, Roanoke, VA, USA

Chandler A. Long, MD Division of Vascular and Endovascular Surgery, Duke University School of Medicine, Durham, NC, USA

Linda L. Maerz, MD, FACS, FCCM Department of Surgery, Yale New Haven Hospital, New Haven, CT, USA

Robert G. Martindale, MD, PhD Division of General Surgery, Oregon Health & Science University, Portland, OR, USA

Stephen A. McClave, MD Division of Gastroenterology, Hepatology and Nutrition, University of Louisville Hospital, Louisville, KY, USA

C. Lindsay McKnight, MD, FACS, CNSC Division of Trauma and Critical Care UTMC, Department of Surgery, University of Tennessee Medical Center, Knoxville, TN, USA

Laleh G. Melstrom, MD, MS Division of Surgical Oncology, Department of Surgery, City of Hope Medical Center, Los Angeles, CA, USA

Laura J. Moore, MD, FACS Department of Surgery, Division of Acute Care Surgery, The University of Texas Health Science Center at Houston, Houston, TX, USA

Michael J. Mosier, MD The Oregon Burn Center and The Oregon Clinic, Portland, OR, USA

Douglas L. Nguyen, MD University of California-Irvine, Orange, CA, USA

Carlos Ortiz-Leyba, MD Department of Internal Medicine and Critical Care Unit, Hospital Quirón Sagrado Corazón, Sevilla, Spain

Michael D. Pasquale, MD Department of Surgery, Lehigh Valley Health Network, Allentown, PA, USA

Stacy Pelekhaty, MS, RD, CNSC Department of Clinical Nutrition, University of Maryland, Baltimore, MD, USA

Mihai V. Podgoreanu, MD FACE Department of Anesthesiology, Duke University School of Medicine, Durham, NC, USA

Stathis Poulakidas, MD Department of Trauma & Burns, Cook County Health and Hospital Systems, Chicago, IL, USA

Christopher R. Reed, MD Department of Surgery, Duke University Medical Center, Durham, NC, USA

Danielle M. Toepfer, RD, LD, CNSC The Oregon Burn Center, Legacy Emanuel Medical Center, Portland, OR, USA

Andy Tully, MD Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA

Nathan Knapp, MD Division of GI and General Surgery, Oregon Health & Science University, Portland, OR, USA

Melissa Warren Division of General Surgery, Department of Surgery, Oregon Health & Science University, Portland, OR, USA

Charles Weissman, MD Department of Anesthesiology and Critical Care Medicine, Hadassah—Hebrew University Medical Center, Hebrew University – Hadassah School of Medicine, Jerusalem, Israel

Vivian M. Zhao, PharmD Nutrition and Metabolic Support Service, Emory University Hospital, Atlanta, GA, USA

Thomas R. Ziegler, MD Division of Endocrinology, Metabolism and Lipids, Emory University Hospital Research Unit, Atlanta Clinical and Translational Science Institute (ACTSI), ACTSI Clinical Research Network, Atlanta, GA, USA

Abbreviations

A

AACE	American Association of Clinical Endocrinologists
ABW	Adjusted body weight
$AcAc^-$	Acetoacetate
ACEI	Angiotensin-converting enzyme inhibitor
ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
ACTS	Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis Trial
ADA	American Diabetes Association
ADH	Antidiuretic hormone
ADL	Activities of daily living
ADP	Adenosine diphosphate
AKI	Acute kidney injury
AKIN	Acute kidney injury network
AG	Anion gap
AGc	Anion gap corrected
AGI	Acute gastrointestinal injury
AgRP	Agouti-related protein
ALI	Acute lung injury
AMPK	Adenosine monophosphate-activated protein kinase
ANP	Atrial natriuretic peptide
ANS	Autonomic nervous system
AQP	Aquaporin
ARDS	Acute respiratory distress syndrome
ASPEN	American Society for Parenteral and Enteral Nutrition
ATP	Adenosine triphosphate
AUC	Area under the curve

B

β-OHB	β-Hydroxybutyrate
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene

BMI	Body mass index
BMR	Basal metabolic rate
BUN	Blood urea nitrogen

C

cAMP	Cyclic AMP
CARS	Compensatory anti-inflammatory response syndrome
CBG	Cortisol-binding globulin
CCCPG	Canadian Critical Care Practice Guidelines
CCI	Chronic Critical Illness
CCK	Cholecystokinin
CD	Crohn's disease
C/EBP-β	CCAAT-enhancer-binding protein-β
CETP	Cholesteryl ester transfer protein
CGM	Continuous glucose monitoring
CI	Confidence interval
CIF	Chronic intestinal failure
CIP	Critical illness polyneuropathy (CIP)
CLOCK	Circadian locomotor output cycles kaput
CNS	Central nervous system
CoA	Coenzyme A
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase 2
CPAP	Continuous positive airway pressure
CREB	cAMP-responsive element binding protein
CREB/CRTC2	cAMP-responsive element-binding protein-regulated transcriptional coactivator-2
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CPT2	Carnitine palmitoyltransferase 2
CRTC2	CREB-regulated transcription coactivator 2
CRRT	Continuous renal replacement therapy
CT	Computed tomography
CyTOF	Cytometry by time-of-flight

D

DAMP	Damage-associated molecular pattern
DHA	Docosahexaenoic acid
DIC	Disseminated intravascular coagulation
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DS	Degree of substitution
DXA	X-ray absorptiometry

E

ECF	Extracellular fluid or Enterocutaneous fistula
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
EEG	Electroencephalogram
EEN	Early enteral nutrition
EMA	European Medicines Agency
EMPD	Electromagnetically guided placement devices
EN	Enteral nutrition
EPA	Eicosapentaenoic acid
ERAS	Enhanced recovery after surgery
ESPEN	European Society for Clinical Nutrition and Metabolism
ESRD	End-stage renal disease

F

FABP	Fatty acid-binding protein
FAO	Food and Agriculture Organization of the United Nations or Fatty acid oxidation
FATPs	Fatty acid transport proteins
FDA	US Food and Drug Administration
FFA	Free fatty acid
FFAR3	Free fatty acid receptor 3
FFM	Fat-free mass
FGF	Fibroblast growth factor
FHH	Familial hypocalciuric hypercalcemia
FM	Fat mass
FOS	Fructooligosaccharides
FOXO1	Forkhead box protein 1

G

GALT	Gut-associated lymphoid tissue
GCS	Glasgow Coma Scale
GDE	Glycogen-debranching enzyme
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GI	Gastrointestinal
GIF	Gastrointestinal failure
GIP	Glucose-dependent insulinotropic polypeptide
GIT	Gastrointestinal tract
GLIM	Global Leadership Initiative on Malnutrition
GLP	Glucagon-like peptide
GnRH	Gonadotropin-releasing hormone

GP	Glycogen phosphorylase
GRV	Gastric residual volumes
GOS	Galactooligosaccharides
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation

H

H2RA	H2-receptor antagonist
HCAR2	Hydroxycarboxylic acid receptor-2
HCMA	Hyperchloremic metabolic acidosis
HDACs	Histone deacetylases
HDL	High-density lipoprotein
HEI	Healthy Eating Index
HES	Hydroxyethyl starch
HHS	Hyperosmolar hyperglycemic state
HF	Heart failure
HMGB1	High-mobility group box1
HPN	Home parenteral nutrition
HRV	Heart rate variability
HSL	Hormone-sensitive lipase
HSP	Heat shock proteins
HTS	Hypertonic saline

I

IABT	Intra-aortic balloon pump
IAH	Intra-abdominal hypertension
IBW	Ideal body weight
IC	Indirect calorimetry
ICAM	Intracellular adhesion molecule
IEF	Immune-enhancing formula
IL	Interleukin
IADL	Instrumental activities of daily living
ICF	Intracellular fluid
ICM	Ischemic cardiomyopathy
ICU	Intensive care unit
I-FABP	Intestinal fatty acid-binding protein
I-FALD	Intestinal failure-associated liver disease
IGF	Insulin growth factor
iNOS	Inducible NO synthase
IP	Inducible protein
IV	Intravenous(ly)

K

KIM-1	Kidney injury molecule-1
KLF	Kruppel-like factor

L

L-FABP	Liver-type fatty acid-binding protein
LAMP-2	Lysosome-associated membrane protein 2
LCT	Long-chain triglycerides
LDL	Low-density lipoprotein
LE	Lipid emulsions
LH	Luteinizing hormone
LIS	Lung Injury Score
LMF	Lipid-mobilizing factor
LODS	Logistic organ dysfunction system
LPS	Lipopolysaccharide
LR	Lactated Ringer's
LRS	Lactated Ringer's solution
LV	Left ventricular

M

MACE	Major adverse cardiac events
MALT	Mucosa-associated lymphoid tissue
MAP	Mean arterial pressure
MAS	Magic-angle spinning
MAS-NMR	Magic-angle spinning NMR spectroscopy
MCP-1	Monocyte chemotactic peptide
MCT	Medium chain triglycerides
MDSC	Myeloid-derived suppressor cell
MI	Myocardial infarction
MIF	Macrophage migration inhibitory factor
MIP	Macrophage inflammatory protein
MNA-FF	Mini-Nutritional Assessment-Full Form
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
MS	Mass spectrometry
α-MSH	α-Melanocyte-stimulating hormone
MRI	Magnetic resonance imaging
MSR	Macrophage scavenger receptor
MST	Malnutrition Screening Tool
mTORC1	Mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1
MUST	Malnutrition Universal Screening Tool

N

NADH/NAD	Nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide (NADH/NAD)
NAG	N-Acetyl-β-D-Glucosaminidase
NF-κB	Nuclear factor kappa B
NGT	Nasogastric tube
NICM	Nonischemic cardiomyopathy
NMR	Nuclear magnetic resonance
NOAC	Novel oral anticoagulant
NO	Nitric oxide
NOS	Nitric oxide synthase
NRS	Nutritional risk screening
Nrf2	Nuclear factor erythroid 2-related factor 2
NSS	Normal saline solution
NUFFE	Nutritional Form for the Elderly
NUTRIC	Nutrition Risk in Critically ill

O

$O2^-$	Superoxide
OKG	Ornithine alpha ketoglutarate
OR	Odds ratio

P

PAF	Platelet-activating factor
PAI	Plasminogen activator inhibitor
PAMP	Pathogen-associated molecular pattern
PCM	Protein-calorie malnutrition
PEM	Protein-energy malnutrition
PICC	Peripherally inserted central catheter
PDH	Pyruvate dehydrogenase
PDK-4	Pyruvate dehydrogenase kinase isozyme 4
PEEP	Positive end-expiratory pressure
PEG	Percutaneous endoscopic gastrostomy
PI3K	Phosphoinositide 3-kinase
PG	Prostaglandin
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1 α
PG-SGA	Patient-Generated Subjective Global Assessment
PICS	Persistent inflammation and immunosuppression
PIF	Proteolysis-inducing factor
PPAR-α	Peroxisome proliferator-activated receptor alpha
PPI	Proton-pump inhibitor

Posm	Plasma osmolality
PN	Parenteral nutrition
PRR	Pattern recognition receptors
PUFA	Polyunsaturated fatty acids
PROPATRIA study	Probiotics in Pancreatitis Trial
PTH	Parathyroid hormone

Q

QoL	Quality of life

R

RAGE	Receptor for Advanced Glycation End Products
RBC	Red blood cell
RBP	Retinol-binding protein
RCT	Randomized controlled trial
RDA	Recommended daily allowance
REDOXS	REducing Deaths due to OXidative Stress trial
RE-ENERGIZE	RandomizEd Trial of ENtERal Glutamine to miniZE thermal Injury trial
REE	Resting energy expenditures
RIFLE	Risk injury failure end-stage renal disease
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RR	Risk ratio
RTA	Renal tubular acidosis

S

SAE	Sepsis-associated encephalopathy
SAFE	Saline versus Albumin Fluid Evaluation
SBE	Standard base excess
SBFT	Small bowel follow through
SBS	Short bowel syndrome
SCCM	Society of Critical Care Medicine
SCFA	Short-chain fatty acid
SCREEN-II	Seniors in the Community: Risk Evaluation for Eating and Nutrition Questionnaire
SGA	Subjective Global Assessment
SHBG	Sex hormone-binding globulin
SIADH	Syndrome of inappropriate antidiuretic hormone
SID	Strong ion difference
SIG	Strong ion gap

SIGN	Scottish Intercollegiate Guidelines Network
sIL-6R	Soluble IL-6 receptor
SILT	Spiral intestinal lengthening and tailoring
SIRS	Systemic inflammatory response syndrome
SIRT3	Silent mating-type information regulator number 3
SNAQ-RC	Short Nutritional Assessment Questionnaire-Residential Care
SNP	Single-nucleotide polymorphisms
SOD	Superoxide dismutase
SOFA	Sequential Organ Failure Assessment
SPN	Supplemental parenteral nutrition
STEP	Serial transverse enteroplasty
sTNF-R	Soluble TNF receptor

T

TAVR	Transcatheter aortic valve replacement
TBG	Thyroid-binding globulin
TBI	Traumatic brain injury
TBSA	Total body surface area
TBW	Total body weight OR total body water
TLC	Total lymphocyte count
TLR4	Toll-like receptor 4
TMAO	Trimethylamine N-oxide
TNF	Tumor necrosis factor
t-PA	Tissue plasminogen activator
TREM-1	Triggering Receptor Expressed on Myeloid Cells
TRH	Thyrotropin-releasing hormone
tRNA	Transfer RNA
TSH	Thyroid-stimulating hormone

U

UC	Ulcerative colitis
UCP	Uncoupling protein
UGI	Upper gastrointestinal
uHGF	Urinary hepatocyte growth factor
ULK1	Unc-51 like autophagy activating kinase-1
uNGAL	Neutrophil gelatinase-associated lipocalin
UPS	Ubiquitin-proteasome system

V

VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor

VIP Vasoactive intestinal polypeptide
VLDL Very low-density lipoprotein

W

WHO World Health Organization
WMD Weighted mean difference

Part I

Normal Metabolism

Introduction to Metabolism

1

C. Lindsay McKnight, Jared H. Griffard, Sneha G. Bhat, Reagan W. Bollig, Christy M. Lawson, Chandler A. Long, and Brian J. Daley

Introduction

Metabolism is the combination of reactions and processes necessary to sustain life [1]. These reactions and processes occur within different levels of the living organism. The production and consumption of energy at the cellular level is the basis of life. Maintaining equilibrium between the production and consumption of energy is paramount to survival, and mismatches lead to infection, illness, disability, organ dysfunction, and death. Most metabolic derangements are the result of a disease process, although some can be inborn. Understanding metabolism at the cellular level has helped the scientific community develop methods of maintaining homeostasis and in turn has provided clinicians with therapies to treat patients with disease processes and optimize outcomes.

History of Metabolism

The word *metabolism* is derived from the root "meta" meaning "change" and "ballein" meaning "to throw [2]." From individual metabolic reactions at the cellular level to the metabolic responses of the organism, the scientific community has been studying metabolism for centuries. Santorio Sanctorius is considered the "founding father of metabolic balance studies" in the seventeenth century [3]. He explored insensible loss through perspiration. He documented his weight before and after specific activities in his book *Ars de Statica Medicina* in 1614. Friedrich Wohler published one of the first articles on metabolic pathways, specifically the synthesis of urea in 1828. The discovery of enzymes by Eduard Buchner in the twentieth century preceded the rapid acceleration of biochemical discovery. Landmark discoveries in metabolism include the citric acid cycle, urea cycle, and glyoxylate cycle.

C. L. McKnight · B. J. Daley (✉)
Division of Trauma and Critical Care UTMC, Department of Surgery, University of Tennessee Medical Center, Knoxville, TN, USA
e-mail: bdaley@utmck.edu

J. H. Griffard
The University of Tennessee Graduate School of Medicine, Knoxville, TN, USA

S. G. Bhat
Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

R. W. Bollig
Division of Trauma and Critical Care UTMC, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

C. M. Lawson
Division of Trauma and Critical Care, Department of Surgery, University of Tennessee Medical Center, Knoxville, TN, USA

C. A. Long
Division of Vascular and Endovascular Surgery, Duke University School of Medicine, Durham, NC, USA

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*, https://doi.org/10.1007/978-3-030-39781-4_1

The understanding of energy metabolism started with Antoine Lavoisier. He focused on heat exchange and developed the first direct calorimeter in the nineteenth century. Subsequently the law of conservation of energy was developed. He discovered that he could directly measure the energy expenditure of an organism by calculating heat dissipation. He demonstrated that "respiration is a slow form of combustion [4]." The development of indirect calorimetry led to a more practical method to obtain the information for resting energy expenditure indirectly from measured oxygen consumption. Liebig, Voit, and Max Rubner were major players in discovering the link between oxygen consumption and metabolism and calculating caloric value of specific energy sources [4]. Modern studies of metabolism involve biotechnology techniques and genomics. Chromatography, X-ray diffraction, nuclear magnetic resonance (NMR) spectroscopy, radioisotope labeling, electron microscopy, and molecular dynamic simulation are all techniques currently used to evaluate metabolic pathways and explore the genetic basis of metabolic disorders.

The Hierarchy of Metabolism

The Mitochondrial Level

Mitochondria are complex double-membrane-bound organelles that play the leading role in cellular metabolism. They are the main energy source in almost all eukaryotes. Mitochondria are composed of five components with unique functions: an outer membrane, intermembrane space, inner membrane, cristae, and matrix space. The outer membrane contains enzymes, which lengthen fatty acids and participates in oxidation and degradation. It also associates with the endoplasmic reticulum membrane where calcium signaling facilitates the transfer of lipids. It contains porins, which make it highly permeable to all molecules. The intermembrane space contains a different protein composition than cytosol. For example, cytochrome C is in the intermembrane space. The inner membrane has five functions: oxidative phosphorylation, generation of adenosine triphosphate (ATP), regulation of metabolite transportation, protein import, and mitochondrial protein modification. The inner membrane has a high protein to phospholipid ratio, and almost all ions and molecules require transporters to cross over the matrix. The electron transport chain sets up a membrane potential across the inner membrane. Cristae are made of abundant inner mitochondrial membranes. This increases the surface area to produce more ATP. Cells that have more demand for ATP, i.e., muscle cells, contain a higher ratio of inner membrane/outer membrane, more cristae, and more mitochondria. The matrix contains most of the protein in the mitochondria. Enzymes, ribosomes, transfer RNA (tRNA), and copies of the mitochondrial DNA genome are within the matrix. Metabolic processes, such as oxidation of pyruvate and fatty acids and citric acid cycle, all take place in the matrix. Damage or dysfunction of mitochondria presents as a neurological or endocrine disorder [5]. Examples include Friedrich's ataxia, Alzheimer's disease, diabetes mellitus, autism, etc.

The Cellular Level

Cellular metabolism is a combination of chemical reactions that occurs to maintain life. Cellular metabolism is divided into two types: anabolism and catabolism. Anabolism is "building" and catabolism is "breaking down." The balance between anabolism and catabolism creates homeostasis. Depending on the needs and stress of the body at the time, it can be in an anabolic or catabolic state. It involves a complex sequence of controlled biochemical reactions creating metabolic pathways. One chemical is transformed into another through the actions of an enzyme. Enzyme regulates pathways in response to changes in the cellular environment. The needs of the cell dictate the flow of biochemical reactions. Glycolysis is an example of a chemical reaction where a substrate is converted into a product through ten steps. In the last step of glycolysis, phosphoenolpyruvate, the substrate, is converted into ATP and pyruvate, the products, by an enzyme called pyruvate kinase. The enzyme acts by transferring a phosphate group from one sub-

strate to another, i.e., adenosine diphosphate (ADP). Temperature, pH, availability of substrates, and cofactors modify the functionality of an enzyme [6]. This is the mechanism behind why patients with physiologic stress develop metabolic derangements.

The Organ Level

Each organ has its own unique metabolic profile [7]. In this section, the metabolic profile of each organ is reviewed. The brain utilizes glucose as its main energy source unless the body enters the later stage of starvation. The brain relies on a continuous source of glucose. In the resting state, the brain uses up to 60% of the total body glucose. The majority of this is used to power the Na^+-K^+ membrane potential and synthesize neurotransmitter synapses to propagate nerve impulses [7].

Very little is known about the role of the lung in metabolism. De novo fatty acid synthesis takes place in the lung as well as several other reactions mainly involving lipid esterification and the synthesis of phosphatidylcholine and prostaglandins. These components of surfactant are made at the gestational age of 24 weeks but not functional until week 34–36 [8]. Surfactant decreases the surface tension of the alveoli.

The liver is the main organ that provides fuel for peripheral organs including the brain and muscle. It is the main center for metabolism and controls the metabolite level in the blood [7]. Sixty-seven percent of carbohydrates are absorbed by the liver. The remaining glucose is absorbed by other tissues. A process called glycogenesis occurs. Glucose is converted into glucose-6-phosphate by hexokinase and glucokinase; then it is converted into glycogen. Glycogen is stored in the liver for later use when blood glucose levels decrease. Glycogen is broken down into glucose through gluconeogenesis in the liver, which then is released into the blood. If the body enters late starvation stage, lactate and alanine from muscle, adipose tissue, and exogenous amino acids become the main precursors for gluconeogenesis [7].

Lipids are also metabolized in the liver. Most fatty acids are absorbed by the liver. In a plentiful state, fatty acids are esterified and secreted into the blood in very low-density lipoprotein (VLDL), but in times of starvation, the liver converts fatty acids into ketone bodies [7].

Amino acid metabolism occurs in the liver as well. Amino acids are the main source for protein synthesis and anabolism. Alanine and aspartate aminotransferases (ALT and AST) are released in the blood stream and indicate liver damage. Catabolism of amino acids results in nitrogen products which are processed into urea. 20–30 g/day of urea is secreted from the liver. This process removes ammonia, a toxin to the central nervous system. Alpha-keto acids derived from amino acid catabolism fuel the liver [7]. The liver also synthesizes nonessential amino acids and most plasma proteins, including albumin and clotting factors within the coagulation cascade.

The kidney's purpose is to excrete metabolic waste products, which helps maintain the osmolarity of blood. Most substances, especially water and water-soluble constituents, are reabsorbed. A lot of energy is consumed for the process of reabsorption. The kidneys consume 10% of the oxygen used in cellular respiration. Glucose is carried into renal cells via sodium-glucose cotransporter. This transporter is driven by the sodium and potassium gradient powered by Na^+-K^+ ATPase. The kidney is an important site for gluconeogenesis when the body is in a state of starvation [7].

Muscle uses glucose, fatty acids, and ketone bodies as major fuel sources. Muscle has vast storage of glycogen. 75% of glycogen stores are in muscle cells. Muscle lacks glucose-6-phosphatase just like the brain, so glycogen is converted to G-6-P and retains the glucose for fuel. When muscle is contracting, the rate of glycolysis exceeds the rate of the citric acid cycle. The burden of metabolism is shared between muscle and the liver through the Cori cycle. Pyruvate is reduced to lactate, which can flow to the liver to be converted into glucose. Alanine is formed in muscle by the transamination of pyruvate. Muscle can absorb and transaminate branched-chain amino acids but cannot form urea. The nitrogen is released into the blood stream as alanine, and then the liver can remove the nitrogen and dispose it in the form of urea. Pyruvate then is converted into glucose or fatty

acid. Resting muscle acts completely different and uses fatty acid as the main fuel source [7].

Metabolic States at the Organism Level

The body can exist in different states of metabolism. The absorptive state is considered the "fed state." It represents the time when the body is digesting and absorbing nutrients. In this state, anabolism exceeds catabolism. Digestion automatically begins with mastication. Carbohydrate breakdown first starts in the mouth while protein and lipid breakdown begins in the stomach. Exogenous glucose and amino acids are transported from the intestine to the blood. Lipids are packaged into chylomicrons and transported to blood via the lymphatic system. The body is preparing to store for leaner times.

Insulin, one of the most important hormonal regulators of metabolism, is secreted by beta cells of the pancreas. Glucose and the parasympathetic nervous system stimulate the secretion of insulin. Insulin initiates protein kinase pathways stimulating glycogen synthesis in muscle and liver. It also suppresses gluconeogenesis in the liver. Glycolysis in the liver is enhanced increasing the synthesis of fatty acids. The absorptive state promotes glucose entering muscle and adipose tissue. Insulin stimulates the synthesis of glycogen by muscle and the liver. Glucose entering adipose tissue provides glycerol 3-phosphate for the creation of triacylglycerols. Insulin promotes the uptake of branched-chain amino acids by muscle (BCAA). BCAA are valine, leucine, and isoleucine. Insulin favors the building of muscle protein and inhibits degradation of proteins. The absorptive state can take up to 4 hours [7].

The postabsorptive state, also known as the fasting state, occurs after nutrition has been digested, absorbed, and stored. In the postabsorptive state, the body relies on glycogen initially. The fasting state is usually broken up into early and late. The early fasting state is when blood glucose levels begin to decrease. Reflexively, insulin levels decrease, and glucagon levels increase. Glucagon is secreted by alpha cells of the pancreas. Glucagon is the signal for the starvation state. Glycogen storage is mobilized when exogenous glucose is not present. Glucagon triggers glycogen breakdown mainly in the liver. Glycogen is rapidly mobilized. Large amounts of glucose are released from the liver into the blood through the hydrolysis of glucose 6-phosphate. Secondary to demands by peripheral tissues, blood glucose levels are maintained between 70 and 120 mg/dL.

When the body is deprived of nutrition for an extended period, it goes into a "survival mode." This is known as the late fasting stage or preabsorptive stage. Certain organs take priority, such as the brain. Ketones are used as the primary energy source. Fatty acid and triglyceride stores are used to make ketones as starvation continues. Ultimately, during late fasting state, protein from muscle is utilized for glucose synthesis. Low insulin levels trigger the decline of glucose entering muscle and adipose tissue. The overall result from glucagon is the markedly increased release of glucose from the liver's glycogen stores. The muscle and liver use fatty acids as fuel when blood glucose is low. Euglycemia is maintained by the mobilization of glycogen and release of glucose by the liver, the release of fatty acids by adipose tissue, and the shift of the primary fuel source from glucose to fatty acids by muscle and the liver.

When the liver's glycogen stores become depleted, gluconeogenesis continues, but this only replaces the glucose that has been converted to lactate and alanine to serve as a precursor for gluconeogenesis. With the brain oxidizing glucose into carbon dioxide and water, a source of carbon is in demand. This source shifts to glycerol from adipose tissue undergoing lipolysis and hydrolysis of muscle protein.

The third state is refeeding. When transitioning from pre-absorptive (late starvation) to absorptive state, fat is processed the same as if in normal metabolic state. When refed, the liver does not initially take up glucose. It is left for the peripheral tissues. The liver remains in a gluconeogenic mode. Newly created glucose is used to reform glycogen storage. As blood glucose levels rise, the liver replaces its glycogen storage and then processes excess glucose for fatty acid synthesis.

Energy Requirements

The total energy expenditure (TEE) is composed of resting energy expenditure (REE) or basal energy expenditure (BEE), the thermogenesis, and the energy expenditure from activity. REE represents the number of calories required for a 24-hour period by the body in a non-active state. The patient's basic metabolic rate (BMR) accounts for 60–70% of the total energy expenditure [1]. The BMR measurement is based on body weight, size, composition, gender, age, race, etc. Thermogenesis accounts for heat loss, diet portion, composition, and timing of ingestion. This accounts for approximately 10% of TEE [1]. Activity accounts for the remaining energy expenditure. The energy cost of activity is the most variable and can range anywhere between 5% and 30% of TEE in a healthy individual. In the critically ill patient, the energy of activity is minimal, but multiplication factors are included to account for physiologic stress.

Normal Energy Requirements

Normal metabolism supports all the physiologic processes necessary for an organism's survival – energy for respiration, digestion, cellular repair, normal supply of building blocks, and enzymatic synthesis. It is driven by insulin. In general, most energy comes from carbohydrates, but lipids and proteins also can be consumed as fuel. One also usually thinks of building blocks as protein, but lipids and carbohydrates also form integral components of growth, repair, and respiration. To simplify, the energy required for normal metabolism is approximately 20–25 kcal/kg for ideal body weight. For the individual patient, there are predictive equations with proven validity.

Abnormal Energy Requirements

In the highly metabolically stressed individual (i.e., burns), the energy expenditure can be double that of normal REE, driven by catecholamines and other acute phase hormones and mediators. This then makes REE about 35–40 kcal in these patients. In such patients measuring energy is best.

The Measurement of Energy Requirements

Direct Calorimetry

Direct calorimetry measures the heat exchange between the body and the environment. Heat is the direct by-product of energy utilization. If practical, direct calorimetry would be the gold standard. A direct calorimeter is a chamber or structure that encompasses the subject. The chamber is closed and has a double wall surrounded by ice. By monitoring the ice melting, the amount of heat dissipation could be measured. This methodology is not practical in the clinical environment.

Indirect Calorimetry

Because a direct calorimeter is not practical in the clinical environment, indirect calorimetry is considered more the "gold standard." Indirect calorimetry (IC) is the most accurate method of measuring energy expenditure in the critically ill population. The measurement of IC is performed using a metabolic cart, which can determine a patient's REE. The metabolic cart measures expired gas to determine the volume of air in the lungs. The amounts of oxygen and carbon dioxide are measured (VO_2 and VCO_2) in 1-minute intervals. REE and respiratory quotient (RQ) can be indirectly determined by these measurements. The RQ is the ratio of exhaled carbon dioxide to the amount of consumed oxygen. The abbreviated Weir equation is used to calculate the 24-hour REE (Table 1.1). The RQ helps guide the amount and composition of energy delivery. An RQ <0.8 signifies lipid catabolism which may be an indicator of underfeeding or of inappropriate administrations of fat. Increasing caloric intake, often with increased carbohydrates, should improve the RQ. An RQ >1 indicates high carbon administration from carbohydrate overfeeding. This can affect the respiratory drive due to hypercarbia. Normalizing RQ and avoiding carbohydrate overfeeding can aid in the weaning of ventilation [1].

IC is helpful in patients with chronic respiratory failure, acute respiratory distress syndrome, and obesity because equations that calculate REE

Table 1.1 Equations and formulas

Weir equation	REE = [3.9 (VO_2) + 1.1 (VCO_2)] 1.44 VO_2 = oxygen uptake (ml/min) VCO_2 = carbon dioxide output (ml/min)
Respiratory quotient	RQ = VCO_2/VO_2
Harris-Benedict equations (calories/day)	Male: (66.5 + 13.8 × weight) + (5.0 × height) − (6.8 × age) Female: (665.1 + 9.6 × weight) + (1.8 × height) − (4.7 × age)
WHO	r^2 = 0.53, F = 37.8, P <0.001. Men: REE (kcal/day) = 66.5 + 13.75 (*weight*) + 5.0 (*height*) − 6.76 (age) REE (kJ) = 278 + 57.5 (*weight*) + 7.74 (*height*) − 19.56 (age)
Ireton-Jones (spontaneously breathing)	EE = 629-11 (age) + 25 (actual body weight) − 609 (BMI >27 factor = 1)
Ireton-Jones (ventilated)	EE = 1784-11 (age) + 5(actual body weight) + 244 (factor = 1 for males) + 239 (Diagnosis of trauma = 1) + 804 (BMI >27 factor = 1)
Penn State	REE = Harris-Benedict equation (0.85) + minute ventilation (33) + maximum body temperature within 24-hour period (175)-6433

are not as accurate in these patient populations. IC can help determine whether a patient is being over- or underfed and can also help troubleshoot if inadequate calorie delivery is the cause of delayed wound healing. Several factors can alter the accuracy of indirect calorimeter results. Ventilator settings need to remain constant during the performance of the test, as almost any change made during the testing session will affect results. FiO_2 >60%, positive end-expiratory pressure (PEEP) >12 cm H_2O, thoracostomy tube leaks, any movement, bedside nursing care, and changing nutrition are all examples of factors that can alter results of the REE from indirect calorimetry.

Equations to Calculate REE

There are approximately 200 equations published that calculate REE [1]. Some deal with specific disease states, ages, ethnicities, obesity, etc. One of the most commonly used equations is the Harris-Benedict equation. This equation was developed in 1919 by using indirect calorimetry to estimate REE. It accounts for age, gender, height, and weight. The accuracy of the Harris-Benedict equation has been validated in the healthy, adequately nourished person to be within +14% of REE measured by indirect calorimetry. The Harris-Benedict equation tends to underestimate REE in malnourished, critically ill patients by approximately 22% (Table 1.1). It also underestimates REE in the obese population.

Other equations include the Penn State, Ireton-Jones, World Health Organization (WHO), Owen, Mifflin, and Liu formulas [9]. For overweight and obese patients, all equations underestimate REE by approximately 8%. Even though all equations underestimate when compared to IC, WHO and Harris-Benedict are the most accurate [9, 10]. The Penn State and Ireton-Jones equations tend to be the most commonly used in surgical and critically ill patients. They contain modifiers for severity of illness, stress states, weight, height, temperature, and other factors that might affect REE (Table 1.1).

Sources of Energy

Carbohydrates, proteins, and fats are the building blocks of the body. Glucose is the preferred fuel for metabolism. Fat is stored for times of starvation, and then when blood glucose levels are depleted, fat will be oxidized. Protein is also utilized with glucose is depleted.

Carbohydrates

Glucose is the main source for energy production and primary form of fuel for many cells. Dietary guidelines recommend carbohydrates to make up 50–60% of daily calorie intake.

Carbohydrates are divided into three classifications: monosaccharide, oligosaccharide, and polysaccharide. Monosaccharides cannot be

hydrolyzed any further and are made up of aldoses and ketoses. Aldoses, including glucose, galactose, mannose, and ribose, contain an aldehydic group. Ketoses like fructose contain a ketonic group. Oligosaccharides contain only a few carbohydrate chains linked by a glycosidic bond and include disaccharides and trisaccharides. Polysaccharides, also called glycans, are carbohydrates that contain ten or more monosaccharide chains. Polysaccharides are subclassified into homopolysaccharides (made up of identical monosaccharide chains) and heteropolysaccharide (made up of different monosaccharide chains). Common homopolysaccharides are starch, glycogen, cellulose, and dextran. Common heteropolysaccharides are pectin and mucopolysaccharide.

Proteins

Proteins are complex formations of amino acids. Daily protein requirements are dependent on the rate of protein catabolism [11]. In any hypermetabolic state, the rate of protein catabolism is significantly increased [12]. Therefore, normal protein requirements of 0.8–1 g/kg are increased in critically ill individuals to a minimum of 1.2–1.5 g/kg [13]. These increased protein requirements are in part due to the production of acute phase reactants in the critically ill, increased wound healing, and mobilization of peripheral protein stores for gluconeogenesis. Starvation and decreased mobility also increase protein turnover [14]. This can lead to acute decrease in lean muscle mass in the critically ill.

Certain amino acids are needed in a higher quantity in stressed states compared to normal conditions. For example, acute phase proteins contain high amounts of tryptophan, tyrosine, and phenylalanine, so in the stressed state there is increased need for these amino acids. Increased muscle breakdown can occur to provide these amino acid components. Loss of lean body mass in ICU patients is linked to increased complication rates including pneumonia, impaired wound healing, and even increased mortality [15].

In critically ill patients, protein losses, including those secondary to ongoing chest or abdominal drainage, severe burns or breakdown of the skin, proteinuria, or intestinal secretions, should be fully replaced. As stress resolves, the individual's protein needs decrease. According to ASPEN and ESPEN guidelines, patients with severe trauma (ISS >18) or multiple complications with moderate trauma may require increased protein intake with immune-enhancing diets that include protein of 2.2–2.5 g/kg daily. There is thought that these diets are associated with less infections, lower incidence of multi-system organ failure, and shorter hospital and ICU lengths of stay. These diets should only be continued, however, for 7–10 days, and then patients can be transitioned back to more standard nutritional repletion [13, 16]. Of note, protein requirements may be even higher than this in patients with burns or severe sepsis, with requirements of even up to 2.5–3 g/kg.

The calculation of a nitrogen balance can help determine the effectiveness of protein intake. A negative energy balance is noted to correlate with increased morbidity and mortality in the critically ill patient [17]. Nitrogen balance is calculated as nitrogen intake minus the output. Protein is 16% nitrogen, so the nitrogen intake is calculated by taking daily protein intake in grams and dividing by 6.25. The output calculating requires a 24-hour urine measurement to obtain a urine urea nitrogen. Urea excretion in the stool is estimated as 4–6 g/d and can be added to the total. It is therefore important to note that in states of diarrhea, the nitrogen output calculation may be inaccurate. Aiming for a positive nitrogen balance of 4–6 g/d is recommended [17].

Protein overfeeding has significant disadvantages, including azotemia and potentially even renal failure. Recent studies in the critically ill population demonstrate that provision of protein is linked to positive outcomes when compared to provision of total energy.

Lipids

Fatty acid oxidation is a mitochondrial aerobic process that breaks down a fatty acid into acetyl CoA units. Acetyl CoA is a common intermediate between metabolic pathways. Fatty acids can

be converted to ketone bodies which are used as fuel for extrahepatic tissues. Cholesterol, steroids, arachidonic acid, and eicosanoids are all derived from fatty acids. Excess fatty acids are stored as triglycerides in adipose tissue.

The maximum lipid delivery is 1–1.2 g/kg/d. An anti-inflammatory lipid profile, which includes omega-3, borage oil, and antioxidants, has not improved outcomes in patients with ARDS or sepsis. Omega-6 fatty acid increases inflammation. Current ASPEN guidelines recommend holding soy-based parenteral fat emulsions for the first week in critically ill patients as these products contain high levels of omega-6 fatty acids, known to be pro-inflammatory. Guidelines recommend a maximum dose of 100 g/wk if there is a concern for essential fatty acid deficiency. Alternatives to soy-based lipid emulsions are now available in the United States. SMOF (soybean oil, medium-chain triglycerides, olive oil, and fish oil) emulsion can be considered in the critically ill patient [13].

Alternate Sources of Energy

There are some new developments that suggest lactate is used by mitochondria as a fuel source and the "buildup" of lactate is not secondary to a lack of oxygen but more of an issue with the mitochondria inability to process the lactate. New research shows the brain can switch to lactate as a fuel source during higher levels of activity using the by-product of muscles as a secondary fuel [18].

Normal Metabolic Processes

The major metabolic pathways include glycolysis, gluconeogenesis, glycogen metabolism, fatty acid metabolism, citric acid cycle, oxidative phosphorylation, and amino acid metabolism.

Cofactors and Enzymes

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

Most commercially available formulas provide daily recommended intake (DRI) for vitamins and trace elements (see Table 1.2) [20]. Patients with severe malnutrition, high losses as with enteric fistulae, bypass procedures, and/or malabsorption may require additional supplementation. Many vitamins act as cofactors for various metabolic processes, including a vital role in the production of ATP. Deficiencies lead to detrimental physiologic conditions.

Vitamin B6 deficiency is associated with hyperhomocysteinemia and hyperglycemic states in surgical intensive care unit patients [20, 21]. Supplementation increases the immune response of critically ill patients [22]. Signs and symptoms or vitamin B1 deficiency are nonspecific and include paresthesias, ascending paralysis of motor neurons, memory loss, high-output cardiac failure, edema, and lactic acidosis. Appropriate supplementation can prevent negative consequences [23]. Vitamin B2 (riboflavin) is a key factor for flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), two important components of oxidative reduction. A large proportion of critically ill individuals have suboptimal vitamin B2 status, which can be significantly improved with supplementation. However, this improvement is transient and deteriorates with discontinuation of the intake [24, 25].

Table 1.2 Recommended daily allowance of vitamins and trace minerals

	M/F	Males	Females		
Fat-soluble vitamins			Typical	Pregnant	Lactating
A (mcg)		900	700	770	1300
D (mcg)	15–20				
E (mg)	15				19
K (mcg)		120	90		
Water-soluble vitamins					
B_1 (mg)		1.2	1.1	1.4	1.4
B_2 (mg)		1.3	1.1	1.4	1.6
B_5 (mg)	5			6	7
B_6 (mg)		1.3–1.7	1.5	1.9	2
B_{12} (mcg)	2.4			2.6	2.8
C (mg)		90	75	85	120
Folate (mcg)	400			600	500
Biotin (mcg)	30				35
Other nutrients					
Choline (mg)		550	425	450	550
Trace elements					
Copper (mcg)	900			1000	1300
Chromium (mcg)		30–35	20–25	30	45
Fluoride (mg)		4	3		
Iodine (mcg)	150			220	290
Iron (mcg)		8	18	27	9
Manganese (mg)		2.3	1.8	2	2.6
Molybdenum (mcg)	45			50	50
Selenium (mcg)	55			60	70
Zinc (mg)		11	8	11	12

Adapted from Ref. [19]

Therapeutic Interventions

Outcome specific data is lacking regarding certain vitamin deficiencies in critical illness; therefore provision of adequate supplementation should be the goal, to provide adequate substrate and cofactors necessary to support the metabolic demands of the stressed patient.

Normal Metabolism

In a homeostatic state, the human body will utilize the equivalent of the kilocalories that are consumed. The substrate that the body preferentially metabolizes is glucose, which undergoes aerobic metabolism in the mitochondria to produce ATP. Complex carbohydrates, fats, and proteins can all be metabolized to provide glucose for aerobic respiration and other substrates that can be utilized to produce ATP necessary for cellular division, growth, and maintenance of homeostasis. When disease processes affect the consumption of nutrients, metabolism of those nutrients, or lead to an increased need for nutrients, this alters the metabolism of the patient.

When nutritional metabolism is marginally changed, the patient's body will reach a new or different steady state without loss of function, which is defined as adaptation. One example of this is an overall decrease in the resting energy expenditure during early starvation to preserve available resources for essential functions. Over time, adaptation allows the body to continually change its composition without a detrimental effect to the patient's overall health. However, once the disturbances become more severe, then the homeostatic capacity may be overcome. This can lead to accommodation, which is defined as

an adaptive response to a disturbance that allows survival but results in some degree of serious consequences to health or physiologic function [26].

Perturbations of Metabolism

Starvation

Starvation leads to a myriad of effects that are progressive in a negatively correlative fashion based on the time frame of starvation. During the initial hours following a meal, the blood glucose levels drop as the cells utilize the available glucose molecules. In response to blood glucose levels dropping, the β cells of the pancreas decrease their insulin secretion and the α cells begin to secrete glucagon. Glucagon acts primarily in the liver, activating a G-coupled receptor and stimulating the transcription and translation of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase to stimulate gluconeogenesis, breaking down glycogen stores into glucose [27]. The glucose molecules are released by the hepatocytes into circulation, which, when coupled with the activity of glucagon on muscle and adipose tissue to prevent uptake of glucose, increases the blood glucose levels. Glucagon also acts peripherally to inhibit fatty acid synthesis through reduced production of pyruvate molecules and inhibiting the activity of acetyl CoA carboxylase [28]. It also has been demonstrated to increase lipolysis in white adipose tissue, with an increase in ketone body production and fatty acid oxidation with decreased fatty acid esterification [29, 30]. In the myocytes, decreased circulating insulin levels lead to decreased activation of glucose transporters, but free fatty acids are still able to cross the cell membranes freely. Due to this process, these fatty acids are preferentially utilized by the kidneys and muscles as substrates for energy, as opposed to their normal mechanism of using glucose.

After approximately 12–24 hours of starvation, the liver's glycogen stores are depleted. This leads to a switch in gluconeogenesis derived from protein stores, with the production of gluconeogenic amino acids that can be utilized by the cells for cellular respiration. At this point, the body enters a catabolic state, and lean body mass is utilized to continue to sustain the energy expenditure. The primary sites of gluconeogenesis are the liver and the kidneys, with this process starting in the kidneys within 4–6 hours after the last meal [31]. Concurrently, the muscles begin hydrolyzing their protein stores to produce glutamine and alanine, which are utilized by the hepatocytes for gluconeogenesis and the myocytes preferentially utilize leucine for oxidation and production of ATP, sparing other essential gluconeogenic substrates [31].

After 2–3 days of starvation, lipolysis increases to provide most of the resting energy expenditure. Fatty acid β-oxidation yields free fatty acids that result in two-carbon chain molecules that can be utilized to produce pyruvate, which will reenter the Krebs cycle to generate ATP. As these free fatty acids are utilized by the hepatocytes, large amounts of acetoacetate and 3-hydroxybutyrate build up. The liver releases these ketone bodies into the systemic circulation, which is utilized by the brain and heart for energy. Due to their structure, ketone bodies can pass through the blood-brain barrier, allowing them to be the preferential energy source for the brain as the starvation state continues. By 21 days of starvation, the brain uses almost exclusively ketone bodies for fuel [32].

Once the fat stores are depleted, proteins in the muscles are the only source remaining and these quickly deplete. Immunosuppression often results, making patients more susceptible to infections such as pneumonia. This further worsens the stressed state of the body, and the metabolic derangements often lead to electrolyte derangements as well. Multiple organs undergo autophagy to provide some fuel for energy, which can lead to death when coupled with electrolyte abnormalities that precipitate cardiac arrhythmias.

Obesity

Obesity is a widespread epidemic that increases the cost of healthcare. Obesity is defined by the WHO as a BMI $\geq$30, and approximately 1/3 of the American population fits within this category [33]. Due to this large subset of patients, there have been many studies on the effect that obesity has on other disease processes [34]. One of the

more interesting results of these studies have demonstrated a protective effect of obesity in several disease processes, namely, ARDS or acute lung injury (ALI) [35]. A recent meta-analysis of 24 studies with over 9 million subjects found that obese patients were at a higher risk of developing ARDS or ALI, but their risk of morality was lower than patients who were not obese [34]. This effect has been coined the "obesity paradox" and is thought to be due in part to the increased levels of adipokines, such as leptin and IL-10, as well as lower levels of IL-6, TNF-α, and MCP-1, the higher energy stores available for obese patients in metabolic stress [33, 36, 37].

Despite the observed effect of the "obesity paradox," the comorbidities associated with obesity, such as diabetes mellitus, obstructive sleep apnea, and hypertension, lead to an increased risk of morbidity in obese patients with acute disease that alters their metabolism [38]. This is due in part to the immunomodulatory changes in obese patients as well as the effects of their comorbidities and the neuroendocrine interactions between the adipose tissue, gastrointestinal tract, and neurologic system.

Metabolic Stressors

Surgical stress, trauma, burn injuries, and critical illnesses can result in an adaptive state where catabolism predominates, leading to energy consumption and tissue breakdown. During these conditions, inflammatory responses are upregulated with numerous interleukins and tumor necrosis factor alpha. The systemic inflammatory response also stimulates the release of other hormones, such as cortisol and glucagon, which can drastically change the metabolic balance in patients. The degree to which the host experiences the stress is directly proportional to the catabolic response; these effects can persist for weeks to months following the injury of illness.

Metabolic stressors create a stressed metabolic milieu. Intially described by Cuthbertson, "the post-shock metabolic response to injury" "ebbs" and "flows [39]." The early post injury patient exhibits a depressed metabolic state (the "ebb"). This phase begins immediately after the inciting insult and is characterized by tissue perfusion. Physiologic stress leads to a catecholamine, cortisol, and glucagon surge, which results in insulin resistance and hyperglycemia by increasing glycogenolysis, lipolysis, and gluconeogenesis. The onset of the "flow" phase is signaled by the restoration of oxygen delivery and metabolic substrate. Elevated circulating catecholamines lead to increased cardiac output and increase oxygen consumption globally in the body. Interleukins, such as IL-1, IL-2, and IL-6, increase the body temperature and cellular turnover of immune cells, leading to increased energy expenditure [40]. Lipolysis is blocked, and protein serves as an endogenous source of fuel during a stressed metabolic state. The initially ebb phase starts immediately after the initial stress and tends to peak around 3–5 days after insult. If the primary threat is not removed (i.e., source control), then the body remains in a deleterious state losing protein and muscle. This is very common in the critically ill population.

The severity of the stressor can be correlated by examining the resting energy expenditure (REE), based on indirect calorimetry. Severe stressors such as sepsis and burns can increase the REE anywhere from 20% to 60% and 40% to 80%, respectively [41, 42]. Even minor stressors, such as a single long bone fracture, can increase the REE 10–30%. These catabolic drivers are exacerbated by the wound healing process which requires increased energy and increased nutrients, increasing both protein catabolism and insulin resistance to allow cellular ATP production [43]. Part of the protein catabolism generates large amounts of alanine and glutamine, as well as other conditionally essential amino acids, as substrates for the increased REE [44]. Cellular sensing pathways for amino acids are further dysregulated in stressed states with increased pulsatile release of growth hormone, leading to increased cellular signaling for protein catabolism to produce conditionally essential amino acids [45, 46].

The body reacts to the initial inflammatory states with a compensatory anti-inflammatory response syndrome (CARS), which can present its own problems for the surgeon(s) caring for the patient. During this time, IL-6 elevation persists, and there is a rapid expansion of myeloid-derived

suppressor cells (MDSCs), which secrete IL-10 and TGF-β and continue to stimulate protein catabolism [47, 48]. These responses result in immunosuppression, lean body mass wasting, and an increased risk of long-term complications, such as chronic kidney disease [49]. As these processes continue over the course of weeks, they become part of a multifactorial syndrome of persistent inflammation-immunosuppression catabolism syndrome (PICS). These prolonged effects of metabolism derangement demonstrate the necessity of proper nutrition during acute inflammatory states.

The primary objective is to decrease the catabolic state by obtaining source control and treatment of the original and subsequent stresses, such as secondary infections. Providing optimal nutritional support with the appropriate energy sources is crucial. Enteral nutrition is preferred over parenteral, but parenteral is preferred over no nutrition if approaching 5–7 days without nutrition. Hard indications for parenteral nutrition include bowel obstruction, high-output fistulas, short gut syndrome, and malabsorptive diseases. Providing nutrition too early can be harmful, so a balance between intestinal and splanchnic perfusion and timing of enteral nutrition is important.

As nutritional supplementation is begun, it is important to watch for refeeding syndrome, defined as the potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving artificial refeeding. The underlying causative factor of refeeding syndrome is the metabolic and hormonal changes caused by rapid refeeding, whether enteral or parenteral. These shifts result from hormonal and metabolic changes and may cause serious clinical complications. The hallmark biochemical feature of refeeding syndrome is hypophosphatemia. However, the syndrome is complex and may also feature abnormal sodium and fluid balance; changes in glucose, protein, and fat metabolism; thiamine deficiency; hypokalemia; and hypomagnesemia.

Genomics Impacting Metabolism

There is considerable promise in genetic studies that identify diseases of metabolism and guide therapy for individual patients. Each individual patient can exhibit a unique response to injury or insult. The uniqueness of the response is controlled by the individual genetic footprint [50]. As the scientific community grows to understand the genetic compositions and alterations, new developments can aid clinicians to improve overall outcomes.

Metabolomics

Metabolomics is the systematic identification and quantification of metabolic products. Mass spectrometry, NMR spectroscopy, and genomic profiling are the techniques used for metabolomic identification. Genomic analysis is increasing in speed and accuracy improving the understanding of metabolites. Both mass spectrometry and NMR spectroscopy can measure large amounts of small molecules. Multiple associations are being investigated such as the relationship between intestinal microbiome and obesity and others.

Inborn Errors in Metabolism

Inborn errors of metabolism are a very large group of rare genetic diseases that result from a defective enzyme causing in a block in a metabolic pathway. This interruption is usually clinically significance and impacts overall outcome. Genetic metabolic errors include urea cycle disorders, organic acidemias, fatty acid oxidation defects, amino acidophathies, carbohydrate disorders, and mitochondrial disorders. The study of this field is ever evolving and holds exciting prospects for the future of medicine.

References

1. Lawson CM, Long CA, Bollig R, Daley BJ. Introduction to metabolism. In: Davis KA, Rosenbaum SH, editors. Surgical metabolism: the metabolic care of the surgical patient. New York/Heidelberg/Dordrecht/London: Springer; 2014. p. 1–21.
2. "Meta" and "Ballein." Merriam-Webster.com. 2019. http://www.merriam-webster.com. 31 Mar 2019.
3. Eknoyan G. Santorio Sanctorius (1561–1636): founding father of metabolic balance studies. Am J Nephrol. 1999;19(2):226–33.

4. Da Poian AT, El-Bacha T, Luz MRMP. Nutrient utilization in humans: metabolism pathways. Nat Educ. 2010;3(9):11.
5. Osellame LD, Blacker T, Duchen M. Cellular and molecular mechanisms of mitochondrial function. Best Pract Res Clin Endocrinol Metab. 2012;26(6):711–23.
6. Robinson PK. Enzymes: principles and biotechnological applications. Essays Biochem. 2015;59:1–41.
7. Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5th ed. New York: W.H. Freeman; 2002.
8. Alvarado A, Arce I. Metabolic functions of the lung, disorders and associated pathologies. J Clin Med Res. 2016;8(10):689–700.
9. de Oliveira EP, Orsatti FL, Teixeira O, Maestá N, Burini RC. Comparison of predictive equations for resting energy expenditure in overweight and obese adults. J Obes. 2011;2011:534714. https://doi.org/10.1155/2011/534714. Epub 2011 Jul 21.
10. 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(2):241–7. https://doi.org/10.1093/ajcn/51.2.241.
11. Marino PL. The ICU book. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007.
12. Williams FN, Herndon DN, Jeschke MG. The hypermetabolic response to burn injury and interventions to modify this response. Clin Plast Surg. 2009;36(4):583–96.
13. McClave S, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, 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. 2016;40(2):159–211.
14. Genton L, Romand JA, Pichard C. Basics in clinical nutrition: nutritional support in trauma. e-SPEN, Eur e-J Clin Nutr Metab. https://clinicalnutritionespen.com/article/S1751-4991(09)00059-6/pdf. Accessed 18 Mar 2019.
15. Preiser JC, van Zanten AR, Berger MM, Biolo G, Casaer MP, Doig G, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care. 2015;19(1):35.
16. McClave SA, DiBaise JK, Mullin GE, Martindale RG. Nutrition therapy in the adult hospitalized patient. Am J Gastroenterol. 2016;111:315–34.
17. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, Laviano A, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36:623–50.
18. Riske L, Thomas RK, Baker GB, Dursun SM. Lactate in the brain: an update on its relevance to brain energy, neurons, glia, and panic disorder. Ther Adv Psychopharmacol. 2017;7(2):85–9.
19. Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. Nut Clin Pract. 2012;27(4):440–91.
20. Hou CT, Wu YH, Huang PN, Cheng CH, Huang YC. Higher plasma pyridoxal 5′-phosphate is associated with better blood glucose responses in critically ill surgical patients with inadequate vitamin B-6 status. Clin Nutr. 2011;30(4):478–83.
21. Hou CT, Wu YH, Cheng C, Huang PN, Huang YC. Higher plasma homocysteine is associated with lower vitamin B6 status in critically ill surgical patients. Nutr Clin Pract. 2012;27(5):695–700.
22. Cheng CH, Chang SJ, Lee BJ, Lin KL, Huang YC. Vitamin B6 supplementation increases immune responses in critically ill patients. Eur J Clin Nutr. 2006;60(10):1207–13.
23. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. Curr Opin Clin Nutr Metab Care. 2011;14(6):610–7.
24. Vasilaki AT, McMillan DC, Kinsella J, Duncan A, O'Reilly DS, Talwar D. Relation between riboflavin, flavin mononucleotide and flavin adenine dinucleotide concentrations in plasma and red cells in patients with critical illness. Clin Chim Acta. 2010;411(21–22):1750–5.
25. Gariballa S, Forster S, Powers H. Riboflavin status in acutely ill patients and response to dietary supplements. J Parenter Enter Nutr. 2009;33(6):65–1.
26. Becher RD, Puyana J. Nutritional support and electrolyte management. In: Moore EE, Feliciano DV, Mattox KL, editors. Trauma 8e. New York: McGraw-Hill; 2019; http://accesssurgery.mhmedical.com/content.aspx?bookid=2057&sectionid=156219787. Accessed 18 Mar 2019.
27. Zhang X, Yang S, Chen J, Su Z. Unraveling the regulation of hepatic gluconeogenesis. Front Endocrinol (Lausanne). 2019;9:802.
28. Berg JM, Tymoczko JL, Starvation SL. Biochemistry. 5th ed. New York: W. H. Freeman; 2002.
29. Richter WO, Robl H, Schwandt P. Human glucagon and vasoactive intestinal polypeptide (VIP) stimulate free fatty acid release from human adipose tissue in vitro. Peptides. 1989;10:333–5.
30. Berg JM, Tymoczko JL, Stryer L. Section 30.3, food intake and starvation induce metabolic changes. In: Biochemistry. 5th ed. New York: WH Freeman; 2002.
31. Marks DB, Marks AD, Smith CM. Fasting. In: Smith C, Marks A, Lieberman M, editors. Basic medical biochemistry – a clinical approach. Baltimore: Williams & Wilkins; 1996. p. 27–34.
32. Gropper SS, Smith JL, Groff JL. Protein. In: Gropper SS, Smith JL, editors. Advanced nutrition and human metabolism. 5th ed. Belmont: Wadsworth Learning; 2009. p. 179–249.
33. Zhi G, Xin W, Ying W, Guohong X, Shuying L. "Obesity paradox" in acute respiratory distress syndrome: asystematic review and meta-analysis. PLoS One. 2016;11(9):e0163677.
34. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010;303:235–41.

35. Gaulton TG, Weiner MG, Morales KH, Gaieski DF, Mehta J, Lautenbach E. The effect of obesity on clinical outcomes in presumed sepsis: a retrospective cohort study. Intern Emerg Med. 2014;9:213–21.
36. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. Am J Physiol Heart Circ Physiol. 2005;288(5):H2031–41.
37. Nguyen AT, Tsai CL, Hwang LY, Lai D, Markham C, Patel B. Obesity and mortality, length of stay and hospital cost among patients with sepsis: a nationwide inpatient retrospective cohort study. PLoS One. 2016;11(4):e0154599.
38. Prospective Studies Collaboration, Whitlock G, Lewington S, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083–96.
39. Cuthbertson DP. Post-shock metabolic response. Lancet. 1942;1:343–37.
40. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340(6):448–54.
41. Plank LD, Hill GL. Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. World J Surg. 2000;24(6):630–8.
42. Kreymann G, Adolph M, Mueller MJ. Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional Medicine Energy expenditure and energy intake—guidelines on parenteral nutrition, chapter 3. Ger Med Sci. 2009;7:25.
43. Martindale R, Shikora S, Nishikawa R, et al. The metabolic response to stress and alterations in nutrient metabolism. In: Shikora S, Matindale R, editors. Nutritional considerations in the internsive care unit. Dubuque: Kendall Hunt Publishing; 2002. p. 11–20.
44. Reeds PJ. Dispensable and indispensable amino acids for humans. J Nutr. 2000;130:1835S–40S.
45. Efeyan A, Comb WC, Sabatini DM. Nutrient-sensing mechanisms and pathways. Nature. 2015;517:302–10.
46. Ingels C, Gunst J, Van den Berghe G. Endocrine and metabolic alterations in sepsis and implications for treatment. Crit Care Clin. 2018;34(1):81–96.
47. Mira JC, Gentile LF, Mathias BJ, Efron PA, Brakenridge SC, Mohr AM, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45:253–62.
48. Mathias B, Delmas AL, Ozrazgat-Baslanti T, Vanzant EL, Szpila BE, Mohr AM, et al. Human myeloid-derived suppressor cells are associated with chronic immune suppression after severe sepsis/septic shock. Ann Surg. 2017;265:827–34.
49. Gentile LF, Cuenca AG, Efron PA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
50. River EP, McIntyre L, Rivers KK. Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity. CMAJ. 2005;173(9):1054–65.

Fluid and Electrolytes

2

Bishwajit Bhattacharya and Linda L. Maerz

Introduction

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

B. Bhattacharya · L. L. Maerz (✉)
Department of Surgery, Yale New Haven Hospital, New Haven, CT, USA
e-mail: linda.maerz@yale.edu

Total Body Water and the Fluid Compartments

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

TBW is comprised of the intracellular and the extracellular compartments. Intracellular fluid (ICF) makes up two thirds of TBW, and extracellular fluid (ECF) accounts for the remaining one third. ECF is subdivided into the intravascular and interstitial spaces. The intravascular space accounts for 25% of the ECF and 8% of the TBW; this space contains the plasma volume. The interstitial space comprises the remaining 75% of the ECF and 25% of the TBW; this space contains a free phase of fully exchangeable water and a bound phase of minimally exchangeable water. The transcellular compartment is an additional ECF designation; this compartment contains cerebrospinal fluid, synovial fluid, the water in cartilage and bone, eye fluids, and lubricants of the serous membranes. This type of fluid is poorly exchangeable and comprises approximately 4% of the TBW. The exchangeable components of the compartments comprising TBW are in dynamic equilibrium [5].

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_2

Effective circulating volume is the portion of the ECF that perfuses the organs. Under normal physiologic conditions, this corresponds to the intravascular volume. This relationship is altered in some disease states. For example, in congestive heart failure and in patients who have arteriovenous fistulae, the intravascular volume and total body salt and water are high, but effective circulating volume is low. A different type of alteration of the physiologic state occurs in bowel obstruction, pancreatitis, and the sepsis syndrome. Under these circumstances, the total ECF remains constant or increases initially, but intravascular volume is significantly decreased due to external losses or vasodysregulation. These conditions result in "third-space loss." This concept was initially recognized over 50 years ago, when experimental models of early hemorrhagic shock and elective operative tissue trauma were used to investigate changes in the body fluid compartments [6]. It was observed that ECF decreased more than the measured loss of plasma volume in these experiments. Shock and operative trauma were hypothesized to cause extracellular fluid to be sequestered in an "unexchangeable" compartment as a result of capillary leak [6, 7]. This heretofore undefined ECF compartment became known as the "loss to the third space," "deficit in functional extracellular volume," or the "nonanatomic third-space loss" [6, 8, 9]. In the ensuing decades, this concept was accepted as convention; some would argue resulting in unnecessarily aggressive resuscitation and perioperative fluid management strategies in an effort to compensate for fluid lost to the third space. The original "third space" literature was reviewed by Brandstrup and colleagues in the early 2000s. They determined that the evidence in the early literature supporting the concept of the third space was based on flawed methodology [10, 11]. However, it is clear that disease processes such as bowel obstruction, pancreatitis, severe sepsis, and septic shock warrant aggressive fluid management strategies because the intravascular volume is markedly diminished in these clinical scenarios. Hypoperfusion is the end result in these cases and is best managed with restoration of circulating volume and treatment of vasodysregulation with vasoactive pressor agents.

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

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

The principles of osmosis dictate the movement of water between fluid compartments. Osmotic equilibrium occurs when two solutions separated by a semipermeable membrane equalize the concentration of osmotically active particles on either side of that membrane as water moves along a concentration gradient. Osmolarity

is measured in milliosmoles per liter, mOsm/L. Osmolality is measured in milliosmoles per kilogram H_2O, mOsm/kg H_2O. Both define the osmotic activity of particles in solution and are considered equivalent if the concentration of solutes is very low [5].

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

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

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

Volume Control Mechanisms

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

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

The principal cells lining the renal collecting ducts control the fine-tuning of body water homeostasis by regulating water resorption through aquaporin-2 (AQP_2), aquaporin-3 (AQP_3), and aquaporin-4 (AQP_4). AQP_3 and AQP_4 are embedded in the basolateral plasma membrane. ADH binds to the vasopressin-2 (V_2)

receptor on the basal membrane of the renal collecting duct. This triggers redistribution of AQP_2 from intracellular vesicles into the apical plasma membrane. Water enters into the cells via AQP_2 and exits through AQP_3 and AQP_4 [21].

The mechanism of action of ADH with respect to the water permeability of the renal collecting duct has therapeutic implications. A number of nonpeptide V_2 antagonists (vaptans) have been developed. The mixed V_2/V_{1a} antagonist conivaptan was approved by the US Food and Drug Administration (FDA) in 2005 for intravenous use in the treatment of euvolemic and hypervolemic hyponatremia. Conivaptan produces aquaresis (solute-free water excretion), resulting in increased serum sodium levels, free water clearance, urine flow, and plasma osmolality [22, 23]. Vaptans developed subsequently include lixivaptan, tolvaptan, and satavaptan. Of these, tolvaptan has been approved by the US FDA. However, ongoing investigation is required to establish the role of these drugs in routine clinical practice [24].

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

Endocrine and hormonal factors also play a role in volume control mechanisms. The renin–angiotensin–aldosterone system is the primary hormonal mediator of volume control. The natriuretic peptide system is an endocrine mechanism that regulates blood volume and electrolyte balance. There are three members of the mammalian natriuretic peptide family: atrial natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [25, 26].

Renal prostaglandins (PGE_2 and PGI_2) may play a role in volume control, especially in conditions such as sepsis and jaundice. Normally, inhibition of prostaglandin production has little effect on renal function. However, nonsteroidal anti-inflammatory agents (inhibitors of cyclooxygenase) can precipitate renal failure in patients with renal dysfunction due to loss of the protective effects of renal prostaglandins [27].

Endothelins are peptide vasoconstrictors involved in volume and pressure regulation [28]. Nitric oxide (NO) is a free radical produced by nitric oxide synthases and is involved in many biologic functions, including volume and pressure regulation [29]. There is interaction between the endothelin and NO systems. In general, NO and endothelin actions oppose one another.

Baseline Water and Electrolyte Requirements

Sensible water losses can be measured and include urine (800–1500 mL/24 h), stool (0–250 mL/24 h), and sweat (minimal). Sweat is a hypotonic mixture of electrolytes and water and does not contribute significantly to daily water loss except in very arid and hot climates. Insensible water losses are unmeasurable and include loss from the skin and lungs. This accounts for 600–900 mL/24 h (8–12 mL/kg/day). Insensible water loss increases 10% for each degree of body temperature >37.2 °C. Therefore, fever is a significant contributor to insensible water loss. The normal daily sodium requirement is 1–2 mEq/kg/24 h; the potassium requirement is 0.25–0.50 mEq/kg/24 h [5].

Parenteral Solutions

Intravenous fluids are used for maintenance and resuscitation of surgical patients. The two broad categories of parenteral solutions are crystalloids and colloids. The appropriate choice of crystalloid or colloid solution depends on main-

tenance fluid requirements, fluid deficits, and ongoing fluid losses.

Lactated Ringer's (LR) solution is a commercially available crystalloid and has a composition similar to plasma. It is usually utilized as a resuscitative fluid to replace loss of fluid with a similar composition to plasma and is ideal when the patient's serum electrolyte concentrations are normal. LR has a relatively low sodium content (130 mEq/L), which makes this solution slightly hypotonic. Hyponatremia may result with excessive or prolonged use or in patients who have impaired renal function and diminished ability to excrete free water. This may become problematic in patients who have traumatic brain injuries and other conditions that mandate a higher Posm. The lactate in LR occurs as sodium-lactate, which dissociates at physiologic pH. The lactate anions are metabolized to bicarbonate and, therefore, do not contribute to acidosis under normal conditions [30].

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

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

Hypertonic saline (HTS) solutions are utilized to replace sodium deficits in symptomatic hyponatremia. Most commonly used are 3% NaCl and 1.5% NaCl. The former should be administered via central venous access; the latter may be administered via peripheral veins. HTS has also been suggested for early resuscitation of hypovolemia in trauma and burn patients. Intravascular volume is increased more quickly, and the total resuscitation volume may be decreased compared to standard crystalloid resuscitation. However, caution should be used because of the potential for induction of significant acid–base and electrolyte abnormalities [31].

Naturally occurring plasma volume expanders include albumin preparations (4, 5, 20, and 25%) and fresh frozen plasma. Only 5 and 25% albumin are available in the United States. Albumin preparations are usually prepared in NSS; therefore, large volume administration can result in HCMA. Additionally, the albumin molecule is of such a molecular weight that it readily passes through capillary pores that open in conditions that create a capillary leak [14, 15]. The SAFE trial demonstrated that albumin administration is as "safe as saline" and that hypoalbuminemia is associated with not only decreased colloid oncotic pressure but also perturbed pharmacologic agent carriage, detoxification, and immune responsivity [32].

Synthetic colloids have been utilized as resuscitative fluids, especially in surgical patients. Hydroxyethyl starch (HES) preparations are the most common. They are categorized by their average molecular weight, degree of substitution (DS) (molar substitution: # hydroxyethyl groups per 100 glucose groups), and concentration. Starches include hetastarch (DS = 0.7), pentastarch (DS = 0.5), and tetrastarch (DS = 0.4). Six percent solutions have been the most commonly used in the United States. The vehicles for the starches differ. Hespan is a 6% solution of hetastarch in a NSS vehicle, while Hextend is the identical starch in a solution with a composition similar to LR. Some interventional trials have noted an association with acute kidney injury or acute renal failure with the use of starch preparations [33]. Resuscitation with starch solutions alone provides little to no free water. Therefore, starch administration must occur in conjunction with maintenance fluid administration to mitigate against hyperoncotic renal injury [34].

Maintenance Fluid Therapy

Maintenance fluid therapy replaces fluids normally lost during the course of a day. Conversely, resuscitative fluid therapy replaces preexisting deficits or additional ongoing losses. Maintenance

and resuscitative fluid therapy may occur simultaneously, but two different solutions are used to achieve differing goals.

Weight-based formulas are used to calculate maintenance water requirements, accounting for both sensible and insensible losses. One of the most commonly used is the "4–2–1 rule":

First 10 kg body weight: 4 cc/kg/h
Second 10 kg body weight: 2 cc/kg/h
Each additional 10 kg body weight: 1 cc/kg/h

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

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

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

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

Resuscitative Fluid Therapy

The goal of resuscitative fluid therapy is to replace preexisting deficits and ongoing fluid losses. Crystalloid is the most common broad category of resuscitative fluid. An isotonic (or nearly isotonic) salt solution without added dextrose is utilized. LR is the most common resuscitative fluid used in surgical patients [35, 36].

The capillary endothelium is permeable to the components of an isotonic salt solution. Therefore, crystalloid distributes between the intravascular and interstitial spaces in proportion to the starting volumes of these spaces. Since the intravascular space comprises 25% of the ECF and the interstitial space comprises 75% of the ECF, the resultant ratio is 1:3. For each liter of crystalloid infused intravenously, 250 cc remains in the intravascular space, and 750 cc diffuses into the interstitial space [12]. Additionally, crystalloid has pro-inflammatory effects [37, 38]. Strategies to limit these inflammatory effects have been investigated [39]. Limited intravascular volume expansion and the pro-inflammatory effects of crystalloid are the cornerstone of the crystalloid versus colloid debate from a historical perspective.

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

The use of exogenously administered albumin in critically ill patients was analyzed in a Cochrane report published in 1998. In the three categories of patients studied (those with hypovolemia, burns, or hypoalbuminemia), the risk of death in the albumin-treated groups was higher than in the comparison groups [40, 41]. This review was criticized for various reasons, including the inclusion characteristics and small volume effects limitations. Subsequently, the SAFE (*S*aline versus *A*lbumin *F*luid *E*valuation) trial indicated no difference between albumin and saline in a double-blind randomized study of approximately 7000 critically ill patients. These patients did not require massive plasma volume administration. Albumin was noted to be as safe as saline in this population [32]. Albumin appears safe in most groups but may not provide a survival

advantage. In patients with traumatic brain injury, there may be a durable increased risk of death with exogenous albumin [40, 41].

The synthetic plasma expanders have historically been used as alternatives to albumin. These include the broad category of HES, delineated above. A paradigm shift in the use of these solutions has occurred within the past few years. In 2012, several papers were published comparing the use of HES to crystalloid in subsets of the critically ill population. Perner et al. demonstrated that patients with severe sepsis receiving HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal replacement therapy, compared to patients receiving Ringer's acetate [42]. Myburgh et al. demonstrated that there was no significant difference in 90-day mortality between randomly selected critically ill patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal replacement therapy [43]. In patients with severe sepsis, Bayer et al. demonstrated that shock reversal was achieved equally fast with synthetic colloids or crystalloids. Use of colloids resulted in only marginally lower required volumes of resuscitation fluid. In addition, they found that both low molecular weight HES and gelatin may impair renal function [44]. In 2013, a systematic review and meta-analysis published in JAMA found that in critically ill patients requiring acute volume resuscitation, use of HES compared with other resuscitation solutions was associated with a significant increased risk of mortality and acute kidney injury [45]. Of note, in 2013, the FDA and the European Medicines Agency (EMA) issued a warning that HES products should not be used in critically ill patients, including patients with sepsis, due to the potential for increased mortality and increased need for renal replacement therapy in these populations [46].

Another Cochrane review of colloids versus crystalloids for fluid resuscitation in critically ill patients was published in 2013. From assessment of randomized controlled trials, the authors concluded that there is no evidence to indicate that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns, or following surgery. The use of HES might increase mortality. Since colloids are not associated with improved survival and are more expensive than crystalloids, continued use in clinical practice may not be justified [47]. When extrapolating these studies to clinical practice, each clinical scenario must be considered carefully, keeping in mind the patient populations assessed in the reviewed literature, the specific types of fluids studied, and the limitations of the studies.

More recently, attention has turned to a more nuanced approach to volume resuscitation in different surgical populations. For instance, the type of crystalloid used for resuscitation in critically ill patients has been revisited. A multicenter retrospective cohort study published in Critical Care Medicine in 2014 demonstrated that among critically ill patients with sepsis, resuscitation with balanced fluids (as opposed to normal saline) was associated with a lower risk of in-hospital mortality [48]. In 2018, the BICAR-ICU Study Group published a multicenter, open-label, randomized controlled phase 3 trial, which demonstrated that in critically ill patients with severe acidemia, sodium bicarbonate decreased the primary composite outcome and 28-day mortality in a cohort of patients with acute kidney injury, where the primary outcome was a composite of death from any cause by day 28 and the presence of at least one organ failure at day 7 [49].

Differences in the temporal and quantitative approach to volume resuscitation in differing surgical subsets are also being addressed in the literature. For instance, a timely and aggressive initial approach to volume resuscitation in the hypotensive and hypovolemic septic patient may be warranted, analogous to the timely approach to administration of empiric broad-spectrum antibiotics in this population [50–54]. A 2018 review takes the resuscitation of septic patients one step further and addresses the importance of de-escalation, cessation, and reversal of volume resuscitation, underscoring the importance of a systematic temporal approach [55].

On the other end of the spectrum, a more measured approach to the intraoperative resuscitation of elective surgical patients is generally warranted, as outlined in enhanced recovery after surgery

(ERAS) protocols [56–58]. However, optimal fluid management in elective patients is not entirely generalizable, as published by the RELIEF investigators, who demonstrated that among patients at increased risk for complications during major abdominal surgery, a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen, and a higher rate of acute kidney injury was noted in the restrictively managed patients [59].

The Relationship Between Disorders of Water Balance and Sodium Balance

Sodium is the primary extracellular cation and principal determinant of plasma osmolality. The concentration of sodium and TBW shares an inverse relationship. As TBW increases, the serum sodium concentration decreases and vice versa. The sodium level thereby is a marker of TBW. Abnormal sodium concentration reflects abnormal TBW content [60].

Disorders of sodium levels are a common occurrence in clinical practice. Such disturbances are usually secondary to changes in water balance and not sodium levels. Sodium concentration is a reflection of body fluid tonicity and not a reflection of total body sodium content [61]. Often clinicians misinterpret changes in sodium levels as changes in total body sodium content. There are scenarios in which sodium content is abnormal, but this occurs less often than instances in which TBW is abnormal.

Disorders of Sodium Metabolism

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

Hyponatremia is defined as a sodium level equal to or less than 135 mEq/L. It is the most common electrolyte abnormality in the hospitalized patient, occurring in as many as 20–25% of hospitalized patients and in 30% of patients in the intensive care unit (ICU). Approximately 4.4% of surgical ward patients develop the abnormality within 1 week of surgery [62]. Hyponatremia is a risk factor for mortality, with 10–15% mortality in chronic hyponatremia and 50% in acute circumstances. Hyponatremia has been demonstrated to be a predictor of inpatient mortality in several patient populations [63–65]. Mortality likely represents the severity of the underlying disease and not accrual mortality from the electrolyte abnormality itself [66]. Hyponatremia in critically ill patients is more likely secondary to elevated secretion of ADH without an osmotic stimulus [67–69]. Critically ill patients are also more likely to have multi-organ failure that is associated with impaired water handling [70]. The inflammatory cascade via interleukin-6 may also play a role in ADH secretion and hyponatremia [71].

Hyponatremia is usually asymptomatic. In severe cases, cerebral edema may occur as fluid tonicity falls, thereby causing inflow of water into cells. Severe hyponatremia may present clinically as nausea, vomiting, lethargy, confusion, seizures, cerebral herniation, coma, and death [72].

Hyponatremia can be classified according to volume status as hypovolemic hyponatremia, euvolemic hyponatremia, and hypervolemic hyponatremia (Table 2.1). Treatment strategies should be guided based upon etiology of the hyponatremia and volume status [61].

Hypovolemic hyponatremia results from a deficit of total body sodium and water with the sodium deficit greater than the water deficit. The decrease in

Table 2.1 Causes of hyponatremia

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

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

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

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

Hyponatremia corrected at too rapid a rate may result in osmotic pontine demyelination (also known as central pontine demyelination or central demyelination syndrome). The development of this syndrome is a risk when there are sudden changes in concentration (more than 12–15 mEq/L per 24 h) or a rapid rate of change (>1–2 mEq/L/h). Clinically, the syndrome presents as generalized encephalopathy followed by behavioral changes, cranial nerve palsies, and quadriplegia 2–3 days after the sodium level is corrected. High-risk patient populations include those with chronic hyponatremia that is rapidly corrected, such as alcoholics, the malnourished, geriatric patients, and those with thermal injury [72–82].

Sodium can be administered as 3% NaCl. The hyponatremia should be corrected at a rate similar to the rate of developing the imbalance. Acute hyponatremia should be corrected more quickly than chronic hyponatremia. Dilutional hyponatremia is more common than total body sodium deficit. Therefore, administration of 3% NaCl can be combined with forced diuresis and volume restriction to remove the excess water load. Vasopressin receptor antagonists (vaptans) have been developed for the treatment of hypervolemic and euvolemic hyponatremia. However, their role in routine clinical practice remains to be determined [24].Vaptans are not approved for the treatment of hypovolemic hyponatremia [83].

Most hyponatremic patients are not symptomatic and do not require treatment with hypertonic saline. Most hyponatremic patients are euvolemic, and the most common diagnosis is syndrome of inappropriate antidiuretic hormone (SIADH). SIADH is a diagnosis of exclusion with specific criteria, including a plasma osmolality <270 mOsm/kg H_2O; urine osmolality >100 mOsm/kg H_2O; euvolemia; elevated urine sodium concentration; absence of adrenal, thyroid, pituitary, or renal insufficiency; and absence of diuretic use [61].

Hypernatremia is a state of serum sodium greater than 145 mEq/L. It occurs in approximately 2% of hospitalized patients and 15% of patients in the intensive care unit. Mortality rates in ICU patients with hypernatremia are greater than 30% [66]. Hypernatremia results from either free water deficit or excess total body sodium and can occur in the setting of hypovolemia, euvolemia, or hypervolemia. Therapy can be correctly guided by assessing volume status and urine sodium to determine the etiology of hypernatremia.

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

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

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

Disorders of Potassium Metabolism

The normal extracellular concentration of potassium range is 3.5–5.0 mEq/L. It is the principal cation in the intracellular fluid, ranging from 140 to 160 mEq/L. This difference in concentration is essential in providing a transmembrane potential required to maintain the excitability of nerve and muscle tissues. Potassium deficiency in dietary intake has been implicated in the development of hypertension, cardiovascular disease, and glucose intolerance [84].

Hypokalemia refers to a serum potassium level of less than 3.5 mEq/L. Causes of hypokalemia include losses through the gastrointestinal (GI) tract via diarrhea, vomiting, or high nasogastric tube (NGT) output through intentional decompression. Hypokalemia may result from intracellular shifting of potassium in a variety of conditions (Table 2.2). Pseudohypokalemia may occur in specimens collected from leukemia patients with profound leukocytosis. Under these circumstances, white blood cells absorb potassium in vitro [85]. Common iatrogenic etiologies include losses via renal excretion caused by potassium-wasting diuretic use.

Mild hypokalemia is usually asymptomatic. In severe cases, it may present as muscle cramps and weakness and in extreme cases progresses to muscle breakdown and necrosis. An ascending muscle paralysis may result in respiratory failure and arrest [86]. Cardiac signs include EKG changes appearing as ST depression, flattened T waves, U waves and QT interval prolongation, and ventricular arrhythmias [87]. Disturbances in cardiac conduction resulting in death can be seen in patients with underlying cardiac disease and digitalis use [88].

Severe hypokalemia should be repleted intravenously or orally depending on the clinical scenario. In cases of hypokalemia due to transcellular shifts, treating the underlying condition is necessary, versus replacement in the case of true depletion. Sustained hypokalemia results from true depletion compared to transient hypokalemia from transcellular shifts. Serum potassium falls approximately 0.3 mEq/L for every 100 mEq/L decrease in total body potassium [89]. A serum potassium level below 3.0 mEq/L should be corrected using intravenous replacement in a monitored setting due to the risk of arrhythmias. If hypomagnesemia is present, it should be corrected first, as such a state promotes excretion of potassium. Hypokalemia accompanies hypomagnesemia about 60% of the time due to reduced Na^+, K-ATPase activity, in which magnesium acts as a dependent enzyme [90, 91]. When serum potassium is below

Table 2.2 Causes of hypokalemia

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

3.0 mEq/L, an additional 8–10 g of magnesium may also be required. Once the serum potassium level falls below 3.0 mEq/L, the amount of replacement required increases in a nonlinear fashion, and a minimum of 100 mEq is required to restore normal levels.

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

Mild hyperkalemia is usually asymptomatic but predominantly affects the muscular and cardiac systems. Muscular symptoms include paresthesias, extremity weakness, and flaccidity. Ascending muscle weakness may involve the trunk and respiratory muscles. Hyperkalemia can lead to cardiac conduction abnormalities. EKG findings include peaked T waves, widening of the QRS complex, AV conduction abnormalities, ventricular fibrillation, and eventual asystole [87].

Hyperkalemia results from (1) an inability to secrete potassium due to renal dysfunction, (2) a shift of potassium out of cells, and (3) excessive administration of potassium. Renal failure is the most common cause of inability to excrete potassium. Traditional teaching has held that there is an inverse relationship between serum potassium levels and pH [92]. However, this has been disproven, and the relationship is complex and not completely understood.

Symptomatic hyperkalemia as demonstrated by EKG changes or asymptomatic patients with a serum potassium level greater than 6.0 mEq/L should be treated emergently. Strategies include [86]:

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

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

Table 2.3 Causes of hyperkalemia

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

Disorders of Calcium Metabolism

Calcium is a divalent cation that plays an important role in several biological processes. Extracellularly, it is the main substrate for the skeletal system and is bound to phosphate as hydroxyapatite. The average adult has 1–2 kg of total body calcium localized in bone as hydroxyapatite. In its intracellular form, calcium plays an important role as a signaling molecule for several pathways, including cardiac, skeletal, and smooth muscle contraction and neurotransmitter release. The concentration of extracellular and intracellular calcium is tightly regulated. The extracellular concentration of calcium is 10,000 times greater than intracellular concentrations. Release

of calcium from its vast stores in the skeletal system is regulated by parathyroid hormone (PTH).

Serum calcium levels normally range from 9.4 to 10 mg/dL. The incidence of hypocalcemia ranges from 70% to 90% when total serum calcium is measured versus 15–50% when ionized calcium is measured [93]. This is due to the high incidence of hypoalbuminemia in critically ill and postoperative patients. Calcium is bound to albumin in serum, though the ionized form is the biologically active form.

Hypocalcemia refers to a serum calcium level of less than 8.5 mg/dL or an ionized level of less than 1.0 mmol/L. There are many reasons for hypocalcemia in the postoperative and critically ill patient population. The etiology is usually multifactorial. Ionized hypocalcemia is common in patients with sepsis, pancreatitis, and severe trauma or postoperatively after plasma volume expansion with hypocalcemic solutions and is associated with increased mortality [93, 94]. Cytokine levels in critically ill patients, especially tumor necrosis factor, interleukin-6, and prolactin, serve as a measure of systemic inflammation and correlate with the degree of hypocalcemia [95, 96].

Mild hypocalcemia is usually asymptomatic. However, severe derangements result in significant physiological consequences. Diminished cardiac contractility can result in refractory hypotension. Arrhythmias include ventricular tachycardia. Prolonged QT interval and marked QRS and ST segment changes may mimic acute myocardial infarction and heart block. Calcium plays an important role in the coagulation process, including the conversion of fibrin to fibrinogen and enhancement of other coagulation factors. Maintaining an ionized calcium level above 0.9 mmol/L has a beneficial cardiovascular and coagulation effect in the resuscitation of patients in massive hemorrhage [97]. Citrate components present in blood products may also exacerbate the hypocalcemia by precipitation. Therefore, calcium levels should be monitored during massive transfusion.

Neurologically, hypocalcemia may present as paresthesias and seizures. Neuromuscular symptoms include spasms and tetany. An acute decline in the serum calcium level can result in laryngospasm and death. Chronic hypocalcemia may present with less pronounced symptoms that include neuromuscular irritability. At the bedside, hypocalcemia can be detected by testing for Chvostek's sign or Trousseau's sign. Chvostek's sign is facial nerve irritability that is elicited by gently tapping the facial nerve. Chvostek's sign is present in approximately 10–25% of normal adults and may be absent in chronic hypocalcemia. Trousseau's sign is a carpopedal spasm that is elicited by decreasing blood flow to the hand with a blood pressure cuff inflated to 20 mm Hg for 3 min. It is absent in one third of hypocalcemic patients. Psychiatric symptoms of hypocalcemia include dementia, psychosis, and depression [98, 99].

Symptomatic hypocalcemia and severe hypocalcemia (0.8 mmol/L) should be treated with intravenous calcium administration [100–102]. Intravenous calcium can be administered as calcium gluconate or calcium chloride. Calcium chloride has the advantage of being immediately available in equal amounts of calcium and chloride. Calcium gluconate must undergo hepatic degluconation to be available in the ionized form. Calcium chloride contains more calcium in terms of milliequivalents than calcium gluconate. Calcium infusions can also be used in the therapy of cardiac drug toxicity involving beta blockers and calcium channel blockers [101, 102].

Hypercalcemia is rare in the ICU setting and occurs in less than 15% of hospitalized patients [93]. Hypercalcemia refers to a serum calcium level greater than 10.4 mg/dL. In the critically ill patient, increased bone reabsorption resulting from paraneoplastic syndromes and prolonged immobilization are common etiologies. Hyperparathyroidism and malignancy causing excessive PTHrP are the most common causes of hypercalcemia in hospitalized patients, occurring in more than 50% of cases [103]. Conversely, among outpatients referred to endocrinologists for hypercalcemia, more than 90% are found to have primary hyperparathyroidism [104]. Other causes include renal failure, thyrotoxicosis, adrenal insufficiency, and drugs. In particular, thiazides may increase proximal tubule reabsorption of calcium [98, 99, 103].

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

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

Disorders of Magnesium Metabolism

Magnesium is a divalent cation that plays an important role in the metabolism of other cations including sodium, potassium, and calcium. Magnesium is also an important cofactor in ATP energy metabolism. It is the second most common intracellular cation and fourth most common extracellular cation [104]. Normal serum concentration ranges from 1.5 to 2.3 mg/dL. The body stores magnesium mainly in the bones, muscles, and soft tissues. Total body magnesium can be low in low albumin states without affecting ionized magnesium levels. Sixty-seven percent of serum magnesium is in the ionized form. Ionized magnesium is the biologically active form that can be measured using ion-selective electrodes, but this technique has limitations with respect to accuracy [105, 106]. There are no known hormonal pathways in the regulation of magnesium. Magnesium homeostasis is achieved through absorption via the kidneys, digestive tract, and bone mobilization. Disorders of magnesium metabolism are seen in 15–60% of patients in the critical care setting [107].

Table 2.4 Causes of hypomagnesemia

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

A serum magnesium level less than 1.5 mg/dL defines hypomagnesemia. There are several etiologies of hypomagnesemia (Table 2.4). In surgical and critically ill patients, common causes are plasma volume expansion, diuretic use, and severe sepsis. Other etiologies are excess GI losses from diarrhea, laxative use, and enteric decompression. It is often seen in association with hypocalcemia, hypokalemia, and hypophosphatemia. Hypokalemia and hypocalcemia are refractory to correction unless magnesium is replaced first [108, 109].

Hypomagnesemia is usually asymptomatic. When symptoms do occur, they are often similar to those associated with hypocalcemia, hypokalemia, and hypophosphatemia due to the close metabolic relationship of the cations. Symptoms include muscle weakness, cramps, seizures, and arrhythmias, namely, torsades de pointes. The treatment for torsades de pointes and symptomatic hypomagnesemia is intravenous replacement of magnesium, 1–2 g over 5 min.

Magnesium also has therapeutic properties in certain clinical scenarios. Magnesium competitively binds to *N*-methyl-d-aspartate receptors to depress the seizure threshold and is therefore used in the treatment of preeclampsia and eclampsia [108–111]. Magnesium also has smooth muscle relaxant properties that make it useful for treating bronchospasm in asthmatics [110, 111].

Hypermagnesemia is usually seen in the setting of renal failure, because normal kidneys can excrete large quantities of magnesium, up to 500 mEq/day [104]. Other etiologies are extensive soft tissue ischemia or necrosis in patients with trauma, sepsis, cardiopulmonary arrest, burns, or shock. Symptoms of hypermagnesemia occur at levels above 4 mg/dL and involve the muscular, neurologic, and cardiac systems. Muscular symptoms range from depressed deep tendon reflexes to muscle paralysis, including respiratory depression at levels above 8–10 mg/dL. Neurologic symptoms include somnolence and lethargy. Cardiovascular symptoms include bradycardia and hypotension unresponsive to volume expansion and vasopressors. Complete heart block resulting in cardiac arrest is seen at levels approaching 20 mg/dL [104, 112]. Hypermagnesemia-related hypotension can be treated with administration of calcium. Excess levels can be removed with hydration and forced diuresis with furosemide. Extreme cases of magnesium toxicity may require dialysis. Hypermagnesemia is a rare phenomenon in the ICU setting, excluding patients undergoing tocolysis with large doses of magnesium.

Disorders of Phosphorous Metabolism

The majority of the body's total reserve of phosphorous is stored in the bones as hydroxyapatite along with calcium [104]. The metabolic pathways of the two ions are closely intertwined. Phosphate plays an important role as a constituent of nucleic acids, phospholipids, complex carbohydrates, glycolytic intermediates, enzymatic phosphoproteins, and nucleotide cofactors for enzymes. Phosphate is also important for energy metabolism as a constituent of ATP. Phosphate levels are regulated by PTH, mainly via three routes: (1) bone reserves, (2) intestine, and (3) kidneys.

A serum phosphate level less than 3.0 mg/dL defines hypophosphatemia, which is classified according to degree of deficiency. Mild hypophosphatemia ranges 2.5–3.0 mg/dL, moderate 1.0–2.5 mg/dL, and severe less than 1 mg/dL. Phosphate depletion refers to low stores of total body phosphate. There are numerous causes of phosphate depletion (Table 2.5). Among hospitalized patients, the overall prevalence of severe hypophosphatemia is less than 1%, whereas mild or moderate hypophosphatemia occurs in 2–5% of these patients [113].

Hypophosphatemia results in several clinical manifestations. Neuromuscular symptoms vary depending on the degree of phosphate depletion, ranging from progressive lethargy, muscle weak-

Table 2.5 Causes of hypophosphatemia

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

ness, and paresthesias to paralysis, coma, and death. Confusion, profound weakness, paralysis, seizures, and other major sequelae are usually limited to those patients who have serum phosphate concentrations lower than 0.8–1.0 mg/dL [114]. Rhabdomyolysis is observed within 2 days in more than one third of patients whose serum phosphate concentrations fall to less than 2 mg/dL [115]. Respiratory muscle weakness may prevent successful weaning from mechanical ventilation [116, 117]. Cardiac symptoms resulting from profound hypophosphatemia include left ventricular dysfunction, heart failure, and ventricular arrhythmias but may not be significant if the serum phosphate concentration is greater than 1.5 mg/dL [118]. Hematologic derangements include acute hemolytic anemia and leukocyte dysfunction. Depletion requires electrolyte replacements via enteric or intravenous routes. Severe depletion warrants intravenous replacement. Replacements should be carried out with caution in patients with renal failure and hypercalcemia due to the risk of metastatic calcifications.

Hyperphosphatemia refers to a serum phosphate level greater than 4.5 mg/dL. Elevated phosphate levels result most often from acute or chronic renal dysfunction in which the renal tubules are unable to clear the daily phosphate load despite maximal inhibition of phosphate reabsorption in the remaining functional nephrons. Cellular damage from rhabdomyolysis, tumor lysis syndrome, hemolysis, and thyrotoxicosis may also result in increased phosphate levels [119]. Iatrogenic causes include excess electrolyte correction, laxative use, and bisphosphonate therapy.

Hyperphosphatemia results in hypocalcemia through three mechanisms: (1) precipitation of calcium, (2) interfering with PTH levels, and (3) decreasing vitamin D levels [120]. Hyperphosphatemia, therefore, clinically presents as hypocalcemia. Tetany, muscle cramps, paresthesias, and seizures may occur. Calcium phosphate precipitation into soft tissues may cause organ dysfunction, particularly renal failure.

Excess phosphate may be removed by increasing urinary excretion with hydration and diuresis, acetazolamide being the most effective [121]. Dialysis may be necessary in acute cases. Patients with chronic renal failure may require oral phosphate binders to prevent hyperphosphatemia. Enteral nutrition should also be modified to decrease the phosphate load when feasible. In the acute care setting, increased dietary protein requirements may prevent phosphate load reduction.

References

1. Cosnett JE. The origins of intravenous fluid therapy. Lancet. 1989;1(8641):768–71.
2. Sabiston DC. The fundamental contributions of Alfred Blalock to the pathogenesis of shock. Arch Surg. 1995;130(7):736–7.
3. Ritz P, Vol S, Berrut G, Tack I, Arnaud MJ, Tichet J. Influence of gender and body composition on hydration and body water spaces. Clin Nutr. 2008;27:740–6.
4. Edelman IS, Leibman J. Anatomy of body water and electrolytes. Am J Med. 1959;27:256–77.
5. Wait RB, DeBusk MG, Nahmias J. Fluids, electrolytes, and acid–base balance. In: Mulholland MW, Lillemoe KD, Doherty GM, Upchurch GR, Alam H, Pawlik TM, editors. Greenfield's surgery: scientific principles and practice. Philadelphia: Wolters Kluwer; 2017. p. 192–213.
6. Shires T, Williams J, Brown F. Acute changes in extracellular fluids associated with major surgical procedures. Ann Surg. 1961;154:803–10.
7. Shires GT. Shock and metabolism. Surg Gynecol Obstet. 1967;124:803–10.
8. Edwards MR, Grocott MPW. Perioperative fluid and electrolyte therapy. In: Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's anesthesia. Philadelphia: Elsevier Saunders; 2015. p. 1767–810.
9. Chan STF, Kapadia CR, Johnson AW, Radcliffe AG, Dudley HAF. Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. Br J Surg. 1983;70:36–9.
10. Brandstrup B, Svensen C, Engquist A. Hemorrhage and operation cause a contraction of the extracellular space needing replacement–evidence and implications? A systematic review. Surgery. 2006;139:419–32.
11. Brandstrup B. Fluid therapy for the surgical patient. Best Pract Res Clin Anaesthesiol. 2006;20:265–83.
12. Vallet B, Robin E, Lebuffe G. Resuscitation from circulatory shock. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Inc.; 2017. p. 623–7.
13. Baldwin AL, Thurston G. Mechanics of endothelial cell architecture and vascular permeability. Crit Rev Biomed Eng. 2001;29(2):247–78.

14. Emerson TE. Unique features of albumin: a brief review. Crit Care Med. 1989;17(7):690–4.
15. Bent-Hansen L. Whole body capillary exchange of albumin. Acta Physiol Scand Suppl. 1991;603:5–10.
16. Rose BD, Post TW. Regulation of plasma osmolality. In: Rose BD, Post TW, editors. Clinical physiology of acid–base and electrolyte disorders. New York: McGraw-Hill; 2001. p. 285–98.
17. Agre P. The aquaporin water channels. Proc Am Thorac Soc. 2006;3(1):5–13.
18. Carbrey JM, Agre P. Discovery of the aquaporins and development of the field. Handb Exp Pharmacol. 2009;90:3–28.
19. Gonen T, Walz T. The structure of aquaporins. Q Rev Biophys. 2006;39(4):361–96.
20. Fu D, Lu M. The structural basis of water permeation and proton exclusion in aquaporins. Mol Membr Biol. 2007;24(5–6):366–74.
21. Fenton RA, Moeller HB. Recent discoveries in vasopressin-regulated aquaporin-2 trafficking. Prog Brain Res. 2008;170:571–9.
22. Moen MD, Keating GM. Intravenous conivaptan. Am J Cardiovasc Drugs. 2008;8(5):341–8.
23. Metzger BL, DeVita MV, Michelis MF. Observations regarding the use of the aquaretic agent conivaptan for treatment of hyponatremia. Int Urol Nephrol. 2008;40:725–30.
24. Bhandari S, Peri A, Cranston I, McCool R, Shaw A, Glanville J, et al. A systematic review of known interventions for the treatment of chronic nonhypovolaemic hypotonic hyponatraemia and a meta-analysis of the vaptans. Clin Endocrinol. 2017;86:761–71.
25. Lee CY, Burnett JC. Natriuretic peptides and therapeutic implications. Heart Fail Rev. 2007;12:131–42.
26. McGrath MF, de Bold ML, de Bold AJ. The endocrine function of the heart. Trends Endocrinol Metab. 2005;16:469–77.
27. Wait RB, Kahng KU. Renal failure complicating obstructive jaundice. Am J Surg. 1989;157:256–63.
28. Remuzzi G, Benigni A. Endothelins in the control of cardiovascular and renal function. Lancet. 1993;342:589–93.
29. Bachmann S, Mundel P. Nitric oxide and the kidney: synthesis, localization, and function. Am J Kidney Dis. 1994;24(1):112–29.
30. Kaplan LJ, Frangos S. Clinical review: acid–base abnormalities in the intensive care unit. Crit Care. 2005;9(2):198–203.
31. Kramer GC. Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care. J Trauma. 2003;54(5 Suppl):S89–99.
32. Finfer S, Bollomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(2):2247–56.
33. Vincent JL, Sakr Y, Reinhart K. Is albumin administration in the acutely ill associated with increased mortality? Results of the SOAP study. Crit Care. 2005;96(6):R745–54.
34. Schortgen F, Girou E, Deye N, Brochard L. The risk associated with hyperoncotic colloids in patients with shock. Intensive Care Med. 2008;34(12):2157–68.
35. Hartmann AF, Senn MJ. Studies in the metabolism of sodium r-lactate. III. Response of human subjects with liver damage, disturbed water and mineral balance, and renal insufficiency to the intravenous injection of sodium r-lactate. J Clin Invest. 1932;11:345–55.
36. Cordell AR. Milestones in the development of cardioplegia. Ann Thorac Surg. 1995;60:793–6.
37. Rhee P, Burris D, Kaufmann C, Pikoulis M, Austin B, Ling G, et al. Lactated Ringer's solution resuscitation causes neutrophil activation after hemorrhagic shock. J Trauma. 1998;44(2):313–9.
38. Deb S, Martin B, Sun L, Ruff P, Burris D, Rich N, et al. Resuscitation with lactated Ringer's solution in rats with hemorrhagic shock induces immediate apoptosis. J Trauma. 1999;46(4):582–8.
39. Cai B, Chen F, Lin X, Miller E, Szabo C, Deithch EA, et al. Anti-inflammatory adjuvant in resuscitation fluids improves survival in hemorrhage. Crit Care Med. 2009;37(3):860–8.
40. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomized controlled trials. BMJ. 1998;317(7153):235–40.
41. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2004;4:CD001208.
42. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34.
43. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901–11.
44. Bayer O, Reinhart K, Kohl M, Kabisch B, Marshall J, Sakr Y, et al. Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: a prospective sequential analysis. Crit Care Med. 2012;40:2543–51.
45. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation. A systematic review and meta-analysis. JAMA. 2013;309:678–88.
46. Wiedermann CJ, Eisendle K. Comparison of hydroxyethyl starch regulatory summaries from the Food and Drug Administration and the European Medicines Agency. J Pham Policy Pract. 2017;10:12. https://doi.org/10.1186/s40545-016-0090-6. eCollection 2017.
47. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013;2:CD000567.
48. Raghunathan K, Shaw A, Nathanson B, Sturmer T, Brookhart A, Stefan MS, Setoguchi S, et al. Association between the choice of IV crystalloid and

in-hospital mortality among critically ill adults with sepsis. Crit Care Med. 2014;42:1585–91.
49. Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, et al. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicenter, open-label, randomized controlled, phase 3 trial. Lancet. 2018;392:31–40.
50. Leisman DE, Doerfler ME, Schneider SM, Masick KD, D'Amore JA, D'Angelo JK. Predictors, prevalence, and outcomes of early crystalloid responsiveness among initially hypotensive patients with sepsis and septic shock. Crit Care Med. 2018;46:189–98.
51. Hayakawa K. Aggressive fluid management in the critically ill: pro. J Intensive Care. 2019;7:9. https://doi.org/10.1186/s40560-019-0361-9. eCollection 2019.
52. Semler MW, Janz DR, Casey JD, Self WH, Rice TW. Conservative fluid management after sepsis resuscitation: a pilot randomized trial. J Intensive Care Med. 2019;10:885066618823183. https://doi.org/10.1177/0885066618823183.
53. Brown RM, Semler MW. Fluid management in sepsis. J Intensive Care Med. 2018;1:885066618784861. https://doi.org/10.1177/0885066618784861.
54. Leisman DE, Goldman C, Doerfler ME, Masick KD, Dries S, Hamilton E, et al. Patterns and outcomes associated with timeliness of initial crystalloid resuscitation in a prospective sepsis and septic shock cohort. Crit Care Med. 2017;45:1596–606.
55. Malbrain MLNG, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care. 2018;8(1):66. https://doi.org/10.1186/s13613-018-0402-x.
56. Simmons JW, Dobyns JB, Paiste J. Enhanced recovery after surgery: intraoperative fluid management strategies. Surg Clin N Am. 2018;98:1185–200.
57. Makaryus R, Miller TE, Gan TJ. Current concepts of fluid management in enhanced recovery pathways. Br J Anaesth. 2018;120:376–83.
58. Zhu ACC, Agarwala A, Bao X. Perioperative fluid management in the enhanced recovery after surgery (ERAS) pathway. Clin Colon Rectal Surg. 2019;32:114–20.
59. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378:2263–74.
60. Wait RB, Kahng KU, Mustafa IA. Fluid, electrolytes, and acid–base balance. In: Greenfield LJ, Mulhholland MW, Oldham KT, Zelenock GB, Lillemoe KD, editors. Surgery: scientific principles and practice. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 244–69.
61. Fried E, Weissman C. Water metabolism. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Inc.; 2017. p. 743–50.
62. Upadhyay A, Jabber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119(7 Suppl 1):S30–5.
63. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290:2581–7.
64. Londono MC, Guevera M, Rimola A, Navasa M, Tauara P, Mas A, et al. Hyponatremia impairs early post transplantation outcome in patients with cirrhosis undergoing liver transplantation. Gastroenterology. 2006;130:1135–43.
65. Zilberberg MD, Exuzides A, Spalding J, Foreman A, Jones AG, Colby C, et al. Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study. BMC Pulm Med. 2008;8:16. PubMed PMID: 18710521.
66. Singh SP. Hypernatremia and hyponatremia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Inc.; 2017. p. 49–51.
67. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342(21):1581–9.
68. Schrier RW. Pathogenesis of sodium and water retention in high output and low output cardiac failure, nephritic syndrome, cirrhosis, and pregnancy (2). N Engl J Med. 1988;319(17):1127–34.
69. Schrier RW. Pathogenesis of sodium and water retention in high output and low output cardiac failure, nephritic syndrome, cirrhosis, and pregnancy (1). N Engl J Med. 1988;319(16):1065–72.
70. Sedlaceck M, Schoolwerth AC, Remillard BD. Electrolyte disturbances in the intensive care unit. Semin Dial. 2006;19(6):496–501.
71. Swart RM, Hoorn EJ, Betjes MG, Zieste R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol. 2011;118:45–51.
72. Fraser CL, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. Am J Med. 1997;102:67–77.
73. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA. 1999;81:2299–304.
74. Stems RH. Severe hyponatremia: the case for conservative management. Crit Care Med. 1992;20:534–9.
75. Cohen BJ, Jordan MH, Chapin SD, Cape B, Laureno R. Pontine myelinolysis after correction of hyponatremia during burn resuscitation. J Burn Care Rehabil. 1991;12:153–6.
76. Laurene R. Central pontine myelinolysis following rapid correction of hyponatremia. Ann Neurol. 1983;13:232–42.
77. Laurene R, Karp BI. Myelinolysis after correction of hyponatremia. Ann Intern Med. 1997;126:57–62.
78. Laureno R, Karp BI. Pontine and extrapontine myelinolysis following rapid correction of hyponatraemia. Lancet. 1988;1:1439–41.

79. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. Medicine. 1993;72:359–73.
80. Stems RH. Neurological deterioration following treatment for hyponatremia. Am J Kidney Dis. 1989;13:434–7.
81. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. J Am Soc Nephrol. 1994;4:1522–30.
82. Stems RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med. 1986;14:1535–42.
83. Lehrich RW, Greenberg A. Hyponatremia and the use of vasopressin receptor antagonists in critically ill patients. J Intensive Care Med. 2012;27(4):207–18.
84. Adrogué HJ, Madias NE. Mechanisms of disease: sodium and potassium in the pathogenesis of hypertension. N Engl J Med. 2007;356:1966–78.
85. Naparstek Y, Gutman A. Case report: spurious hypokalemia in myeloproliferative disorders. Am J Med Sci. 1984;288:175–7.
86. Romito B, Dhillon A. Hyperkalemia and hypokalemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Inc.; 2017. p. 52–5.
87. Slovis C, Jenkins R. ABC of clinical electrocardiography: conditions not primarily affecting the heart. BMJ. 2002;324:1320–3.
88. Schulman M, Narins RG. Hypokalemia and cardiovascular disease. Am J Cardiol. 1990;65:4E–9.
89. Gennari FJ. Hypokalemia. N Engl J Med. 1998;339:451–8.
90. Whang R, Welt LA. Observations in experimental magnesium depletion. J Clin Invest. 1963;42:305–13.
91. Wong NLM, Sutton RA, Navichak V, Quame GA, Dirks JH. Enhanced distal absorption of potassium by magnesium-deficient rats. Clin Sci. 1985;69:626–39.
92. Burnell JM, Scribner BH, Uyeno BT, Villamil MF. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. J Clin Invest. 1956;35:935–9.
93. Hassan M, Cooney RN. Hypocalcemia and hypercalcemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Inc.; 2017. p. 61–3.
94. Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia. A pervasive metabolic abnormality in the critically ill. Am J Kidney Dis. 2001;37:689–98.
95. Zaloga GP. Ionized hypocalcemia during sepsis. Crit Care Med. 2000;28:266–8.
96. Müller B, Becker KL, Kränzlin M, Schächinger H, Huber PR, Nylèn ES, et al. Disordered calcium homeostasis of sepsis: association with calcitonin precursors. Eur J Clin Investig. 2000;30:823–31.
97. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. J Trauma. 2008;65(4):951–60.
98. Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med. 1992;20:251–61.
99. Aguilera IM, Vaughan RS. Calcium and the anaesthetist. Anaesthesia. 2000;55:779–90.
100. Carlstedt F, Lind L. Hypocalcemic syndromes. Crit Care Clin. 2001;17:139–53.
101. Strubelt O, Diederich KW. Experimental investigations of the antidotal treatment of nifedipine overdosage. J Toxicol Clin Toxicol. 1986;24(2):135–49.
102. Tai YT, Lo CW, Chow WH, Cheng CH. Successful resuscitation and survival following massive overdose of metoprolol. Br J Clin Pract. 1990;44:746–7.
103. Forster J, Querusio L, Burchard KW, Gann DS. Hypercalcemia in critically ill surgical patients. Ann Surg. 1985;202:512–8.
104. Bringhurst FR, Demay MB, Kronenberg HM. Hormones and disorders of mineral metabolism. In: Melmed S, Polonsky K, Larsen PR, Kronenberg H, editors. Williams textbook of endocrinology. Philadelphia: W.B. Saunders; 2011. p. 1237–304.
105. Johansson M. Weak relationship between ionized and total magnesium in serum of patients requiring magnesium status. Biol Trace Elem Res. 2007;115(1):13–21.
106. Ben Rayana MC, Burnett RW, Covington AK, D'Orazio P, Fogh-Andersen N, Jacobs E, et al. IFCC guideline for sampling, measuring and reporting ionized magnesium in plasma. Clin Chem Lab Med. 2008;46(1):21–6.
107. Gudzenko V. Hypomagnesemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care medicine. Philadelphia: Elsevier Inc.; 2017. p. 59–60.
108. Norhona JL, Matuschak GM. Magnesium in critical illness: metabolism, assessment, and treatment. Intensive Care Med. 2002;28:667–79.
109. Topf JM, Murray PT. Hypomagnesemia and hypermagnesemia. Rev Endocr Metab Disord. 2003;4:195–206.
110. Dacey MJ. Hypomagnesemic disorders. Crit Care Clin. 2001;17:155–73.
111. Fox C, Ramsoomair D, Carter C. Magnesium: its proven and potential clinical significance. South Med J. 2001;94:1195–201.
112. Zalman AS. Hypomagnesemia. J Am Soc Nephrol. 1999;10(7):1616–22.
113. Daily WH, Tonnesen AS, Allen SJ. Hypophosphatemia: incidence, etiology and prevention in the trauma patient. Crit Care Med. 1990;18:1210–4.
114. Vanneste J, Hage J. Acute severe hypophosphatemia mimicking Wernicke's encephalopathy. Lancet. 1986;1(8471):44.
115. Singhal PC, Kumar A, Desroches L, Gibbons N, Mattana J. Prevalence and predictors of rhabdomyolysis in patients with hypophosphatemia. Am J Med. 1992;92:458–64.

116. Aubier M, Murciano D, Lecocguic Y, Viires N, Jacquens Y, Squara P, Pariente R. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med. 1985;313:420–4.
117. Newman JH, Neff TA, Ziporin P. Acute respiratory failure associated with hypophosphatemia. N Engl J Med. 1977;296(19):1101–3.
118. Bollaert PE, Levy B, Nace L, Laterre PF, Larcan A. Hemodynamic and metabolic effects of rapid correction of hypophosphatemia in patients with septic shock. Chest. 1995;107(6):1698–701.
119. Vachvanichsanong P, Maipang M, Dissaneewate P, Wongchanchailert M, Laosombat V. Severe hyperphosphatemia following acute tumor lysis syndrome. Med Pediatr Oncol. 1995;24:63–6.
120. Sutlers M, Gaboury CL, Bennett WM. Severe hyperphosphatemia and hypocalcemia: a dilemma in patient management. J Am Soc Nephrol. 1996;7(10):2056–61.
121. Rejai S, Singh SP. Hyperphosphatemia and hypophosphatemia. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of critical care. Philadelphia: Elsevier Inc.; 2017. p. 56–8.

Acid–Base Physiology

3

Christopher R. Reed, Amy Liepert, and Suresh "Mitu" Agarwal

General Principles

Physiologic Basis for Acid–Base Disorders and Their Compensation

Normal arterial blood pH is maintained in a very narrow range, between 7.35 and 7.45. Changes seen in pH are a reflection of an inverse change in hydrogen ion (H^+) concentration. By formula, pH is a negative logarithm of H^+ concentration:

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

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

Calculation of pH in a buffer solution is performed by using the Henderson–Hasselbalch equation. In blood, measurable quantities of CO_2 and HCO_3^- are used as acid and base equivalents, respectively: $\mathrm{pH} = \mathrm{p}K_a + \log$ (base/acid) or $\mathrm{pH} = \mathrm{p}K_a + \log [HCO_3^-]/[H_2CO_2]$. As H_2CO_2 is not measured, the proportionality constant between P_{CO_2} and $[H_2CO_2]$, 0.03, is utilized to give us:

$$\mathrm{pH} = \mathrm{p}K_a + \log\left[\mathrm{HCO_3}^-\right] / \left[0.03 \times \mathrm{P_{co_2}}\right]$$

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

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

Chemical Buffering Systems

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

C. R. Reed · S. M. Agarwal (✉)
Department of Surgery, Duke University Medical Center, Durham, NC, USA
e-mail: agarwal@surgery.wisc.edu

A. Liepert
Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_3

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

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

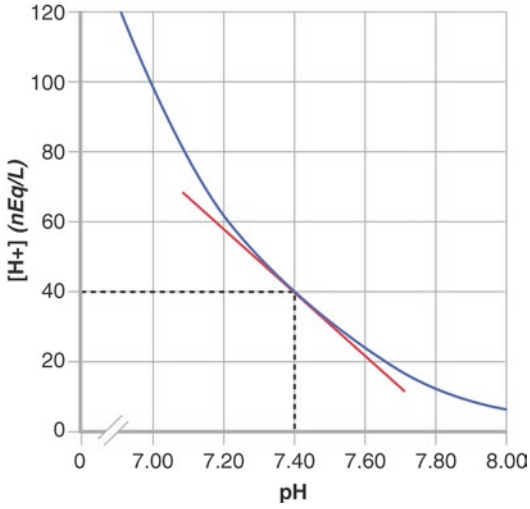

Fig. 3.1 The relationship between the plasma hydrogen ion concentration ([H+]) and the pH of the blood (pH = –log10[H+]). (Modified from Ref. [151])

Buffering solutions, weak acids or bases and their conjugate bases and acids, are the first line of defense against significant changes in pH. These can be found in abundance both in the intra- and extracellular compartments. The most important extracellular buffers are those in the bicarbonate and carbon dioxide system described above. Other buffering systems, such as phosphates, cellular proteins, and hemoglobin, also contribute but have a less profound impact upon the maintenance of pH.

Physiologic Determinants of Acid–Base Maintenance

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

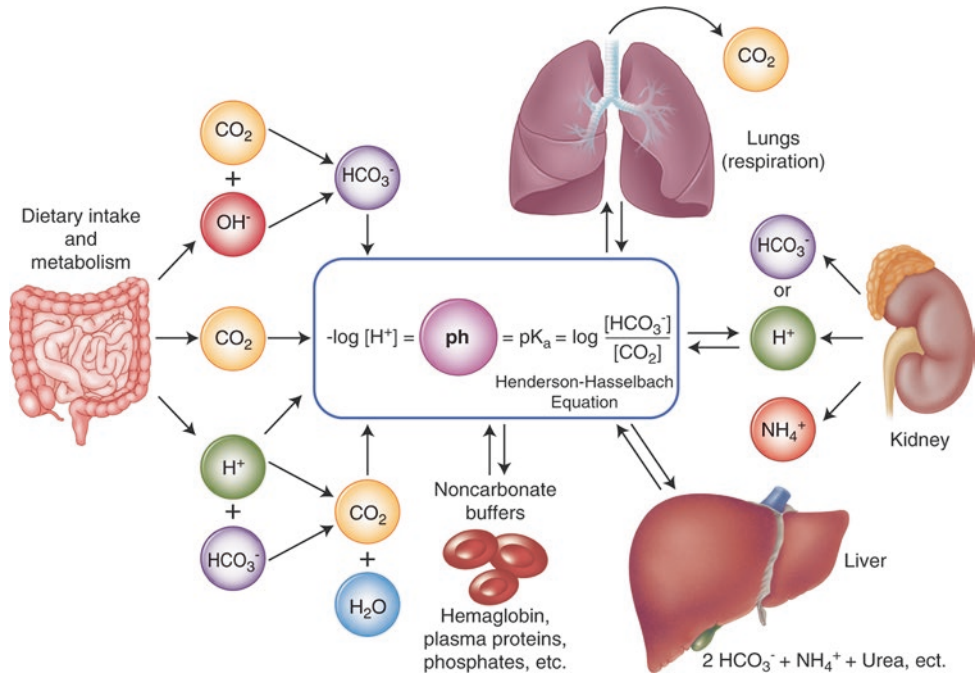

Fig. 3.2 Systematic contributions to acid–base balance. (Modified from Ref. [151])

Renal System

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

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

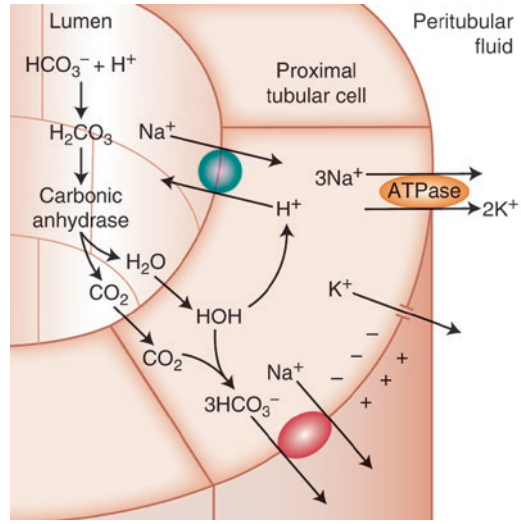

Fig. 3.3 Proximal tubular bicarbonate reabsorption is activated by the Na+ and K+-ATPase pump in the peritubular cell membrane. Exchanging peritubular K+ for intracellular Na+ keeps the intracellular [Na+] low, allowing Na+ to move down its concentration gradient from the tubular lumen through the Na+–H+ antiporter to the cell interior. HCO3– filtered across the glomerular capillaries combines with secreted H+ to form H2CO3. Rapid dissociation of H2CO3 to CO2 and H2O in the presence of luminal carbonic anhydrase permits movement into the cell, where redissociation occurs. Ultimately, the reabsorbed H+ is resecreted in exchange for Na+, and HCO3– moves down an electrical gradient from the cell interior to the peritubular space, where it is reabsorbed into the systemic circulation. (Modified from Ref. [151])

Renal Reabsorption of Bicarbonate and Excretion of Acid

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

Acid excretion from the kidneys occurs in the proximal and distal collecting tubules through an active mechanism. This process may be inhibited by urine pH of less than 4.5, but this mechanism may be nullified by the presence of urinary buffers (Figs. 3.4 and 3.5). Ammonia and phosphates are the most prevalent of these buffers. In conditions such as renal insufficiency where ammonia is deficient, metabolic acidosis may result. Ammonia production, which occurs in the proximal tubule and collecting tubule, is stimulated by acidemia and hypokalemia and inhibited by alkalemia and hyperkalemia (Fig. 3.6). Traditional approaches to the question of renal acid handling have focused on H^+ excretion, emphasizing the importance of ammonia (NH_3) and its related

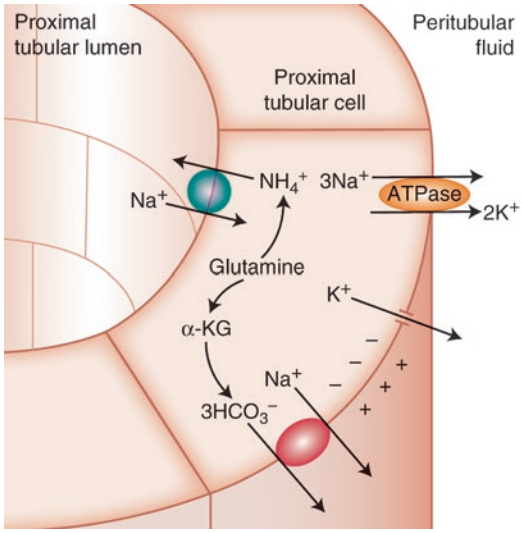

Fig. 3.4 All of the ammonia used to buffer urinary H+ in the collecting tubule is synthesized in the proximal convoluted tubule, and glutamine is assumed to be the main source of this ammonia. As glutamine is metabolized, α-ketoglutarate (α-KG) is formed, which ultimately breaks down to bicarbonate, which is then secreted into the peritubular fluid by an NA+–HCO2– cotransporter. (Modified from Ref. [151])

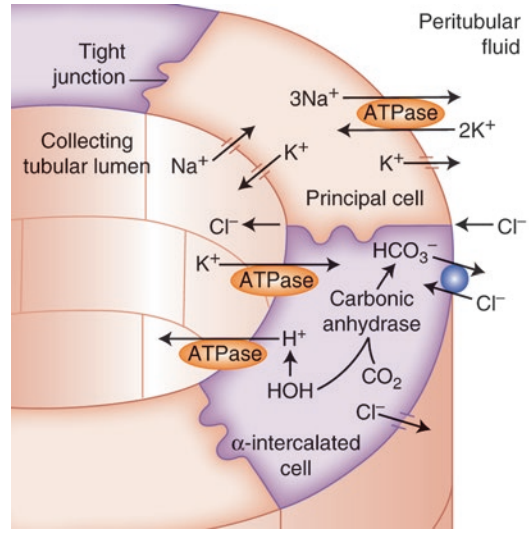

Fig. 3.5 Secretion of H+ from the cortical collecting tubule is indirectly linked to Na+ reabsorption. Intracellular potassium is exchanged for sodium in the principal cells, whereas H+ is actively transported by an adenosine triphosphate (ATPase) pump from the α-intercalated cells. Aldosterone stimulates H+ secretion by entering the principal cell, where it opens Na+ channels in the luminal membrane and increases NA+ and K+-ATPase activity. The movement of cationic Na+ into the principal cells then creates a negative charge within the tubular lumen. K+ moves from the principal cells and H+ from the α-intercalated cells down this electrochemical gradient and into the lumen. When K+ is depleted, principal cell K+ secretion is reduced, and K+ reabsorption via an ATPase pump in the α-intercalated cell is stimulated. Aldosterone apparently also stimulates the H+-ATPase directly in the intercalated cell, further enhancing H+ secretion. HCO3 is returned to the blood across the peritubular membrane in exchange for Cl–, thus maintaining electroneutrality. (Modified from Ref. [151])

cation, ammonium (NH_4^+). However, H^+ excretion actually is irrelevant as water provides an essentially infinite source of free H^+. Indeed, the kidney does not excrete H^+ to any greater degree in the form of NH_4^+ than in the form of H_2O. The purpose of renal ammoniagenesis is to allow the excretion of Cl^- without Na^+ or K^+. This purpose is achieved by supplying a weak cation (NH_4^+) that is excreted along with Cl^-. The mechanisms of RTA are currently being reinterpreted by some authors in the light of a growing body of evidence showing that abnormal chloride conductance, rather than H^+ or HCO_3^- handling, is responsible for these disorders [1].

Kidney–Liver Interaction

The importance of NH_4^+ to systemic acid–base balance rests not on its carriage of H^+ or its direct action on the plasma pH (normal plasma NH_4^+ concentration <0.01 mEq/L) but on its excretion with Cl^-. Production of NH_4^+ is not restricted to the kidney. Hepatic ammoniagenesis (as well as glutaminogenesis) is also important for systemic acid–base balance and is also tightly controlled by mechanisms sensitive to plasma pH [2]. This reinterpretation of the role of NH_4^+ in acid–base balance is supported by the evidence that hepatic glutaminogenesis is stimulated by acidosis [3]. Metabolism of nitrogen by the liver can yield urea, glutamine, or NH_4^+. Normally, the liver releases only a very small amount of NH_4^+, incorporating most of its nitrogen into either urea or glutamine. Hepatocytes enzymes facilitate

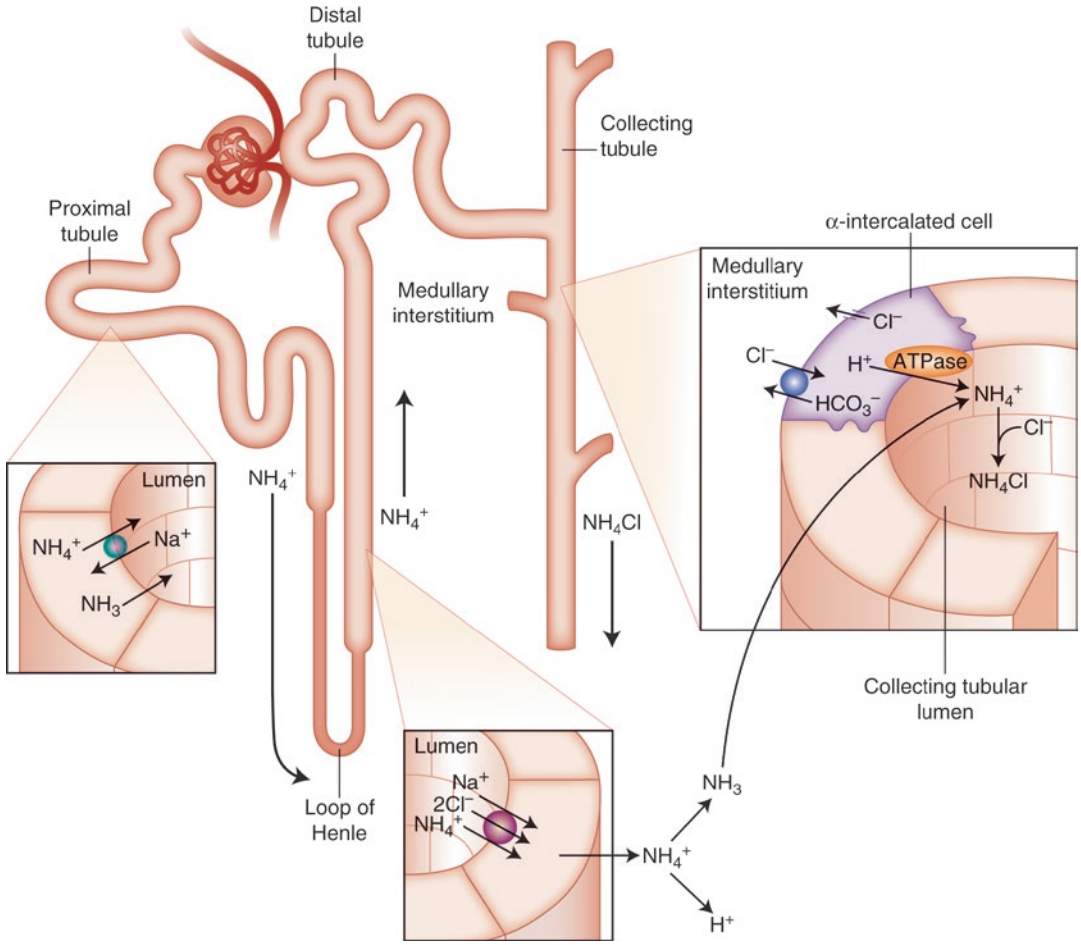

Fig. 3.6 The ammonia used to buffer urinary hydrogen ions is synthesized in the proximal convoluted tubule. It then diffuses into the proximal tubular lumen or can become acidified within the cell, forming ammonium, which can enter the tubular lumen by substituting for hydrogen ions on the Na+–H+ antiporter. Ammonium flows through the thick ascending limb of the loop of Henle, where it is transported from the tubule into the medullary interstitium by replacing potassium on an Na+–K+–2Cl transporter. In the interstitium, ammonium dissociates to ammonia, which diffuses down its concentration gradient into the lumen of the collecting tubule. Here ammonia combines with secreted H+ to form ammonium; NH4+ is then excreted as NH4Cl to maintain electroneutrality. A bicarbonate molecule is regenerated for each H+ eliminated in the urine. ATPase, adenosine triphosphatase. (Modified from Ref. [151])

production of these end products, which allow regulation of plasma NH_4^+ at suitably low levels. The kidneys, however, use glutamine to generate NH_4^+ and facilitate Cl^- excretion. Thus, production of glutamine by the liver can be seen as having an alkalinizing effect on plasma pH because the kidneys use this substance to excrete Cl^-.

Further support for this scenario comes from the discovery that hepatocytes are anatomically organized according to their enzymatic content [4]. Hepatocytes with a propensity to produce urea are positioned closer to the portal venule; those with a propensity to produce glutamine are positioned farther downstream [5]. The upstream (urea-producing) hepatocytes have the first chance at the NH_4^+ delivered. However, acidosis inhibits ureagenesis, thereby leaving more NH_4^+ available for the downstream (glutamine-

producing) hepatocytes. The leftover NH_4^+ is thus, in a sense, packaged as glutamine for export to the kidney, where it is used to facilitate Cl^- excretion.

Gastrointestinal Tract

The GI tract is often not given the attention it deserves as a component of acid–base physiology until regulation of the massive amounts of ionic molecules it handles is perturbed [6]. The gut handles strong ions very differently along its length. In the stomach, Cl^- is pumped out of the plasma and into the lumen, thereby reducing the SID and the pH. Simultaneously, as the Cl^- ion is pumped into the lumen, HCO_3^- is pumped in the opposite direction into the plasma via an exchanger. The SID is increased by the loss of Cl^- and the pH rises, producing the so-called alkaline tide that occurs at the beginning of a meal, when gastric acid secretion is maximal [7].

In the duodenum, Cl^- is reabsorbed and the plasma pH is normalized. Only slight changes in plasma pH are evident in the normal duodenal circulation because Cl^- is returned to the circulation almost as soon as it is removed. However, if gastric secretions are removed from the patient, whether by catheter suctioning or vomiting, Cl^- will be progressively lost and the SID will steadily increase and acidosis ensues. Loss of H^+ initiates alkalosis by abruptly increasing the HCO_3^- in circulation; however, Cl^- loss is the primary persistent lesion that maintains alkalosis. Consider that although H^+ is lost as HCl, it is also lost with every molecule of water removed from the body. When Cl^-, a strong anion, is lost without the corresponding loss of a strong cation, the SID is increased, and, therefore, the plasma H^+ concentration is decreased. When H^+ is lost as water rather than as HCl, the SID does not change; thus, the plasma H^+ concentration does not change either.

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

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

The small intestine may contribute strong ions to the plasma. This contribution is most apparent when mesenteric blood flow is compromised and lactate is produced, sometimes in large quantities. This is typically most pronounced after advanced ischemia and infarction. Interestingly, the intestine does not appear to be a source of lactate in sepsis, and actually removed lactate in an experimental models of endotoxemia [8, 9]. However, whether the GI tract is capable of regulating strong ion uptake in a compensatory fashion under normal circumstances has not been well studied. There is some evidence that the gut may modulate systemic acidosis in experimental endotoxemia by removing anions from the plasma [10]; however, the full capacity of the gut to affect acid–base balance remains to be determined.

Respiratory Regulation of Carbon Dioxide

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

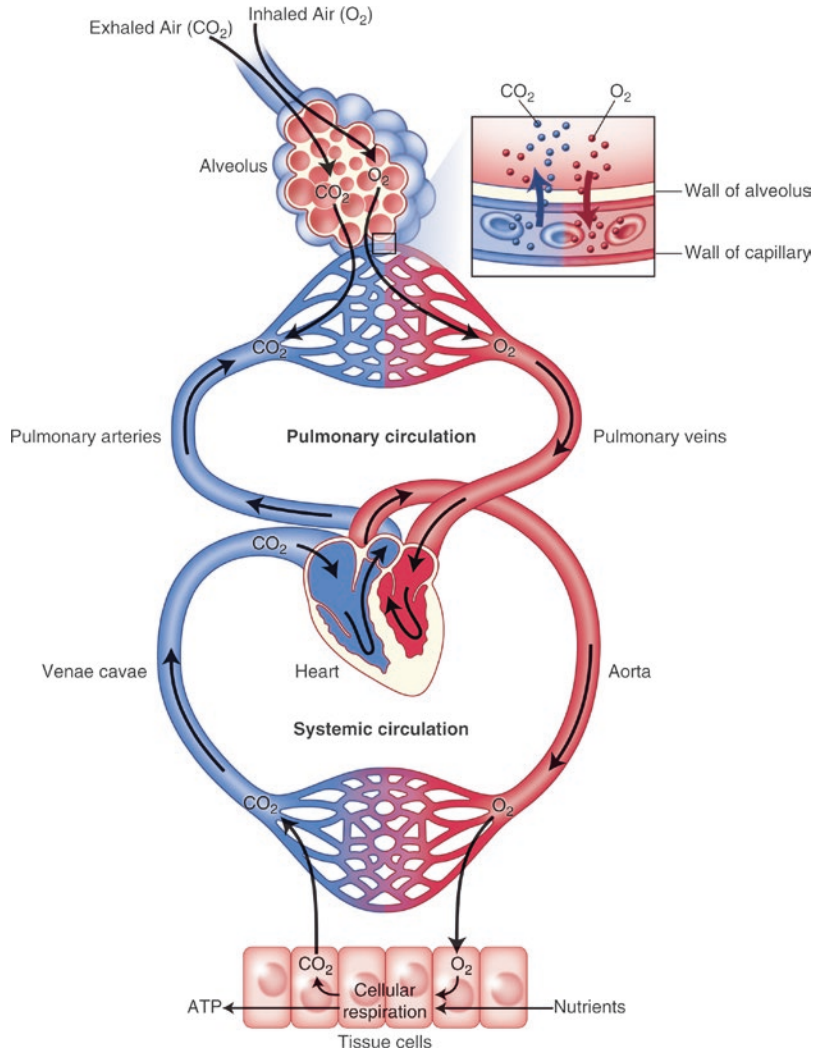

Fig. 3.7 Oxygen and carbon dioxide exchange between respiratory and circulatory systems. ATPase, adenosine triphosphate. (Modified from Ref. [151])

Description and Classification of Acid–Base Disorders

There are three widely accepted methods of describing and classifying acid–base abnormalities. Essentially, they differ from one another only with the assessment of the metabolic component of the abnormality. All three treat P_{CO_2} as an independent variable. The first method quantifies the metabolic component by using the bicarbonate ion (HCO_3^-) concentration (in the context of P_{CO_2}); the second, by using the standard base excess (SBE); and the third, by using the SID. In practice, these three methods usually yield virtually identical results when used to quantify the acid–base status of a given blood sample [1, 11–16]. Thus, the only significant distinctions between the methods are conceptual, related to how each one approaches the understanding of the mechanism of the disorder [14–17]. In this chapter, we emphasize Stewart's physicochemical determinants of pH in the blood and the tissues utilizing the approach of the SID to describe acid–base status in each compartment; however, it is a simple matter to convert from one approach to the other if desired [3]. Traditional techniques of assessing acid–base status relied largely on the difference in anion gap. This usually results in a

similar assessment of acid–base derangement but may provide an incomplete picture without considering non-bicarbonate buffers. This can lead to errors in clinical practice as the other components, such as derangements in weak anions and cations, may be missed.

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

The essential element of this physicochemical approach is the emphasis on independent and dependent variables. Only changes in the independent variables can bring about changes in the dependent variables. That is, movement of H^+ or HCO_3^- cannot affect plasma H^+ or HCO_3^- concentrations unless changes in the SID, Atot, or P_{CO_2} also occur. Several reviews of this approach are available in the literature [1, 12–23]. In what follows, we discuss the clinical application of this approach to the diagnosis and treatment of individual acid–base disorders.

Assessment of Acid–Base Balance

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

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

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

First, interpretation of arterial blood gas values and blood chemistries depends on the reliability of the data. Advances in clinical chemistry have improved the sensitivity of instruments used to measure electrolyte concentrations (e.g., ion-specific electrodes) and have greatly enhanced the speed and ease of analysis. Inevitably, however, prolonged exposure to the atmosphere results in a lowering of the P_{CO_2}, and over time, there may be contributions from ongoing cellular metabolism in the specimen. Accordingly, prompt measurement is always advisable. Even with prompt measurement, laboratory errors may occur, and information may be incorrectly

Table 3.1 Acid–base disorder subtypes

Disorder	pH	Parameter		
		HCO_3^- concentration (mEq/L)	P_{CO_2} (mm g)	SBE (mEq/L)
Metabolic acidosis	< 7.35	< 22	$= (1.5 \times HCO_3^-) + 8$ $= 40 + SBE$	< −5
Metabolic alkalosis	> 7.45	> 26	$= (0.7 \times HCO_3^-) + 21$ $= 40 + (0.6 \times SBE)$	> +5
Acute respiratory acidosis	< 7.35	$= \left[\left(P_{CO_2} - 40\right)/10\right] + 24$	> 45	= 0
Chronic respiratory acidosis	7.35–7.45	$= \left[\left(P_{CO_2} - 40\right)\right]/3 + 24$	> 45	$= 0.4 \times \left(P_{CO_2} - 40\right)$
Acute respiratory alkalosis	> 7.45	$= 24 - \left[\left(40 - P_{CO_2}\right)/5\right]$	< 35	= 0
Chronic respiratory alkalosis	7.35–7.45	$= 24 - \left[\left(40 - P_{CO_2}\right)/2\right]$	< 35	$= 0.4 \times \left(P_{CO_2} - 40\right)$

reported. Samples drawn from indwelling lines may be diluted by fluid or drug infusions (a notorious source of error).

Second, interpretation of arterial blood gas values may be problematic in patients with severe hypothermia (e.g., trauma patients undergoing damage control interventions, who often are severely hypothermic and sometimes experience severe acidosis), in that the findings may not reflect the actual blood gas values present. Because blood samples are "normalized" to a temperature of 37 °C before undergoing analysis, the results obtained in samples from a patient whose body temperature is significantly lower than 37 °C (98.6 °F) may not be accurate. To obviate this potential problem, the results may have to be adjusted to take the patient's actual temperature into account. At present, however, such temperature correction is not routinely done, and there has been some controversy regarding whether it has real clinical value [24, 25].

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

Metabolic Acid–Base Disorders

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

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

cations than strong anions (as with transfusion of large volumes of banked blood containing sodium citrate).

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

Metabolic Acidoses

Pathophysiology

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

Anion Gap Acidoses

Determination of Anion Gap

The AG has been used by clinicians for more than 30 years and has evolved into a major tool for evaluating acid–base disorders [26]. It is calculated—or, rather, estimated—from the difference between the routinely measured concentrations of serum cations (Na^+ and K^+) and the routinely measured concentrations of anions (Cl^- and HCO_3^-). Normally, albumin accounts for the bulk of this difference, with phosphate playing a lesser role. Sulfate and lactate also contribute a small amount to the gap (normally, <2 mEq/L); however, there are also unmeasured cations (e.g., Ca^{2+} and Mg^{2+}), which tend to offset the effects of sulfate, except when the concentration of one is abnormally increased. Plasma proteins other than albumin can be either positively or negatively charged, but in the aggregate, they tend to be electrically neutral [27], except in rare cases of abnormal paraproteins (as in multiple myeloma). In practice, the AG is calculated as follows:

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

Because of its low extracellular concentration, K^+ is often omitted from the calculation. In most laboratories, normal values fall into the range of 3–16 mEq/L when K^+ is included and 3–12 mEq/L when it is not. In the past few years, the introduction of more accurate methods of measuring Cl^- concentration has led to a general lowering of the normal AG range [28, 29]. Because of the various measurement techniques employed at various institutions, however, each institution is expected to report its own normal AG values.

Clinical Utility of Anion Gap

The primary value of the AG is that it quickly and easily limits the differential diagnosis in a patient with metabolic acidosis. When the AG is increased, the explanation is almost invariably one of the following five disorders: ketosis, hyperlactatemia, poisoning, renal failure, and sepsis [30].

In addition to these disorders, however, there are several conditions that can alter the accuracy of AG estimation and are particularly frequent in critical illness [31, 32]. Systemic hypovolemic status usually increases the concentrations of all of the ions. Severe hypoalbuminemia lowers the AG, with each 1 g/dL decline in the serum albumin reducing the apparent AG by 2.5–3 mEq/L;

accordingly, some recommend adjusting the AG for the prevailing albumin concentration [33]. Alkalosis (respiratory or metabolic) is associated with an increase of as much as 3–10 mEq/L in the apparent AG as a consequence of enhanced lactate production (from stimulated phosphofructokinase enzymatic activity), reduction in the concentration of ionized weak acids (A^-) (as opposed to Atot, the total concentration of weak acids), and, possibly, the additional effect of dehydration (which, as noted, has its own impact on AG calculation). A low Mg^{2+} concentration with associated low K^+ and Ca^{2+} concentrations is a known cause of an increased AG, as is the administration of sodium salts of poorly reabsorbable anions (e.g., β-lactam antibiotics) [34]. Certain parenteral nutrition formulations (e.g., those containing acetate) may increase the AG. In rare cases, citrate may have the same effect in the setting of multiple blood transfusions, particularly if massive doses of banked blood are used (as during liver transplantation) [35]. None of these rare causes, however, will increase the AG significantly [36], and they usually are easily identified.

In the past few years, some additional causes of an increased AG have been reported. The nonketotic hyperosmolar state of diabetes has been associated with an increased AG of uncertain and probably multifactorial etiology [37]. Unmeasured anions have been reported in the blood of patients with sepsis [38, 39], patients with liver disease [40, 41], and experimental animals that received endotoxin [42]. These anions may be the source of much of the unexplained acidosis seen in patients with critical illness [43].

The accepted clinical utility of the AG notwithstanding doubt has been cast on its diagnostic value in certain situations [31, 39]. Some investigators have found routine reliance on the AG to be "fraught with numerous pitfalls" [31]. The primary problem with the AG is its reliance on the use of a supposedly normal range produced by albumin and phosphate. Concentrations of albumin and phosphate may be grossly abnormal in patients with critical illness, and these abnormalities may change the normal AG range in this setting. Moreover, because these anions are not strong anions, their charge is altered by changes in pH. These concerns have led some authors to advocate adjusting the normal AG range on the basis of the patient's albumin [33] or even phosphate [14] concentration. Each 1 g/dL of albumin carries a charge of 2.8 mEq/L at a pH of 7.4 (2.3 mEq/L, pH = 7.0; 3.0 mEq/L, pH = 7.6), and each 1 mg/dL of phosphate carries a charge of 0.59 mEq/L at a pH of 7.4 (0.55 mEq/L, pH = 7.0; 0.61 mEq/L, pH = 7.6). Thus, the normal AG for a given patient can be conveniently estimated as follows [17]:

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

or, in international units,

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

In one study, when this formula for calculating a patient-specific normal AG range was used to determine the presence of unmeasured anions in the blood of critically ill patients, its accuracy was 96%, compared with an accuracy of 33% with the routine AG (normal range = 12 mEq/L) [17]. This technique should be employed only when the pH is less than 7.35; even in this situation, it is accurate only within 5 mEq/L. When more accuracy is needed, a slightly more complicated method of estimating unmeasured anions is required [40, 44].

Strong Ion Gap

An alternative to relying on the traditional AG is to use a parameter derived from the SID. By definition, the SID must be equal and opposite to the sum of the negative charges contributed by A^- and total CO_2. This latter value (A^- + total CO_2) has been termed the effective strong ion difference (SIDe) [37]. The apparent strong ion difference (SIDa) is obtained by measuring concentrations of each individual ion. The SIDa and the SIDe should

both equal the true SID. If the SIDa differs from the SIDe, unmeasured ions must be present. If the SIDa is greater than the SIDe, these unmeasured ions are anions; if the SIDa is less than the SIDe, they are cations. The difference between the SIDa and the SIDe has been termed the strong ion gap (SIG) to distinguish it from the AG [40]. Unlike the AG, the SIG is normally 0 and is not affected by changes in the pH or the albumin concentration. SIG has been shown to have prognostic value in the setting of trauma-related shock. In a study performed in 78 trauma patients, SIG measured early in the course of shock predicted mortality better than any other parameter, including AG, anion gap corrected (AGc), SBE, pH, and lactate with an area under the curve (AUC) of 0.96 [45].

Lactate

In many forms of critical illness, lactate is an important correlate of both metabolic acidosis and outcomes [46]. In particular, lactate concentrations have been shown to correlate with outcomes in patients with hemorrhagic [47] and septic shock [48]. Traditionally, lactate has been viewed as the predominant source of the metabolic acidosis that occurs in sepsis [49]. In this view, lactate is released primarily from the musculature and the gut as a consequence of anaerobic metabolism given tissue dysoxia, and the amount of lactate produced is believed to correlate with the total oxygen debt, the magnitude of hypoperfusion, and the severity of shock [46].

This view has been challenged for decades by the observations that during sepsis, even in profound shock, resting muscle does not produce lactate. Indeed, various studies have shown that the musculature and gut may actually consume lactate during endotoxemia [9, 50, 51]. More recently, authors have suggested that a global "hypermetabolic" state in which lactate production is increased sufficient to overwhelm clearance mechanisms may actually be a major contributor to hyperlactatemia during sepsis, rather than anaerobic metabolism [52].

Interestingly, lactic acid has a pKA of <4, meaning that is 99% dissociated at even remotely physiologic pH [53] and thus essentially only exists as lactate in both intra- and extracellular physiologic compartments. Therefore, the concept of lactate's causal relationship in metabolic acidosis that commonly accompanies its abundance has been challenged since at least 1978 [54]. In experimental models of cellular respiration using skeletal muscle, nonmitochondrial ATP molecule hydrolysis releases protons that are implicated in the acidosis of intense exercise, which is also accompanied by lactate release. Therefore, skeletal muscle hyperlactatemia may be seen as tightly associated with metabolic acidosis during critical illness or hypermetabolism, despite the entrenched concept of its causal relationship in development of systemic lactic acidosis [55]. Evidence from studies of cardiomyocytes concurs that acid release during ischemia is independent of lactate generation [56]. Although the source and interpretation of hyperlactatemia in critically ill patients remain controversial, there is a strong association between lactate accumulation and metabolic acidosis.

Lactate has been suggested as a biomarker for gut ischemia and associated abdominal sepsis. There is little question that the gut can release lactate if it is severely hypoperfused. It appears, however, that if the gut is adequately perfused, it does not release lactate during sepsis. Under such conditions, the mesentery either is neutral with respect to lactate release or takes up lactate [9, 50]. Perfusion is likely to be a major determinant of mesenteric lactate metabolism. In a canine model of sepsis induced by infusion of endotoxin, production of lactate by the gut could not be demonstrated when flow was maintained with dopexamine [51].

Both animal studies and human studies have shown that the lung may be a prominent source of lactate in the setting of acute lung injury [9, 57–60]. These studies do not address the underlying pathophysiologic mechanisms of hyperlactatemia in sepsis, but they do suggest that the conventional wisdom regarding lactate as evidence of tissue dysoxia is, at best, an oversimplification [61]. Indeed, many investigators have begun to offer alternative explanations for the development of hyperlactatemia in this set-

ting [58, 61–65]. One proposed mechanism is metabolic dysfunction from mitochondrial enzymatic derangements, which can lead to increased lactate generation and release. In particular, pyruvate dehydrogenase (PDH), the enzyme responsible for moving pyruvate into the Krebs cycle, is inhibited by endotoxin [66]. The role of aerobic hypermetabolism and increased production of lactate exceeding capacity for its removal during catabolism has also been investigated and suggested to contribute, especially during sepsis [67].This suggests that hyperlactatemia in sepsis occurs as a consequence of increased aerobic metabolism rather than of tissue hypoxia or PDH inhibition.

Such findings are consistent with the known metabolic effects of lactate production on cellular bioenergetics [59]. Lactate production alters cytosolic, and hence mitochondrial, redox states, so that the increased ratio of reduced nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide (NADH/NAD) supports oxidative phosphorylation as the dominant source of ATP production. Finally, the use of catecholamines, especially epinephrine, also results in hyperlactatemia, presumably by stimulating cellular metabolism (e.g., increasing hepatic glycolysis), and was associated with acidosis in the ICU [60, 68]. It is noteworthy that this phenomenon does not appear to occur with either dobutamine or norepinephrine [69] and does not appear to be related to decreased tissue perfusion.

Historically, hyperlactatemia has been subdivided into type A, in which the mechanism is tissue hypoxia, and type B, in which there is no hypoxia [70, 71]. This distinction may, however, be an artificial one. Disorders such as sepsis may be associated with hyperlactatemia through a variety of mechanisms some conventionally labeled type A and others type B. A potentially useful method of distinguishing between anaerobically produced lactate and lactate from other sources is to measure the serum pyruvate concentration. The normal lactate-to-pyruvate ratio is 10:1 [72], with ratios greater than 25:1 considered to be evidence of anaerobic metabolism [65]. This approach makes biochemical sense because pyruvate is shunted into lactate during anaerobic metabolism, dramatically increasing the lactate-to-pyruvate ratio. However, the precise test characteristics, including normal ranges and sensitivity and specificity data, have not yet been defined for patients; furthermore, the relative importance of anaerobic metabolism versus other sources of lactate during sepsis remains under study. Accordingly, this method remains investigational.

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

The vast majority of metabolic acidoses in association with hyperlactatemia are seen with the l-isomer. The d-isomer of lactate may also be associated with acidosis, but this is not detected by normal lactate analysis and must be requested as a separate test. This is typically only seen in patients with abnormal bowel anatomy which allows for bacterial overgrowth [73].

Sodium Bicarbonate

The efficacy of $NaHCO_3$ to treat metabolic acidosis with hyperlactatemia remains unproven [74]. In perhaps the most widely quoted study on this topic, hypoxic lactatemia was induced in anesthetized dogs by ventilating them with hypoxic gas [75]. These animals were then assigned to treatment with $NaHCO_3$ or placebo, and, surprisingly, the group receiving $NaHCO_3$ actually had higher plasma concentrations of both lactate and H^+ than the control group did. Furthermore, the $NaHCO_3$-treated animals exhibited decreases in cardiac output and blood pressure that were not seen in the control group. One possible explanation for these findings is that the HCO_3^- was converted to CO_2, and this conversion raised the P_{CO_2} not only

in the blood but also inside the cells of these animals with a fixed minute ventilation; the resulting intracellular acidosis might have been detrimental to myocardial function. This hypothesis has not, however, been supported by subsequent experimental studies, which have not documented paradoxical intracellular acidosis or even detrimental hemodynamic effects after $NaHCO_3$ treatment of hypoxic acidosis [76]. Furthermore, it is not clear how this type of hypoxic acidosis, induced in well-perfused animals, relates to the clinical conditions in which hyperlactatemia occurs in critically ill patients. The results of clinical studies have been mixed, but, overall, they do not support the use of $NaHCO_3$ therapy for metabolic acidosis with hyperlactatemia [74].

Ketoacidosis

Ketone body production is a relatively common cause of metabolic acidosis with AG and arises from excessive production of acetone, acetoacetate, and β-hydroxybutyrate. Both acetoacetate and β-hydroxybutyrate are strong anions (pK 3.8 and 4.8, respectively) [77]. Their presence, like the presence of lactate, decreases the SID and increases the H^+ concentration.

Ketones are formed through beta oxidation of fatty acids, a process that is inhibited by insulin. In diabetics, hyperglycemia may produce an osmotic diuresis that leads to volume contraction. This state is associated with elevated cortisol and catecholamine secretion, which further stimulates free fatty acid production [78]. In addition, an increased glucagon level relative to the insulin level leads to a decreased malonyl coenzyme A level and an increased carnitine palmitoyl acyl transferase level—a combination that also increases ketogenesis.

Treatment of DKA includes administration of insulin and large amounts of fluid (0.9% saline is usually recommended); potassium replacement is usually required as well. Fluid resuscitation reverses the hormonal stimuli for ketone body formation, and insulin allows the metabolism of ketones and glucose. Administration of $NaHCO_3$ may produce a more rapid rise in the pH by increasing the SID, but there is little evidence that this result leads to better outcomes. Furthermore, to the extent that the SID is increased by increasing the plasma Na^+ concentration, the SID will be too high once the ketosis is cleared, thus resulting in a so-called overshoot alkalosis. In any case, such measures are rarely necessary and should be avoided except in cases of very extreme acidosis (i.e., pH <6.9 [79, 80]).

A common problem in the treatment of DKA is the persistence of acidemia after the ketosis has resolved. This hyperchloremic metabolic acidosis occurs as Cl^- replaces keto acids, thus maintaining a decreased SID and pH. There appear to be two reasons for this phenomenon. First, exogenous Cl^- is often provided in the form of 0.9% saline, which, if given in large enough quantities, will result in a so-called dilutional acidosis [80]. Second, some degree of increased Cl^- reabsorption apparently occurs as ketones are excreted in the urine. It has also been suggested that the increased tubular Na^+ load produces electrical–chemical forces that favor Cl^- reabsorption [81–83].

AKA is usually less severe than DKA. It typically is the result of patients, who suffer from chronic alcoholism, discontinuing solid food while continuing to consume alcohol. This syndrome occurs when the alcohol consumption is acutely discontinued. These patients typically present with a history of vomiting and acute abdominal pain which has forced them to stop drinking. Treatment consists of administration of fluids and (in contrast to treatment of DKA) glucose rather than insulin [84]. Insulin is contraindicated in AKA patients because it may cause precipitous hypoglycemia [85]. Thiamine must also be given to keep from precipitating Wernicke encephalopathy.

Acidosis Secondary to Toxin Ingestion

Metabolic acidosis with an increased AG is a major feature of various types of intoxication (Table 3.2). Generally, it is more important to recognize these conditions and provide specific

Table 3.2 Classic causes of anion gap metabolic acidosis

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

therapy for them than it is to treat the acid–base imbalances that they produce.

Salicylates

Toxic ingestion of salicylates in adults typically presents with early respiratory alkalosis, mixed metabolic acidosis–respiratory alkalosis, or a pure metabolic acidosis. The metabolic component of acidosis is typically seen in association with organic acid (keto acid and lactate) retention due to the activity of salicylate on cellular metabolism. Treatment is focused initially upon securing the patient's airway if indicated and then removing the offending agent by performing gastric lavage for a recent ingestion. In an awake and alert patient (or after definitive airway is secured), activated charcoal administration may prevent further absorption from the GI tract. Refractory acidosis and toxicity is treated with aggressive hydration and subsequent alkalinization of the urine with $NaHCO_3$. Hemodialysis may be necessary for severe poisoning [86].

Alcohols

Alcohol intoxication may be suspected based on clinical presentation and history. This toxidrome is characterized by an increased osmolar gap metabolic acidosis ($P_{osm} = 2 \times Na^+ + Glucose/18 + BUN/2.8$) owing to unaccounted alcoholic acids in circulation without other osmolytes to account for this gap (mannitol, IV contrast) [87].

Ethylene Glycol

Antifreeze ingestion may present as a patient who appears intoxicated but with an atypical sweet oral odor. Over time, these patients may progress to severe neurological impairment, including seizures or coma. In the appropriate clinical context, initial treatment should not be delayed for laboratory confirmation and includes aggressive volume resuscitation, alcohol dehydrogenase inhibition (i.e., ethanol or fomepizole), thiamine and pyridoxine supplementation, and, if necessary, hemodialysis. Fomepizole, an alcohol dehydrogenase inhibitor, may be a better choice than ethanol as it is dialyzable and titratable and has a predictable rate of elimination [88]. Finally, metabolic acidosis is associated with worse outcomes owing to increased tissue penetration of protonated glycolic acid derivatives; therefore, it is recommended that all patients with ethylene glycol intoxication and accompanying acidosis be treated with IV $NaHCO_3$.

Methanol

The acidemia caused by methanol may be related to the production of lactate as well as from the intoxicant itself. Without rapid treatment (similar to those for ethylene glycol intoxication), CNS toxicity and retinal damage may occur.

Isopropyl Alcohol

Intoxication with isopropyl alcohol may be the result of ingestion or excessive absorption through the skin. Although isopropanol and its metabolite, acetone, may cause an osmolar gap, they do not typically cause a systemic metabolic acidosis. Treatment is centered around symptomatic control; however, if worsening acidosis or cardiovascular collapse ensue, hemodialysis may be necessary in severe cases [87].

Renal Failure

Renal failure may produce a hyperchloremic metabolic acidosis, especially when it is chronic, the buildup of sulfates and other acids frequently increases the AG; however, the increase usually is not large [89]. Uncomplicated renal failure rarely produces severe acidosis, except when it is accompanied by high rates of acid generation (e.g., from hypermetabolism) [90]. In all cases, the SID is decreased and will remain unchanged until therapy is provided. An observational study on 64 maintenance hemodialysis patients and 14 control subjects

showed that acidosis was secondary to three causes: hyperphosphatemia, hyperchloremia, and increased unmeasured anions [91]. Hyperchloremia and the accumulation of unmeasured anions accounted for similar acidifying effects and for almost 90% of the acidosis in this type of patient. Hemodialysis permits the removal of sulfate and other ions and allows the restoration of normal Na^+ and Cl^- balance, thus returning the SID to a normal (or near-normal) value. However, those patients who do not yet require dialysis and those who are between treatments often require some other therapy aimed at increasing the SID. $NaHCO_3$ may be used for this purpose, provided that the plasma Na^+ concentration is not already elevated.

Acidosis Secondary to Rhabdomyolysis

The extensive muscle tissue breakdown associated with myonecrosis may also be a source of positive-AG metabolic acidosis. The acidosis results from accumulation of organic acids, but the myoglobinuria associated with the disorder may also induce renal failure. In most cases, the diagnosis is a clinical one and can be facilitated by measuring creatine kinase or aldolase levels. Early identification and aggressive resuscitation may prevent the onset of renal failure and improve the prognosis [92].

Acidosis of Unknown Origin

Several causes of AG acidosis have been reported that have yet to be elucidated. An unexplained AG in the nonketotic hyperosmolar state of diabetes has been reported [37]. In addition, even when very careful measurement techniques have been employed, unmeasured anions have been reported in the blood of patients with sepsis [38, 39, 93], patients with liver disease [40], and animals to which endotoxin had been administered [41]. Furthermore, unknown cations also appear in the blood of some critically ill patients [20, 39, 94, 95]. The significance of these findings remains to be determined.

Prognostic Significance of Positive-AG Metabolic Acidosis

Several studies have examined whether the presence of unmeasured anions in the blood is associated with particular outcomes in critically ill patients. Two such studies focused on trauma patients. In one, the investigators examined 2152 sets of laboratory data from 427 trauma patients and found that the SIG altered the acid–base disorder diagnosis in 28% of the datasets [96]. Simultaneous measurements of blood gas, serum electrolyte, albumin, and lactate values were used to calculate the base deficit, the AG, and the SIG. Unmeasured anions (defined by the presence of an elevated SIG) were present in 92% of patients; hyperlactatemia and hyperchloremia occurred in only 18% and 21% of patients, respectively. The arterial SBE at ICU admission was poorly predictive of hospital survival, and its predictive ability was only slightly improved by controlling for unmeasured ions. In this dataset, survivors could not be differentiated from nonsurvivors in the group as a whole on the basis of the SIG. However, in the subgroup of patients whose lactate level was normal at admission, there was a significant difference in the SIG between survivors and nonsurvivors, although no such differences were noted in the conventional measures (i.e., SBE and AG).

The poor predictive ability of the SBE, the AG, and even the SIG has been confirmed by studies of general ICU patients. In one study, analysis of data from 300 adult ICU patients demonstrated statistically significant but weak correlations between these measures and hospital mortality [97]. In another study, however, pretreatment SIG was found to be a very strong predictor of outcome in 282 patients who had sustained major vascular injury [98]. All but one of the nonsurvivors had an initial emergency department (ED) pH of 7.26 or lower, an SBE of −7.3 mEq/L or lower, a lactate concentration of 5 mmol/L or higher, and an SIG of 5 mEq/L or higher. All of the acid–base descriptors were strongly associated with outcome, but the SIG was the one that discriminated most strongly. The investigators concluded that initial ED acid–base variables,

especially SIG, could distinguish survivors of major vascular injury from nonsurvivors. A subsequent prospective study in 78 trauma patients by the same group showed again the high predictive ability of SIG with an AUC of 0.96 (95% CI 0.89–0.99) when predicting mortality, which was superior to SBE (0.63), lactate (0.60), AG (0.8), AGc (0.86), and pH (0.50) [39].

Even though the uncorrected AG and the SBE correlate poorly with the arterial lactate concentration in trauma patients [99], several investigators have proposed that these parameters be used as surrogate measures of the severity of shock or lack of resuscitation. Various studies have shown that the SBE is a poor predictor of lactatemia and mortality in both medical patients and surgical or trauma patients and that it cannot be substituted for direct measurement of the serum lactate concentration [31, 100, 101]. Some investigators, however, have found that the SBE can be used as a marker of injury severity and mortality and as a predictor of transfusion requirements [102–104]. Unfortunately, the SBE can determine only the degree of acid–base derangement, never the cause. In many critically injured patients, abnormalities in body water content, electrolyte levels, and albumin concentration limit any potential correlation between SBE and lactate concentration, even when other sources of acid are absent.

Several reports in the trauma literature have focused on the prognostic value of persistently elevated lactate levels during the first 24–48 h after injury. In one study, involving 76 patients with multiple injuries who were admitted directly to the ICU from the operating room or the ED, serum lactate levels and oxygen transport were measured at ICU admission and at 8, 16, 24, 36, and 48 h [105]. In those patients whose lactate levels returned to normal within 24 h, the survival rate was 100%, and in those whose lactate levels returned to normal between 24 and 48 h, the survival rate was 75%. However, in those whose lactate levels did not return to normal by 48 h, the survival rate was only 14%. Thus, the rate of normalization of the serum lactate level is an important prognostic factor for survival in a severely injured patient.

It is important, however, to understand that metabolic acidosis can no longer be considered as a generic term when trying to assess outcome early in the course of disease, given that the type of metabolic acidosis (i.e., hyperchloremic, SIG) influences outcome as demonstrated by Gunnerson and colleagues [105, 106].

Non-anion Gap Acidosis (Hyperchloremic)

Hyperchloremic metabolic acidosis occurs as a result of either an increase in the level of Cl^- relative to the levels of strong cations (especially Na^+) or a loss of cations with retention of Cl^-. The various causes of such an acidosis (Tables 3.3 and 3.4) can be distinguished on the basis of the history and the measured Cl^- concentration in the urine [107, 108]. When acidosis occurs, the kidney normally responds by increasing Cl^- excretion; the absence of this response usually identifies the kidney's mishandling as the primary lesion. Extrarenal hyperchloremic acidoses occurs because of exogenous Cl^- loads (iatrogenic acidosis) or because of loss of cations from the GI tract without proportional loss of Cl^- (gastrointestinal acidosis).

Table 3.3 Non-anion gap metabolic acidosis

Renal tubular acidosis
Types I, II, and IV
Diarrhea
High-output enterocutaneous fistula
Pancreatic fistula
Iatrogenesis (i.e., saline resuscitation)
Parenteral nutrition

Table 3.4 Causes of elevated lactate

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

Gastrointestinal Tract Loss

Fluid secreted into the gut lumen contains more Na^+ than Cl^-; the proportions are similar to those seen in plasma. Massive loss of this fluid, particularly if lost volume is replaced with fluid containing equal amounts of Na^+ and Cl^-, will result in a decreased plasma Na^+ concentration relative to the Cl^- concentration and a reduced SID. Such a scenario can be prevented by using solutions such as lactated Ringer's solution (LRS) instead of water or saline. LRS has a more physiologic SID than water or saline and therefore does not produce acidosis except in rare circumstances [109].

Renal Tubular Acidosis

Most cases of RTA can be correctly diagnosed by determining urine and plasma electrolyte levels and pH and calculating the SIDa in the urine (Table 3.3) [110]. However, caution must be exercised when the plasma pH is greater than 7.35 because urine Cl^- excretion may be turned off. In such circumstances, it may be necessary to infuse sodium sulfate or furosemide. These agents stimulate excretion of Cl^- and K^+ and may be used to unmask the defect and to probe K^+ secretory capacity.

Establishing the specific mechanisms of RTA beyond the general concepts of tubular ammonium excretion insufficiency and $NaHCO_3$ wasting has proved difficult. It is likely that much of the difficulty results from the attempt to understand the physiology from the perspective of regulation of H^+ and HCO_3^- concentrations. In all types of RTA, a major characteristic defect is the inability to excrete Cl^- in proportion to excretion of Na^+, although the precise reasons for this inability vary by RTA type. Treatment is largely dependent on whether the kidney will respond to mineralocorticoid replacement and whether there is Na^+ loss that can be counteracted by administering $NaHCO_3$.

Classic distal (type I) RTA responds to oral $NaHCO_3$ replacement or sodium citrate; generally, the required dosage of $NaHCO_3$ is in the range of 50–100 mEq/day. Hypokalemia is also common in this type of RTA; thus, K^+ replacement is also frequently required until the metabolic acidosis is completely treated. There is also a common hyperkalemic variant of type I RTA in which the central defect appears to be impaired Na^+ transport in the cortical collecting duct. Patients with this condition also respond to $NaHCO_3$ replacement.

Proximal (type II) RTA is characterized by defects in the reabsorption of both Na^+ and K^+. It is an uncommon disorder and usually occurs as part of Fanconi syndrome, in which reabsorption of glucose, phosphate, urate, and amino acids is also impaired. Treatment of type II RTA with $NaHCO_3$ results in increased excretion. Therefore, large amounts of $NaHCO_3$ are required, and thiazide diuretics have been used with varying degrees of success.

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

Iatrogenic Acidosis

Two of the most common causes of hyperchloremic metabolic acidosis are iatrogenic, and both involve administration of exogenous Cl^-. One of these potential causes is parenteral nutrition. Metabolic acidosis is the most common acid–base derangement associated with parenteral nutrition. This has long been recognized as a common problem among critically ill patients supported with this nutritional modality [111]. Modern parenteral nutrition formulas contain weak anions (e.g., acetate) in addition to Cl^-, and the proportions of these anions can be titrated according to the acid–base status of the patient. Other contributory mechanisms include direct administration of cationic amino acids, amino acids containing sulfur groups, and thiamine deficiency, which is common among malnourished patients [112]. If sufficient amounts

of weak anions are not provided in the formula, the plasma Cl^- concentration will increase, reducing the SID and causing acidosis. Patients receiving TPN should undergo frequent monitoring of acid–base status along with electrolytes at the initiation of therapy, especially those who are critically ill and at risk for refeeding syndrome and other derangements. Enteral nutrition appears to be much safer with respect to acid–base homeostasis, likely owing to the gut's intrinsic roles as a barrier to and regulator of acids. However, there has been even less investigation into the formula- and volume-specific effects of enteral nutrition on whole-body acid–base homeostasis than there has been with normal dietary intake.

The other potential cause is fluid resuscitation with saline, which can give rise to a so-called dilutional acidosis, a problem first described more than 40 years ago [113, 114]. Some authors have argued that dilutional acidosis is, at most, a minor issue [115]. This argument is based on studies showing that in healthy animals, large doses of NaCl produce only a minor hyperchloremic acidosis [116]. These studies have been interpreted as indicating that dilutional acidosis occurs only in extreme cases and even then is mild. However, this line of reasoning cannot be applied to critically ill patients, for two reasons. First, it is common for patients with sepsis or trauma to require large-volume resuscitation; sometimes, such patients receive crystalloid infusions equivalent to 5–10 times their plasma volumes in a single day. Second, critically ill patients frequently start with considerable acid–base derangements, i.e., renal insufficiency. Furthermore, critically ill patients may not be able to compensate for acid–base imbalance normally (e.g., by increasing ventilation), and they may have abnormal buffer capacity as a result of hypoalbuminemia. In ICU and surgical patients [117–119], as well as in animals with experimentally induced sepsis [120], saline-induced acidosis does occur and can produce significant acidemia.

The reason why administration of saline causes acidosis is that solutions containing equal amounts of Na^+ and Cl^- affect plasma concentrations of Na^+ and Cl^- differently [121]. Although some authors continue to argue that a simple "dilutional" effect of fluids on the amount of base (HCO_{3^-}) is sufficient to explain the phenomenon [122], this concept has been questioned [123]. The normal serum Na^+ concentration is 35–45 mEq/L higher than the normal Cl^- concentration. Adding, for example, 154 mEq/L of each ion in 0.9% saline will result in a greater relative increase in the Cl^- concentration than in the Na^+ concentration. This does not explain, however, why critically ill patients are more susceptible to this disorder than healthy persons are.

It appears that many critically ill patients have a significantly lower SID than healthy persons do, even when these patients have no evidence of a metabolic acid–base derangement [124]. The positive charge of the SID is balanced by the negative charges of A^- and total CO_2, but many critically ill patients are hypoalbuminemic, and A^- tends to be reduced. Because arterial P_{CO_2} is maintained for other reasons, a reduction in A^- leads to a reduction in SID so that a normal pH can be maintained. Thus, a typical ICU patient may have an SID of 30 mEq/L rather than 40–42 mEq/L. If a metabolic acidosis then develops in this patient, the SID will decrease further. If this patient is subsequently resuscitated with large volumes of 0.9% saline, a significant metabolic acidosis will result.

The clinical implication for management of ICU patients is that if large volumes of fluid are to be given for resuscitation, fluids that are more physiologic than saline should be used. One alternative is LRS, which has a more physiologic ratio of Na^+ content to Cl^- content and thus has an SID that is closer to normal (roughly 28 mEq/L, compared with an SID of 0 mEq/L for saline). Of course, the assumption here is that the lactate in LRS is metabolized, which, as noted (see above), is almost always the case. Volume resuscitation also reduces the weak acid concentration, thereby moderating the acidosis. One ex vivo study concluded that administration of a solution with an SID of approximately 24 mEq/L will have a neutral effect on the pH as blood is progressively diluted [125].

Unexplained Hyperchloremic Acidosis

Critically ill patients sometimes manifest hyperchloremic metabolic acidosis for reasons that cannot be determined. Often other coexisting types of metabolic acidosis are present, making the diagnosis difficult. In many instances, the presence of unexplained anions may be the cause [38–40]. However, anions such as amino acids, uric acid, and organic acids were shown to contribute to SIG only in 7.9% in critically ill patients with metabolic acidosis [126, 127], whereas in other cases, there is a hyperchloremic acidosis [93]. Saline resuscitation may be responsible for much of this acidosis (see above), but experimental evidence from endotoxemic animals suggests that as much as a third of the acidosis cannot be explained in terms of current knowledge [120].

One potential explanation for unexplained hyperchloremic acidosis is partial loss of the Donnan equilibrium between plasma and interstitial fluid. The severe capillary leakage that accompanies this loss of equilibrium results in loss of albumin from the vascular space, which means that another ion must move into this space to maintain the charge balance between the two compartments. If Cl^- moves into the plasma space to restore the charge balance, a strong anion is replacing a weak anion, and a hyperchloremic metabolic acidosis results. This hypothesis appears reasonable but, at present, remains unproven. Given mounting evidence for balanced crystalloids as the resuscitation medium of choice, use of 0.9% NaCl should be reserved only for critically ill patients in whom the clinical situation clearly indicates its use over LRS or similar crystalloid [128].

Metabolic Alkaloses

Pathogenesis and Differential Diagnosis

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

Table 3.5 Metabolic alkalemia causes

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

Chloride-Sensitive Metabolic Alkaloses

Chloride-responsive metabolic alkalosis usually occurs as a result of loss of Cl^- from the stomach (e.g., through vomiting or gastric drainage). Treatment consists of replacing the lost Cl^-, typically with NaCl. Because chloride-responsive alkalosis is usually accompanied by volume depletion, the most common therapeutic option is normal saline along with KCl. Hypovolemia

stimulates aldosterone secretion, which results in reabsorption of Na^+ and loss of K^+. Saline is effective even though it contains Na^+ because the administration of equal amounts of Na^+ and Cl^- yields a larger relative increase in the Cl^- concentration than in the Na^+ concentration.

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

Chloride-Resistant Metabolic Alkaloses

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

Other Causes of Metabolic Alkalosis

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

Diagnostic Evaluation and Management

Metabolic Acidosis

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

Even fairly profound acidosis appears to be well-tolerated by healthy persons, particularly when the duration of the acidosis is short. For example, healthy individuals may achieve an arterial pH lower than 7.15 and a lactate concentration higher than 20 mEq/L during maximal exercise, with no lasting effects [129]. Over the long term, however, even mild acidemia (pH <7.35) may lead to bone disease and protein catabolism. Furthermore, critically ill patients may not be able to tolerate even brief episodes of acidemia [130]. There do appear to be significant differences between respiratory and metabolic acidoses (and even among different types of metabolic acidosis) with respect to patient outcome, and these differences suggest that the underlying disorder may be more important than the absolute degree of acidemia [106, 107, 131].

If prudence dictates that symptomatic therapy is to be provided, the likely duration of the disorder should be taken into account. When the disorder is expected to be a short-lived one (e.g., diabetic ketoacidosis), maximizing respiratory compensation is usually the safest approach. Once the disorder resolves, ventilation can be quickly reduced to normal levels, and there will be no lingering effects from therapy. If the SID is increased (e.g., by administering $NaHCO_3$), there is a risk of alkalosis when the underlying disorder resolves. When the disorder is likely to be a more chronic one (e.g., renal failure), therapy aimed at restoring the SID to normal is indicated. In all cases, the therapeutic target can be accurately determined from the SBE. As noted (see above), the SBE corresponds to the amount by

which the current SID differs from the SID necessary to restore the pH to 7.4, given a P_{CO_2} of 40 mm Hg [20]. Thus, if the SID is 30 mEq/L and the SBE is −10 mEq/L, the target SID is 40 mEq/L. Accordingly, the plasma Na^+ concentration would have to increase by 10 mEq/L for $NaHCO_3$ administration to correct the acidosis completely.

It should be noted that the target SID is the SID at the equilibrium point of the SID, P_{CO_2}, and Atot and that it may not be equal to 40 mEq/L, as in the example given. By convention, P_{CO_2} is set at 40 mm Hg, but the SBE is not corrected for abnormalities in Atot. In many hypoalbuminemic patients, Atot is lower than normal; thus, the SID at the equilibrium point will be less than 40 mEq/L [132]. Also, it is rare that the choice would be made to correct the acid–base abnormality completely. Therefore, the target SID should be used as a reference value, but in most cases, partial correction is all that is required.

If increasing the plasma Na^+ concentration is inadvisable for other reasons (e.g., hypernatremia), $NaHCO_3$ administration is inadvisable. It is noteworthy that $NaHCO_3$ administration has not been shown to improve outcome in patients with hyperlactatemia and metabolic acidosis [74]. In addition, $NaHCO_3$ administration is associated with certain disadvantages [133]. Large (hypertonic) doses, if given rapidly, may actually reduce blood pressure [134] and may cause sudden, severe compensatory increases in Pa_{CO_2} [135]. Accordingly, it is important to assess the patient's ventilatory status before $NaHCO_3$ is administered, particularly if the patient is not on a ventilator. $NaHCO_3$ infusion also affects serum K^+ and Ca^{2+} concentrations, which must be monitored closely.

Dichloroacetate has been utilized for treatment of congenital metabolic acidoses due to its ability to stimulate pyruvate dehydrogenase, which results in a decrease in the production of lactate. However, due to the observation of toxicity, including limb paralysis and other neuropathies, it is no longer recommended for use in the treatment of metabolic acidosis with hyperlactatemia [136–139].

THAM (tris-hydroxymethyl aminomethane) is a synthetic buffer that consumes CO_2 and readily penetrates cells [133, 140]. It is a weak base (pK = 7.9) and, as such, is unlike other plasma constituents. The major advantage of THAM is that it does not alter the SID, which means that there is no need to be concerned about having to increase the plasma Na^+ concentration to achieve a therapeutic effect. Accordingly, THAM is often used in situations where $NaHCO_3$ cannot be used because of hypernatremia. Although THAM has been available since the 1960s, there is surprisingly little information available regarding its efficacy in humans with acid–base disorders. In small uncontrolled studies, THAM was capable of reversing metabolic acidosis secondary to ketoacidosis or renal failure without causing obvious toxicity [141]. However, adverse reactions have been reported, including hypoglycemia, respiratory depression, and even fatal hepatic necrosis, especially when using greater concentrations. In Europe, a mixture of THAM, acetate, $NaHCO_3$, and disodium phosphate is available. This mixture, known as tribonate (Tribonat, Pharmacia and Upjohn, Solna, Sweden), seems to have fewer side effects than THAM alone does, but as with THAM, experience with its use in humans is still quite limited.

Respiratory Acid–Base Disorders

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

Pathophysiology

CO_2 is produced by the body at a rate of 220 mL/min, which equates to production of 15 moles of carbonic acid each day [142]. By way of compari-

son, total daily production of all the nonrespiratory acids managed by the kidney and the gut amounts to less than 500 mmol per day. Pulmonary ventilation is adjusted by the central respiratory center in response to increased Pa_{CO_2}, decreased pH, and decreased Po_2. Normal Pa_{CO_2} (40 mm Hg) is attained by precisely matching alveolar ventilation to metabolic CO_2 production. Pa_{CO_2} changes in predictable ways as a compensatory ventilatory response to the altered arterial pH produced by metabolic acidosis or alkalosis (see Table 3.1).

Respiratory Acidosis

Mechanism

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

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

Patients whose renal function is intact can eliminate Cl^- in the urine; after a few days, the SID rises to the level required to restore the pH to a value of 7.35 [143]. It is unclear whether this amount of time is necessary because of the physiologic constraints of the system or because of benefits from not being overly sensitive to transient changes in alveolar ventilation. In any case, this response yields an increased pH for any degree of hypercapnia. According to the Henderson–Hasselbalch equation, the increased pH results in an increased HCO_3^- concentration for a given P_{CO_2}. Thus, the "adaptive" increase in the HCO_3^- concentration is actually the consequence, not the cause, of the increased pH. Although the HCO_3^- concentration is a convenient and reliable marker of metabolic compensation, it is not the mechanism of the compensatory response. This point is not merely a semantic one: as noted previously, only changes in the independent variables of acid–base balance (P_{CO_2}, Atot, and SID) can affect the plasma H^+ concentration, and HCO_3^- concentration is not an independent variable.

Management

Treatment of Underlying Ventilatory Impairment

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

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

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

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

Control of Hypoxemia

In patients breathing room air, the Pa_{CO_2} cannot exceed 80 mm Hg before life-threatening hypoxemia results, implicating hypoxemia as an earlier threat to life than acidosis mediated by. Accordingly, supplemental oxygen is required in the treatment of these patients. Unfortunately, increasing oxygenation in surgical patients is rarely sufficient treatment by itself, and it generally proves necessary to address the ventilatory defect. When the underlying cause can be addressed quickly (as when the effects of narcotics are reversed with naloxone), endotracheal intubation may be avoidable. In the majority of patients, however, this is not the case, and mechanical ventilatory support must be initiated by either noninvasive methods (i.e., bi-level positive airway pressure [BiPAP]) or endotracheal intubation. Mechanical support is indicated for patients who are unstable or at risk for instability and patients in whom CNS function is deteriorating. In patients who exhibit signs of respiratory muscle fatigue, mechanical ventilation should be instituted before respiratory failure occurs. Therefore, it is not the absolute Pa_{CO_2} value that is the most important consideration in this situation but, rather, the clinical condition of the patient.

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

BiPAP can be a useful initial treatment for patients with hypercapnia and acidosis. This technique is appropriate in the management of those patients whose sensorium is not impaired and is generally contraindicated after recent foregut surgery [144]. Rapid infusion of $NaHCO_3$ in patients with respiratory acidosis may induce acute respiratory failure if alveolar ventilation is not increased to account for the increased CO_2. Thus, if $NaHCO_3$ is to be given, it must be administered slowly, with alveolar ventilation adjusted appropriately. Furthermore, it must be remembered that $NaHCO_3$ works by increasing the plasma Na^+ concentration; if this effect is not possible or not desirable, $NaHCO_3$ should not be given.

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

Permissive Hypercapnia

There has been considerable interest in ventilator-associated lung injury and strategies to decrease barotrauma. Overdistention of alveoli can result

in tissue injury and microvascular permeability, which lead to interstitial and alveolar edema. In animal studies, prolonged use of elevated airway pressures and increased lung volumes resulted in increased pathologic pulmonary changes and decreased survival when compared with ventilatory strategies employing lower pressures and volumes [145, 146]. In a large multicenter clinical trial, simply lowering the tidal volume on the ventilator from 12 mL/kg to 6 mL/kg in patients with acute lung injury resulted in a 9% absolute reduction in mortality risk [147]. Although the protocol followed in this trial did not advocate a reduced minute ventilation and hence an elevated Pa_{CO_2}, this approach, often referred to as permissive hypercapnia or controlled hypoventilation, has been increasingly used clinically. Uncontrolled studies suggest that permissive hypercapnia may reduce mortality in patients with severe ARDS [131]. This strategy is not, however, without risks. Sedation is mandatory, and neuromuscular blocking agents are frequently required. Intracranial pressure rises, as does transpulmonary pressure; consequently, this technique is unusable in patients with brain injury or right ventricular dysfunction. There is controversy regarding how low the pH can be allowed to fall. Some authors have reported good results with pH values of 7.0 or even lower [4], but most have advocated more modest pH reductions (i.e., 7.25).

Respiratory Alkalosis

Respiratory alkalosis is a frequently encountered acid–base disorder. It occurs in residents of high-altitude locales and in persons with any of a wide range of pathologic conditions, the most important of which are salicylate intoxication, early sepsis, hepatic failure, and hypoxic respiratory disorders. Respiratory alkalosis also occurs in association with pregnancy and with pain or anxiety. Hypocapnia appears to be a particularly strong negative prognostic indicator in patients with critical illness [148]. Like acute respiratory acidosis, acute respiratory alkalosis results in a small change in the HCO_3^- concentration, as dictated by the Henderson–Hasselbalch equation. If hypocapnia persists, the SID begins to decrease as a consequence of renal Cl^- reabsorption. After 2–3 days, the SID assumes a new and lower steady state [149].

Severe alkalemia is unusual in respiratory alkalosis. Management therefore is typically directed toward the underlying cause [150].

Pseudorespiratory Alkalosis

The presence of arterial hypocapnia in patients experiencing profound circulatory shock has been termed pseudorespiratory alkalosis [114]. This condition occurs when alveolar ventilation is supported, but the circulation is grossly inadequate. In such circumstances, the mixed venous P_{CO_2} is significantly elevated, but the Pa_{CO_2} is normal or even decreased as a consequence of reduced CO_2 delivery to the lung and increased pulmonary transit time. Overall CO_2 clearance is therefore markedly decreased, and profound tissue acidosis—usually both metabolic and respiratory—ensues. The metabolic component of the acidosis comes from tissue hypoperfusion in association with hyperlactatemia. Arterial oxygen saturation may also appear adequate despite tissue dysoxia. Pseudorespiratory alkalemia indicates a rapidly fatal circulatory insufficiency that will be fatal unless the underlying hemodynamic failure is addressed.

References

1. Corey HE. Stewart and beyond: new models of acid-base balance. Kidney Int. 2003;64(3):777–87.
2. Bourke E, Haussinger D. pH homeostasis: the conceptual change. Contrib Nephrol. 1992;100:58–88.
3. Oliver J, Bourke E. Adaptations in urea ammonium excretion in metabolic acidosis in the rat: a reinterpretation. Clin Sci Mol Med Suppl. 1975;48(6):515–0.
4. Atkinson DE, Bourke E. pH homeostasis in terrestrial vertebrates; ammonium ion as a proton source. In: Heisler N, editor. Mechanisms of systemic regulation: acid–base regulation, ion-transfer and metabolism. New York: Springer; 1995. p. 3–26.
5. van Straten G, van Steenbeek FG, Grinwis GC, Favier RP, Kummeling A, van Gils IH, et al. Aberrant expression and distribution of enzymes of the urea

cycle and other ammonia metabolizing pathways in dogs with congenital portosystemic shunts. PLoS One. 2014;9(6):e100077. PubMed PMID: 24945279. Pubmed Central PMCID: 4063766.
6. Gennari FJ, Weise WJ. Acid-base disturbances in gastrointestinal disease. Clin J Am Soc Nephrol. 2008;3(6):1861–8. PubMed PMID: 18922984.
7. Moore EW. The alkaline tide. Gastroenterology. 1967;52(6):1052–4.
8. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Splanchnic buffering of metabolic acid during early endotoxemia. J Crit Care. 1997;12(1):7–12. PubMed PMID: 9075059.
9. Bellomo R, Kellum JA, Pinsky MR. Transvisceral lactate fluxes during early endotoxemia. Chest. 1996;110(1):198–204.
10. Kellum JA, Bellomo R, Kramer DJ, Pinksky MR. Splanchnic buffering of metabolic acid during early endotoxemia. J Crit Care. 1997;12(1):7–12.
11. Schlichtig R, Grogono AW, Severinghaus JW. Human $PaCO_2$ and standard base excess compensation for acid-base imbalance. Crit Care Med. 1998;26:1173–9.
12. Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. J Appl Physiol. 2003;95(6):2333–44.
13. Fidkowski C, Helstrom J. Diagnosing metabolic acidosis in the critically ill: bridging the anion gap, Stewart, and base excess methods. Can J Anaesth. 2009;56:247–56.
14. Kellum JA. Clinical review: reunification of acid-base physiology. Crit Care. 2005;9(5):500–7.
15. Kurtz I, Kraut J, Ornekian V, Nguyen MK. Acid-base analysis: a critique of the Stewart and bicarbonate-centered approaches. Am J Physiol Renal Physiol. 2008;294(5):F1009–31.
16. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol. 1983;61(12):1444–61.
17. Kellum JA. Determinants of blood pH in health and disease. Crit Care. 2000;4(1):6–14.
18. Sirker AA, Rhodes A, Grounds RM, Bennett ED. Acid-base physiology: the 'traditional' and the 'modern' approaches. Anaesthesia. 2002;57(4):348–56.
19. Wooten EW. Science review: quantitative acid-base physiology using the Stewart model. Crit Care. 2004;8(6):448–52.
20. Kellum JA. Disorders of acid-base balance. Crit Care Med. 2007;35(11):2630–6.
21. Corey HE. Bench-to-bedside review: fundamental principles of acid-base physiology. Crit Care. 2005;9(2):184–92.
22. Jones NL. A quantitative physicochemical approach to acid-base physiology. Clin Biochem. 1990;23(3):189–95.
23. Leblanc Martine KJ. Biochemical and biophysical principles of hydrogen ion regulation. In: Critical care nephrology. Philadelphia: Saunders; 1998. p. 261–77.
24. Hansen JE, Sue DY. Should blood gas measurement be corrected for the patient's temperature? N Engl J Med. 1980;303(6):341.
25. Delaney KA, Howland MA, Vassallo S, Goldfrank LR. Assessment of acid-base disturbances in hypothermia and their physiologic consequences. Ann Emerg Med. 1989;18(1):72–82.
26. Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. Medicine. 1980;59(3):161–87.
27. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. J Lab Clin Med. 1992;120(5):713–9.
28. Sadjadi SA. A new range for the anion gap. Ann Intern Med. 1995;123(10):807.
29. Winter SD, Pearson JR, Gabow PA, Schultz AL, Lepoff RB. The fall of the serum anion gap. Arch Intern Med. 1990;150(2):311–3.
30. Harrison TR. Harrison's principles of internal medicine. In: Braunwald E, Isselbacher KJ, Petersdorp RG, editors. Acidosis and alkalosis. 11th ed. New York: McGraw-Hill; 1987.
31. Salem MM, Mujais SK. Gaps in the anion gap. Arch Intern Med. 1992;152(8):1625–9.
32. Oster JR, Perez GO, Materson BJ. Use of the anion gap in clinical medicine. South Med J. 1988;81(2):229–37.
33. Gabow PA. Disorders associated with an altered anion gap. Kidney Int. 1985;27(2):472–83.
34. Whelton A, Carter GG, Garth MA, Darwish MO, Walker WG. Carbenicillin-induced acidosis and seizures. JAMA. 1971;218(13):1942–3.
35. Kang Y, Aggarwal S, Virji M, Pasculle AW, Lewis JH, Freeman JA, Martin LK. Clinical evaluation of autotransfusion during liver transplantation. Anesth Analg. 1991;72(1):94–100.
36. Narins R. Metabolic acid-base disorders: pathophysiology, classification and treatment. In: Fluid, electrolyte, and acid-base disorders. New York: Churchill Livingstone; 1985. p. 269–384.
37. Arieff AI, Carroll HJ. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. Medicine. 1972;51(2):73–94.
38. Mecher C, Rackow EC, Astiz ME, Weil MH. Unaccounted for anion in metabolic acidosis during severe sepsis in humans. Crit Care Med. 1991;19(5):705–11.
39. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. J Crit Care. 1993;8(4):187–97.
40. Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care. 1995;10(2):51–5.
41. Kirschbaum B. Increased anion gap after liver transplantation. Am J Med Sci. 1997;313(2):107–10.
42. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Hepatic anion flux during acute endotoxemia. J Appl Physiol. 1995;78(6):2212–7.

43. Mehta KK, Janes A, Carlson RW. The relationship between anion gap and elevated lactate. Crit Care Med. 1986;14(4):405.
44. Schlichtig R. [Base excess] vs [strong ion difference]. Which is more helpful? Adv Exp Med Biol. 1997;411:91–5.
45. Kaplan LJ, Kellum JA. Comparison of acid-base models for prediction of hospital mortality after trauma. Shock. 2008;29(6):662–6.
46. Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med. 1992;20(1):80–93.
47. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation. 1970;41(6):989–1001.
48. Blair E. Acid-base balance in bacteremic shock. Arch Intern Med. 1971;127(4):731–9.
49. Madias NE. Lactic acidosis. Kidney Int. 1986;29(3):752–74.
50. van Lambalgen AA, Runge HC, van den Bos GC, Thijs LG. Regional lactate production in early canine endotoxin shock. Am J Phys. 1988;254(1 Pt 1):E45–51.
51. Cain SM, Curtis SE. Systemic and regional oxygen uptake and delivery and lactate flux in endotoxic dogs infused with dopexamine. Crit Care Med. 1991;19(12):1552–60.
52. Suetrong B, Walley KR. Lactic acidosis in sepsis: It's not all anaerobic: implications for diagnosis and management. Chest. 2016;149(1):252–61. PubMed PMID: 26378980.
53. National Center for Biotechnology Information. PubChem Database. Lactic acid, CID=612. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/lactic_acid.
54. Zilva JF. The origin of the acidosis in hyperlactataemia. Ann Clin Biochem. 1978;15(1):40–3. PubMed PMID: 24406.
55. Robergs RA, McNulty CR, Minett GM, Holland J, Trajano G. Lactate, not lactic acid, is produced by cellular cytosolic energy catabolism. Physiology. 2018;33(1):10–2. PubMed PMID: 29212886.
56. Dennis SC, Gevers W, Opie LH. Protons in ischemia: where do they come from; where do they go to? J Mol Cell Cardiol. 1991;23(9):1077–86. PubMed PMID: 1658348.
57. Brown SD, Clark C, Gutierrez G. Pulmonary lactate release in patients with sepsis and the adult respiratory distress syndrome. J Crit Care. 1996;11(1):2–8.
58. Kellum JA, Kramer DJ, Mankad S, Bellomo R, Lee K, Pinsky MR. Release of lactate by the lung in acute lung injury. Chest. 1997;111(5):1301–5.
59. Connett RJ, et al. Defining hypoxia: a systems view of VO_2, glycolysis, energetics, and intracellular PO_2. J Appl Physiol. 1990;68(3):833–42.
60. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, Nabet P, Larcan A. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med. 1997;23(3):282–7.
61. De Backer D. Lactic acidosis. Intensive Care Med. 2003;29(5):699–702.
62. De Backer D, Creteur J, Zhang H, Norrenberg M, Vincent JL. Lactate production by the lungs in acute lung injury. Am J Respir Crit Care Med. 1997;156(4 Pt 1):1099–104.
63. Stacpoole PW. Lactic acidosis and other mitochondrial disorders. Metabolism. 1997;46(3):306–21.
64. Fink MP. Does tissue acidosis in sepsis indicate tissue hypoperfusion? Intensive Care Med. 1996;22(11):1144–6.
65. Gutierrez G, Wulf ME. Lactic acidosis in sepsis: a commentary. Intensive Care Med. 1996;22(1):6–16.
66. Kilpatrick-Smith L, Kilpatrick-Smith L, Deas J, Erecińska M, Silver IA. Cellular effects of endotoxin in vitro. II. Reversibility of endotoxic damage. Circ Shock. 1983;11(2):101–11.
67. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. Ann Surg. 1996;224(1):97–102.
68. Bearn AG, Billing B, Sherlock S. The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. J Physiol. 1951;115(4):430–41.
69. Zilva JF. The origin of acidosis in hyperlactatemia. Ann Clin Biochem. 1978;15:40–3.
70. Madias NE, Homer SM, Johns CA, Cohen JJ. Hypochloremia as a consequence of anion gap metabolic acidosis. J Lab Clin Med. 1984;104(1):15–23.
71. Cohen RD, Woods HF. Lactic acidosis revisited. Diabetes. 1983;32(2):181–91.
72. Kreisberg RA. Lactate homeostasis and lactic acidosis. Ann Intern Med. 1980;92(2 Pt 1):227–37.
73. Uribarri J, Oh MS, Carroll HJ. D-lactic acidosis. A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. Medicine. 1998;77(2):73–82.
74. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. Chest. 2000;117(1):260–7.
75. Graf H, Leach W, Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science. 1985;227(4688):754–6.
76. Rhee KH, Toro LO, McDonald GG, Nunnally RL, Levin DL. Carbicarb, sodium bicarbonate, and sodium chloride in hypoxic lactic acidosis. Effect on arterial blood gases, lactate concentrations, hemodynamic variables, and myocardial intracellular pH. Chest. 1993;104(3):913–8.
77. Magder S. Pathophysiology of metabolic acid-base disturbances in patients with critical illness. In: Critical care nephrology. Philadelphia: Saunders; 1998. p. 279–96.
78. Alberti KG. Diabetic emergencies. Br Med Bull. 1989;45(1):242–63.

79. Duhon B, Attridge RL, Franco-Martinez AC, Maxwell PR, Hughes DW. Intravenous sodium bicarbonate therapy in severely acidotic diabetic ketoacidosis. Ann Pharmacother. 2013;47(7–8):970–5. PubMed PMID: 23737516.
80. Gattinoni L, Carlesso E, Maiocchi G, Polli F, Cadringher P. Dilutional acidosis: where do the protons come from? Intensive Care Med. 2009;35(12):2033–43. PubMed PMID: 19763537.
81. Bakerman S, Bakerman P, Strausbauch P. ABC's of interpretive laboratory data. In: Bakerman's ABC's of interpretive laboratory data. 4th ed. Scottsdale, AZ: Interpretive Laboratory Data; 2002.
82. Androque HJ, Tannen RL. Fluids and electrolytes. In: Kokko JP, Tannen RL, editors. Ketoacidosis, hyperosmolar states, and lactic acidosis. Philadelphia: WB Saunders; 1996.
83. Good DW. Regulation of bicarbonate and ammonium absorption in the thick ascending limb of the rat. Kidney Int Suppl. 1991;33:S36–42.
84. Fulop M. Alcoholic ketoacidosis. Endocrinol Metab Clin N Am. 1993;22(2):209–19.
85. Wrenn KD, Slovis CM, Minion GE, Rutkowski R. The syndrome of alcoholic ketoacidosis. Am J Med. 1991;91(2):119–28.
86. Proudfoot AT, Krenzelok EP, Brent J, Vale JA. Does urine alkalinization increase salicylate elimination? If so, why? Toxicol Rev. 2003;22(3):129–36.
87. Whiteney GM, Szerlip HM. Acid base and electrolyte disorders. In: Dubose Jr TD, Hamm LL, editors. Acid-base disorders in the critical care setting. Philadelphia: WB Saunders; 2002.
88. Fraser AD. Clinical toxicologic implications of ethylene glycol and glycolic acid poisoning. Ther Drug Monit. 2002;24(2):232–8.
89. Widmer B, Gerhardt RE, Harrington JT, Cohen JJ. Serum electrolyte and acid base composition. The influence of graded degrees of chronic renal failure. Arch Intern Med. 1979;139(10):1099–102.
90. Harrington JT, Cohen JJ. Metabolic acidosis. In: Kasirer JP, Cohen JJ, editors. Acid-base. Boston: Little, Brown and Co; 1982.
91. Liborio AB, Daher EF, de Castro MC. Characterization of acid-base status in maintenance hemodialysis: physicochemical approach. J Artif Organs. 2008;11(3):156–9.
92. Abassi ZA, Hoffman A, Better OS. Acute renal failure complicating muscle crush injury. Semin Nephrol. 1998;18(5):558–65.
93. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJ, Libório AB, Park M. Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. Crit Care Med. 2009;37(10):2733–9.
94. Forni LG, McKinnon W, Lord GA, Treacher DF, Peron JM, Hilton PJ. Circulating anions usually associated with the Krebs cycle in patients with metabolic acidosis. Crit Care. 2005;9(5):R591–5.
95. Forni LG, McKinnon W, Hilton PJ. Unmeasured anions in metabolic acidosis: unravelling the mystery. Crit Care. 2006;10(4):220.
96. Martin M, Murray J, Berne T, Demetriades D, Belzberg H. Diagnosis of acid-base derangements and mortality prediction in the trauma intensive care unit: the physiochemical approach. J Trauma. 2005;58(2):238–43.
97. Rocktaeschel J, Morimatsu H, Uchino S, Bellomo R. Unmeasured anions in critically ill patients: can they predict mortality? Crit Care Med. 2003;31(8):2131–6.
98. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med. 2004;32(5):1120–4.
99. Mikulaschek A, Henry SM, Donovan R, Scalea TM. Serum lactate is not predicted by anion gap or base excess after trauma resuscitation. J Trauma. 1996;40(2):218–22. discussion 222–4.
100. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP. Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. Crit Care Med. 1990;18(3):275–7.
101. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg. 2003;185(5):485–91.
102. Rutherford EJ, Morris JA Jr, Reed GW, Hall KS. Base deficit stratifies mortality and determines therapy. J Trauma. 1992;33(3):417–23.
103. Davis JW, Kaups KL, Parks SN. Base deficit is superior to pH in evaluating clearance of acidosis after traumatic shock. J Trauma. 1998;44(1):114–8.
104. Davis JW, Kaups KL. Base deficit in the elderly: a marker of severe injury and death. J Trauma. 1998;45(5):873–7.
105. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. J Trauma. 1993;35(4):584–8. discussion 588–9.
106. Gunnerson KJ. Clinical review: the meaning of acid-base abnormalities in the intensive care unit part I - epidemiology. Crit Care. 2005;9(5):508–16.
107. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006;10(1):R22.
108. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med. 1988;318(10):594–9.
109. Jovaisa T, Vicka V, Linkaite G, Guseinovaite J, Ringaitiene D, Norkiene I. Use of lactated ringers solution does not eliminate the risk of strong ion difference-related metabolic acidosis following on-pump cardiac surgery. J Biol Regul Homeost Agents. 2016;30(4):1085–90. PubMed PMID: 28078858.

110. Ring T, Frische S, Nielsen S. Clinical review: renal tubular acidosis–a physicochemical approach. Crit Care. 2005;9(6):573–80.
111. Kushner RF. Total parenteral nutrition-associated metabolic acidosis. JPEN J Parenter Enteral Nutr. 1986;10(3):306–10. PubMed PMID: 3086592.
112. Dounousi E, Zikou X, Koulouras V, Katopodis K. Metabolic acidosis during parenteral nutrition: pathophysiological mechanisms. Indian J Crit Care Med. 2015;19(5):270–4. PubMed PMID: 25983433. Pubmed Central PMCID: 4430745.
113. Cheek DB. Changes in total chloride and acid-base balance in gastroenteritis following treatment with large and small loads of sodium chloride. Pediatrics. 1956;17(6):839–48.
114. Shires GT, Holman J. Dilution acidosis. Ann Intern Med. 1948;28(3):557–9.
115. Garella S, Chang BS, Kahn SI. Dilution acidosis and contraction alkalosis: review of a concept. Kidney Int. 1975;8(5):279–83.
116. Garella S, Tzamaloukas AH, Chazan JA. Effect of isotonic volume expansion on extracellular bicarbonate stores in normal dogs. Am J Phys. 1973;225(3):628–36.
117. Waters JH, Bernstein CA. Dilutional acidosis following hetastarch or albumin in healthy volunteers. Anesthesiology. 2000;93(5):1184–7.
118. Waters JH, Miller LR, Clack S, Kim JV. Cause of metabolic acidosis in prolonged surgery. Crit Care Med. 1999;27(10):2142–6.
119. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg. 2001;93(4):811–6.
120. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock. 1998;9(5):364–8.
121. Gattinoni L, Carlesso E, Maiocchi G, Polli F, Cadringher P. Dilutional acidosis: where do the protons come from? Intensive Care Med. 2009;35(12):2033–43.
122. Doberer D, Funk GC, Kirchner K, Schneeweiss B. A critique of Stewart's approach: the chemical mechanism of dilutional acidosis. Intensive Care Med. 2009;35(12):2173–80.
123. Ring T. Mixing bicarbonates: dilution acidosis from first principles. Intensive Care Med. 2009;35(12):2183–4; author reply 2185–6
124. Kellum JA. Recent advances in acid-base physiology applied to critical care. In: Vincent J-L, editor. Yearbook of intensive care and emergency medicine. Heidelberg: Springer; 1998.
125. Morgan TJ, Venkatesh B, Hall J. Crystalloid strong ion difference determines metabolic acid-base change during in vitro hemodilution. Crit Care Med. 2002;30(1):157–60.
126. Gilbert EM, Haupt MT, Mandanas RY, Huaringa AJ, Carlson RW. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Respir Dis. 1986;134(5):873–8.
127. Moviat M, Terpstra AM, Ruitenbeek W, Kluijtmans LA, Pickkers P, van der Hoeven JG. Contribution of various metabolites to the "unmeasured" anions in critically ill patients with metabolic acidosis. Crit Care Med. 2008;36:752–8.
128. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378(9):829–39. PubMed PMID: 29485925. Pubmed Central PMCID: 5846085.
129. Lindinger MI, Heigenhauser GJ, McKelvie RS, Jones NL. Blood ion regulation during repeated maximal exercise and recovery in humans. Am J Phys. 1992;262(1 Pt 2):R126–36.
130. Forrest David WK, Russell J. Impact of acid-base disorders on individual organ systems. In: Critical care nephrology. Philadelphia: Saunders; 1998. p. 313–26.
131. Hickling KG, Walsh J, Herderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med. 1994;22:1568–78.
132. Gunnerson KJ, Srisawat N, Kellum JA. Is there a difference between strong ion gap in healthy volunteers and intensive care unit patients? J Crit Care. 2010;25:520–4.
133. Gehlbach BK, Schmidt GA. Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit – the role of buffers. Crit Care. 2004;8:259–65.
134. Kette F, Weil MH, Gazmuri RJ. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure. JAMA. 1991;266:2121–6.
135. Hindman BJ. Sodium bicarbonate in the treatment of subtypes of acute lactic acidosis: physiologic considerations. Anesthesiology. 1990;72:1064–76.
136. Bersin RM, Arieff AI. Improved hemodynamic function during hypoxia with Carbicarb, a new agent for the management of acidosis. Circulation. 1988;77:227–33.
137. Spital Aaron GS. Correction of acid-base derangements. In: Critical care nephrology. Philadelphia: Saunders; 1998. p. 327–44.
138. Stacpoole PW, Moore GW, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, et al. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. N Engl J Med. 1992;327:1564–9.
139. Stacpoole PW, Moore GW, Kornhauser DM. Toxicity of chronic dichloroacetate. N Engl J Med. 1979;300:372.

140. Bleich HL, Schwartz WB. Tris buffer (THAM). An appraisal of its physiologic effects and clinical usefulness. N Engl J Med. 1966;274(14):782–7.
141. Arieff AI. Bicarbonate therapy in the treatment of metabolic acidosis. In: Chernow B, editor. The pharmacologic approach to the critically ill patient. Philadelphia: Williams & Wilkins; 1994.
142. Gattinoni L, Lissoni A. Pathophysiology and diagnosis of respiratory acid-base disturbances in patients with critical illness. In: Critical care nephrology. Philadelphia: Saunders; 1998. p. 297–311.
143. Rose BD, Post TW. Clinical physiology of acid-base and electrolyte disorders. 5th ed. New York: McGraw-Hill, Medical Pub. Division; 2001. x, 992 pp.
144. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
145. Tsuno K, Miura K, Takeya M, Kolobow T, Morioka T. Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. Am Rev Respir Dis. 1991;143(5 Pt 1):1115–20.
146. Sugiura M, McCulloch PR, Wren S, Dawson RH, Froese AB. Ventilator pattern influences neutrophil influx and activation in atelectasis-prone rabbit lung. J Appl Physiol. 1985;77:1355–65.
147. [no authors listed]. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8.
148. Gennari FJ. Acid-base. In: Cohen JJ, editor. Respiratory alkalosis. Boston: Little Brown and Co.; 1982.
149. Cohen JJ, Madias NE, Wolf CJ, Schwartz WB. Regulation of acid-base equilibrium in chronic hypocapnia. Evidence that the response of the kidney is not geared to the defense of extracellular (H^+). J Clin Invest. 1976;57:1483–9.
150. Adrogue HJ, Madias NE. Management of life-threatening acid-base disorders. Second of two parts. N Engl J Med. 1998;338(2):107–11.
151. Ashley SW, editor. ACS surgery: principles and practice. Hamilton, ON: B. C. Decker; 2014.

4 Metabolomics and Other "-Omic" Approaches to Characterize Perioperative Trajectories

Mihai V. Podgoreanu

Surgery and Critical Illness as a Model to Understand Vulnerability and Resilience to Physical Stressors at the Individual and Population Level

The Host Response to Physical Stressors, Surgery, Trauma, and Injury

Major surgery is a global healthcare burden. With around 244 million procedures performed annually, up to 4% of patients are suffering perioperative deaths, 15% are having serious postoperative morbidity, and 5–15% are being readmitted within 30 days [1, 2]. Surgical trauma and injury trigger a robust stress response, normally self-limiting and resolving, but that can in some instances exceed the body's internal tolerances, becoming the primary mechanism driving further injury and perioperative organ dysfunction [3, 4]. In the spectrum of degrees of surgical insult, cardiac surgery is an extreme example, where consequences of surgical trauma are compounded by ischemia-reperfusion and physiologic responses to cardiopulmonary bypass or other mechanical circulatory support devices (a "three-hit" model of injury). The magnitude of surgical stress response and resulting extent of postoperative organ dysfunction, as well as postoperative recovery trajectories, reflect the complex intersection between a number of procedural variables and an individual's age, gender, pre-existing health status, medication profile, fluid management, and degree of postoperative pain. Furthermore, acute sterile surgical stressors are often followed by secondary insults that may be either sterile or pathogen-induced (such as postoperative infection). Consequently, the so-called "two-hit" model of inflammatory insult has become the commonly accepted paradigm for stressful injury. The components of host response from the initial surgical insult are more clearly defined than those resulting from secondary events. What has become clear is that the cognate signals from either sterile surgical injury or pathogen-induced sources converge on the same recognition/response pathways. Interestingly, while host responses to the initial sterile "hit" of surgery are modified primarily by the magnitude of the insult and patient-specific (*endogenous*) factors, evidence suggests that *exogenous factors* such as patient management and pathogen virulence more prominently influence the overall responsiveness to secondary insults [5].

The demographics of patients undergoing surgery shows an unprecedented population aging

M. V. Podgoreanu (✉)
Department of Anesthesiology, Duke University School of Medicine, Durham, NC, USA
e-mail: mihai.podgoreanu@duke.edu

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_4

and increased prevalence of multi-morbidities, which further compounds the burden of surgical trauma as aging is a major risk factor for perioperative organ injury. Among the very elderly, there is a threefold increased risk of death; over 40% will experience significant postoperative complications requiring extended ICU stays [6, 7], with many ICU survivors continuing to display excess mortality and high incidence of post-ICU syndrome following hospital discharge [8, 9].

Physical Resilience to Surgical Stressors

An emerging paradigm separates responses to physical stressors, like surgical trauma, into two key steps – deviation from the baseline (e.g., preoperative) state and return to the original state (e.g., postoperative recovery) [10]. Consequently, stress resistance can be characterized by the two different components, respectively, (a) ability to resist the deviation from baseline (*robustness*), as measured by the magnitude of deviation from the original preoperative state following surgical stress and time to a peak value, and (b) ability to fully recover after such deviation (*resilience*), as measured by time to recovery and completeness of functional postoperative recovery, which is not a progressive linear process. How these two key aspects of the surgical stress response can be differentially affected by age and other preoperative factors, their impact on maintenance of organ function or recovery from organ dysfunction in individual surgical patients, and the underlying molecular mechanisms involved represent active areas of investigation [11, 12]. Nevertheless, increasing evidence points to the critical role of metabolism and mitochondrial function in determining risk versus resilience [13].

We submit that surgery and critical illness represent an ideal epidemiological paradigm to study susceptibility and resilience to physical stressors at the individual and population levels (Fig. 4.1). Compared to studying complex diseases in ambulatory populations, this acute care clinical setting is unique in several regards. First, preoperative patient characteristics are known, allowing for assessment of prestress baseline and other preoperative calibrations, at least for elective surgeries. Surgical patients arrive to the operating room with a burden of complex diseases resulting from the interaction of environmental exposures and perturbations with their genetic background over their life span. Each patient's unique genetic fingerprint is matched by a unique preoperative metabolic phenotype, representing the composite readout of host-genetic controlled metabolic processes, diet, lifestyle, microbial activity, and comorbid conditions. These factors determine in part an individual's physiological ability to tolerate surgical stress (the allostatic load) [14]. Surgical patients are then subjected to the perioperative environment, appropriately called "controlled trauma," and consist of varying types of surgical injury, exposure to extracorporeal circulation, intra-abdominal air insufflation, anesthetic and other pharmacologic interventions, neoadjuvant therapies, microbial contamination and decontamination, perioperative nutritional strategies, etc. (i.e., *the perioperative exposome*). These defined stressors and stages during the conduct of surgery represent the second unique characteristic of the perioperative environment. The interaction of perioperative exposures with the genomic background and baseline metabolic phenotype results in interindividual variation in dynamic systemic host responses [15], which include altered metabolic phenotypes [16], leading to a normal recovery trajectory or a complicated one (Fig. 4.1) [17]. Increasing evidence suggests that the intense environmental perturbations/stressors associated with major surgery can unmask underlying genetic susceptibilities. The high degree of direct observation, monitoring, and data density, in terms of physiological and biochemical assessments, and serial access to biofluids (plasma, serum, urine, cerebrospinal fluid, bronchoalveolar lavage) and tissue to characterize molecular responses represent the third unique characteristic of the perioperative environment.

Despite increased appreciation for the importance of enhanced recovery after surgery (ERAS) [18, 19], postoperative patient trajectories and in particular the ability to maintain or recover appro-

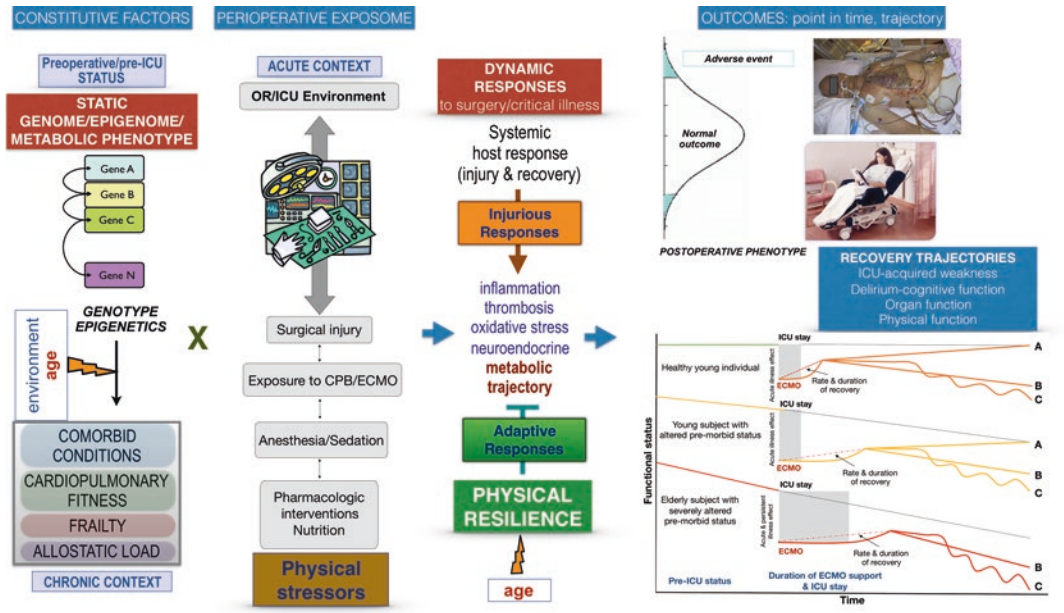

Fig. 4.1 Surgery and the perioperative period offer a unique scientific paradigm to perform in-depth characterization of injury and recovery signatures at the clinical, physiological, cellular, and molecular levels in humans. Possible adverse outcomes (organ injury and dysfunction) and trajectories of recovery are depicted, reflecting the interaction between preoperative/pre-ICU status, comorbidities, genetic/epigenetic/metabolic susceptibility to injury, duration of ICU stay, dynamic host responses to critical illness, and putative age-dependent resilience mechanisms. Precision perioperative care must have the ability to generate and model rich multi-"omic" and phenotypic data in restrictive clinical environments such as the operating rooms and intensive care units that are simultaneously highly controlled and heterogeneous, on a time scale that matches key decision-making events that mark the perioperative period. Trajectories of recovery can be characterized by acute functional decline in the ICU followed by recovery (A) constant decline over time (B) or repeated acute exacerbations and partial recoveries (C). Hatched lines indicate the trajectories of functioning that would have occurred if the subject had not developed critical illness. (Modified from Podgoreanu [15] and Iwashyna [17])

priate function following the controlled trauma of surgery remain poorly described, lacking both a precise phenotypic framework and mechanistic understanding [20]. What little we do know about recovery from surgery as a primary outcome relies on cross-sectional incidence data with infrequent assessments, which limits characterization of speed of recovery and underlying mechanisms. At the same time, there is increased appreciation of the translational bottlenecks and failures to manipulate key pathogenic processes involved in the host response to major surgical trauma and the ensuing critical illness and organ injury/dysfunction, resulting in a complete lack of effective perioperative organ protective therapeutics (unexpected failed clinical trials for candidates that should, by all accepted metrics, have been efficacious; at the time of this publication, no single FDA-approved drug for cardio-, neuro-, or renal protection or targeting/modifying acute inflammatory or metabolic responses in surgical trauma and critical illness). This is in spite of an ever-increasing basic level of understanding, with numerous advances in defining novel molecules, signaling and synthetic pathways, and gene regulatory networks contributing to inflammation and metabolic deregulation; some contributed by our group [21–29]. The emphasis on describing in greater molecular detail the heterogeneity in patients' responses to surgical stress using an ever-increasing array of high-throughput "-omics" methods, coupled with the development of "Big Data" mining approaches and correlative methods (clustering algorithms, machine learn-

ing), has resulted in an exponential increase in the number of potential hypotheses to be tested through formal experimental mechanistic evaluation of causality. An overly reductionist, non-integrative approach to understand the multiscale control structure of inflammation and metabolic regulation may explain in part the current state. Another explanation may come from the ongoing wide application of "one size fits all" perioperative bundles, as opposed to precision (or stratified) perioperative care. Some of these concepts, approaches, and challenges are further discussed below.

The Role of Metabolic Phenotypes and Metabolic Trajectories in Precision Perioperative Medicine

Precision perioperative medicine – the tailored management and/or prevention of postoperative complications according to the specific characteristics of a stratified individual, subpopulation, or population to enhance perioperative care [30] – can potentially address many of these persistent needs. It can account for varying susceptibility of patients to different diseases and importantly their fluctuating responses to specific surgical treatments. These characteristics are derived from the integrated evaluation of phenotype, genotype, and treatment bioresponses realized through a systems biomedicine "-omic" approach. *Stratified perioperative care*, based on a deeper analysis of systems biology in the surgical environment, remains an urgent unmet need.

Precision medicine can be broadly divided into precision prevention and precision treatment [31]. *Precision treatment* aims at developing a personalized perioperative treatment strategy while taking into account patient's genetics, environment, and lifestyle as well as individual treatment response parameters to predict posttreatment outcome. The approach entails high-throughput technologies to interrogate individuals' networks of metabolism, epigenetics, and genetics to guide individualized therapy. Existing perioperative risk calculators have only modest accuracy and generally lack actionability (i.e., modification of several components of these risk scores has limited impact on postoperative outcomes). With many fundamental biological processes that predispose to adverse perioperative outcomes and impaired recovery after surgery manifesting themselves in all tissues, a new paradigm is emerging that quantitative assessment of circulating cell phenotypes and molecular biomarkers in biofluids will be informative in identifying early risks for perioperative complications. On the other hand, *precision prevention* encompasses an array of measures focused on assessing the risk of an individual toward particular disease and devising a preventive intervention to decrease this risk and prevent the development of disease. While precision prevention can aim to change individual behavior, it can also target "precise" groups or entire communities by modifying care delivery systems, optimizing transmission through social networks, or instituting targeted policies or macroenvironmental changes that are different by community [32]. For perioperative medicine, these include areas of pre-habilitation, improving adherence to medication, and preoperative nutritional and metabolic optimization.

Integral to the concept of precision medicine is the granular assessment of perioperative phenotypes. *Perioperative phenomics* refers to the systematic and comprehensive study of a set of phenotypes that can be produced over the perioperative course, which entails the acquisition of high-dimensional phenotypic data on an organism-wide scale [33]. In this context, *deep phenotyping* is an approach to integrate multiple phenotypes measured at different resolutions, from molecules to cells to broader views of physiology and behaviors. This includes expanding our view of what constitutes a "useful" phenotype by incorporating measurements not traditionally assessed for perioperative outcomes but that shed light on relevant aspects of perioperative biology, as well as including digital phenotypes from perioperative monitors and state-of-the-art sensor technology, to provide more granular insights into perioperative trajectories. One burgeoning aspect of deep phenotyping is the broad multi-analyte determination of a patient's *metabolic phenotype*, based

on measurements of small molecule metabolites in biofluids or tissue samples [34].

Metabolic phenotype or metabotype is a concept used to describe a particular metabolic state of a biological system and can be defined as presence or absence of particular metabolites, absolute or relative concentrations, ratios of metabolites, or coordinated metabolic signatures [35]. Since its original definition, metabolomics has been interventional in nature, focusing on changes in metabolite profiles caused by an intervention such as drug administration, surgery, or onset of disease [36].

Longitudinal studies have revealed that healthy subjects are characterized by a stable metabolic space over time, where their metabolic phenotypes are able to vary according to daily stressors and external stimuli (i.e., metabolic allostasis). In the absence of major pathophysiological events, the phenotype is stable also over a time scale of almost 10 years. When an individual is subjected to a prolonged or intense stressful situation, he or she might not be able to maintain the original equilibrium and could drift/shift toward a new (possibly stable) equilibrium. Importantly, when a stressful situation ends, the metabolic phenotype is able to revert toward the original metabolic space, and the original condition is restored (i.e., metabolic resilience). In this context, the metabotype can represent an operative tool to evaluate the human responses to a diversity of stimuli with the aim of estimating human pathophysiological resilience (Fig. 4.2) [12].

A number of unique characteristics make metabolic phenotypes particularly suited to understand perioperative patient trajectories. First, metabolic phenotypes and profiles are jointly modulated by interactions of genes, diet, and symbiotic gut microorganisms. Second, they are responsive to perioperative perturbations and influence an individual's recovery from surgery; thus changes in the levels of such metabolites can be used as biomarkers for intervention efficacy or side effects. Because metabolic phenotypes are predictive of interventional outcomes, they can be used as a systems-based approach to monitor and shape the "patient journey" [37].

Several powerful spectroscopic techniques are suitable for perioperative metabolomic implementation, driven by improved analytical performance and size/cost reductions. The main techniques are high-resolution nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). Both technologies are able to detect hundreds of metabolites in biofluids and are most powerful when used together. Blood (plasma or serum) and urine are the most commonly used biofluids due to the minimally invasive and potential for longitudinal sampling. They represent snapshots (plasma/serum) or time-averaged (urine) representations of the metabolic state of the patient, reflecting biochemical processes that occur in multiple organs and tissues. More detailed and specific information can be obtained by complementing biofluid signatures with directly sampled tissue from areas affected by the disease process. Rigorous standard operating procedures for sample handling and acquisition across multiple time points are essential [34, 38–44]. Furthermore, magic angle spinning (MAS) NMR spectroscopy is well suited to real-time surgical investigations, allowing diagnostic information on metabolites in intact tissue biopsy specimens without any sample preparation.

The field of metabolic phenotyping was further advanced by the development of methods for metabolic characterization and determination of the human serum [45] and urine metabolome [46], the lipid species existing in mammalian cells, and the standardization of sample handling, analysis, and bioinformatics [47]. Although initially limited to offline exploration of disease mechanisms and population-based epidemiological studies, analytical and computational advances have created the possibility of applying this technology within the time frame of the perioperative patient journey. Spectroscopic profiling to characterize metabolic phenotypes can start by conducting global *untargeted assays*, where the metabolites are not selected a priori, followed by quantitative *targeted assays*. Inflammation, for instance, can be assayed using global lipidomic profiles [48], supplemented by a quantitative analysis of eicosanoids [49].

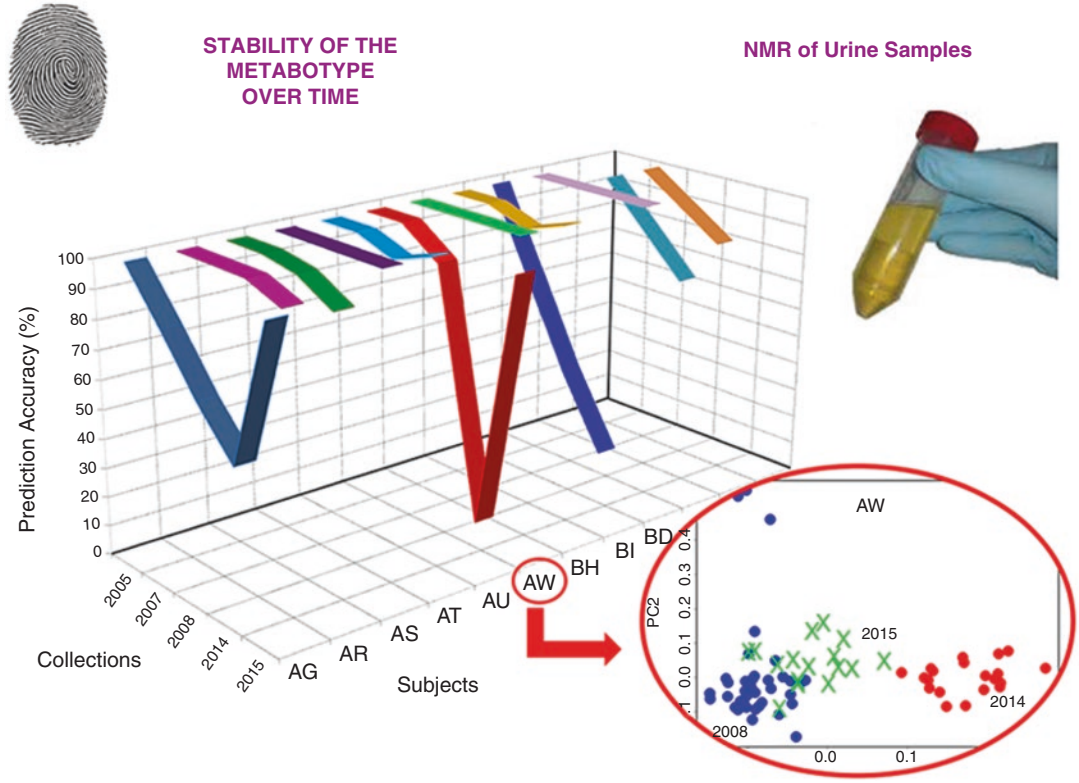

Fig. 4.2 Longitudinally followed urine metabotypes are characterized by limited intraindividual baseline variability (*metabolic allostasis*) in the absence of major pathophysiological events. Prolonged or intense stressful conditions, however, result in significant metabotype shifts (e.g., subjects AG and AW), which return to the original unperturbed state once the stressful event ends (*metabolic resilience*). (From Ref. [12])

A number of applications of metabolic phenotyping for risk prediction and monitoring of surgical, critically ill, and injured patients are described below.

Metabolic Phenotyping for Risk Stratification in Surgical and Critically Ill Patients

Metabolic phenotyping has been used for static and dynamic patient stratification (reviewed by [50]). A number of studies have employed *static patient stratification*, which can predict disease risk or disease subtypes based on metabolic molecular classifiers measured at baseline in biofluids. Examples include risk of incident cardiovascular disease [51, 52] and risk for long-term adverse cardiovascular events. For instance, Shah et al. used targeted MS profiling of baseline plasma metabolites to identify a signature of dicarboxylic acylcarnitines, medium-chain acylcarnitines, and fatty acids predictive of future cardiovascular events (death and myocardial infarction) [53]. In a separate study, high plasma levels of choline and betaine were associated with increased risk of major adverse cardiac events (MACE) in patients undergoing elective coronary angiography but only when levels of microbiome-derived trimethylamine N-oxide (TMAO) were also high [54]. Other static metabolomic studies reported on heart failure subtypes [55], diabetes risk [56], risk of stroke recurrence in patients with transient ischemic attacks [57], hypertension risk [58], and risk of all-cause mortality [59]. For comprehensive reviews of the role of metabolomics in the diagnosis and prognosis of cardiovascular disease, see [60, 61].

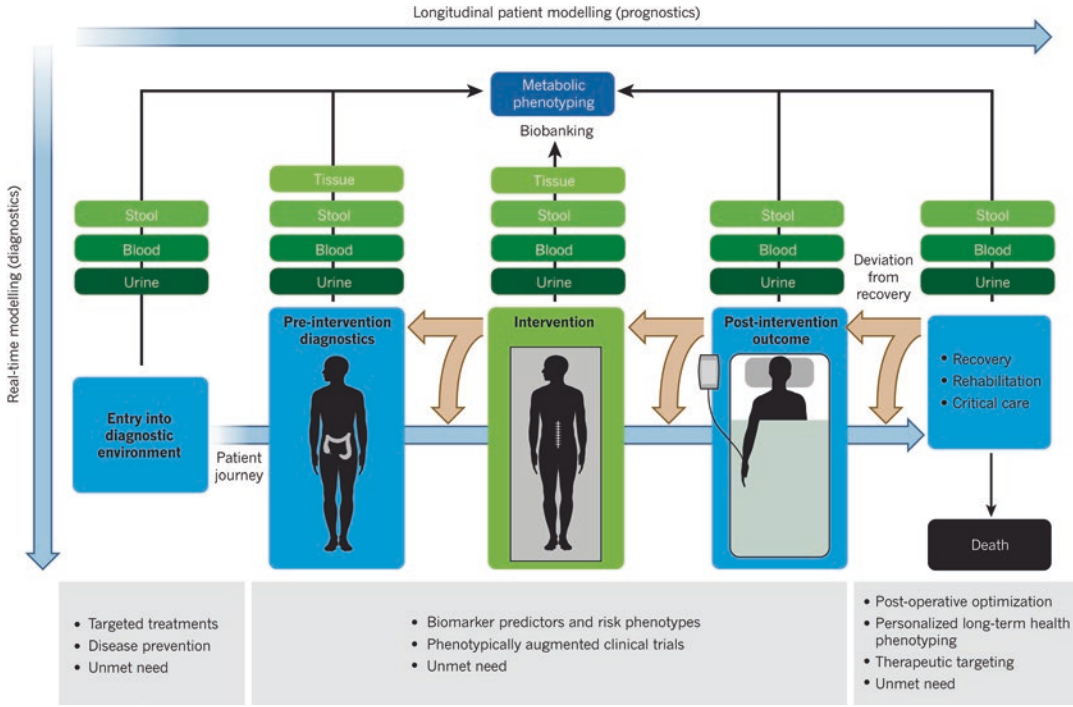

Fig. 4.3 A scheme illustrating the paradigm of phenotyping the patient journey and of conducting phenotypically augmented clinical trials. Schematic of the patient journey indicating the nodes at which metabolic phenotyping can contribute to shaping clinical opinions. (From Ref. [37])

Conversely, *dynamic patient stratification* can model the physiological and molecular responses to treatment and predict posttreatment outcomes [62–64]. Nicholson et al. [37] introduced the concept of a patient's *metabolic trajectory*, whereby multivariate metabolic information obtained from biofluid, stool, or tissue samples prior to, during, and after a patient undergoes treatment can be used to monitor patients through dynamic metabolic processes to aid diagnosis, monitor treatment effect, and predict outcomes including complications and need for ICU admission. While the approach can be used for any therapeutic intervention, this longitudinal metabotyping is particularly useful for surgical procedures, where rapid changes in patient physiology demand fast decision-making and early identification of postoperative complications. With bedside application of MS-based targeted metabolomics becoming a real possibility (data acquisition for a targeted metabolite panel can be achieved in <3 h) [65], this information is actionable in the perioperative and critical care setting, informing among others individualized amounts and content of enteral vs parenteral nutrition [66], nucleotide or antioxidant supplementation, and goals of resuscitation beyond plasma lactate levels. This concept is illustrated in Fig. 4.3. Patients enter the perioperative environment either as an elective admission or as an emergency. Opportunities exist for collection of samples for metabolic phenotyping at any point along the perioperative patient journey, including when deviations from recovery occur. The differences in metabolic profiles for a given patient at different times during the perioperative continuum represent the metabolic trajectory. Such "phenotypically enhanced patient journey" [16] can be used for preoperative patient optimization and stratification and to inform postoperative recovery, rapidly adjust treatment plans, and give mechanistic information related to therapeutic responder or nonresponder status [37].

Additional examples of specific surgical applications of predictive metabolomics studies follow.

Applications in Cardiovascular Surgery

Metabolic profiling of plasma samples was performed perioperatively in children undergoing surgical correction of congenital heart disease (preoperative baseline and at 6 h, 24 h, and 48 h, postoperatively). Changes in metabolic and inflammatory profiles were seen over the time course from surgery to recovery, compared with the preoperative state. The metabolic profiles were most deranged at 6 h, consistent with the magnitude of the inflammatory response. Figure 4.4 contrasts the metabolic trajectories of a patient with a prolonged and complicated postoperative period (based on length of mechanical ventilation, ICU length of stay, and RACHS score) to that of a patient with a rapid clinical recovery [67]. In a cohort of infants undergoing cardiac surgery, metabolic profiling identified changes in perioperative levels of aspartate, glutamate, methylnicotinamide, and kynurenic acid to be independently predictive of mortality and ICU length of stay [68].

Several studies have reported on the myocardial responses to acute myocardial injury or planned surgical ischemia-reperfusion. In a population of patients undergoing alcohol septal ablation for hypertrophic obstructive cardiomyopathy, a human model of planned myocardial infarction (MI) that recapitulates spontaneous MI, targeted mass spectrometry-based metabolite profiling identified changes in circulating levels of metabolites participating in pyrimidine metabolism, the TCA cycle, and the pentose phosphate pathway as early as 10 minutes after MI in an initial derivation group and was validated in a second, independent group. Coronary sinus sampling distinguished cardiac derived from peripheral metabolic changes. To assess generalizability, the planned MI-derived metabolic signature (consisting of aconitic acid, hypoxanthine, trimethylamine N-oxide, and threonine) differentiated with high-accuracy patients with spontaneous MI [69]. We applied a similar approach to cardiac surgical patients undergoing planned global myocardial ischemia-reperfusion and identified clear differences in metabolic fuel uptake based on the pre-existing ventricular state (left ventricular dysfunction, coronary artery disease, or neither) as well as altered metabolic signatures predictive of postoperative hemodynamic course and perioperative MI, informing the ultimate removal of glucose from cardioplegia solutions at our institution [70]. While simultaneous assessment of coronary sinus effluent in addition to the peripheral blood improves cardiac specificity of the observed signatures, direct measurements of metabolites in myocardial tissue allow marked enrichment and easier detection of potential biomarkers compared to plasma, as well as an assessment of how metabolic substrates are utilized in the tissue of interest. Such studies are possible in cardiac surgical patients where atrial tissues are routinely removed. For example, one study using high-resolution ^{1}H-NMR spectroscopy identified alterations in myocardial ketone metabolism associated with persistent atrial fibrillation, and the ratio of glycolytic end products to end products of lipid metabolism correlated positively with time of onset of postoperative atrial fibrillation [71].

For longer-term prediction, a MS-targeted analysis of 69 serum metabolites in a cohort of patients undergoing coronary artery bypass grafting was able to accurately predict adverse postoperative events over an observation period of 4.3 ± 2.4 years [72]. Short-chain dicarboxylic acylcarnitines, ketone-related metabolites, and short-chain acylcarnitines were independently predictive of adverse outcomes following multivariate adjustment.

There is a fundamental gap in understanding how aging increases cardiac vulnerability to surgical stress and ischemia-reperfusion injury, particularly in patients with ventricular dysfunction. A number of observations draw a link among aging, loss of mitochondrial function, disturbed cardiac energy metabolism, and impaired recovery from IR injury of aged hearts, but the underlying mechanisms remain ambiguous. Evidence is emerging, however, that bioenergetic maladaptations in heart failure are reversible [73]. Schechter et al. employed an integrated phospho-

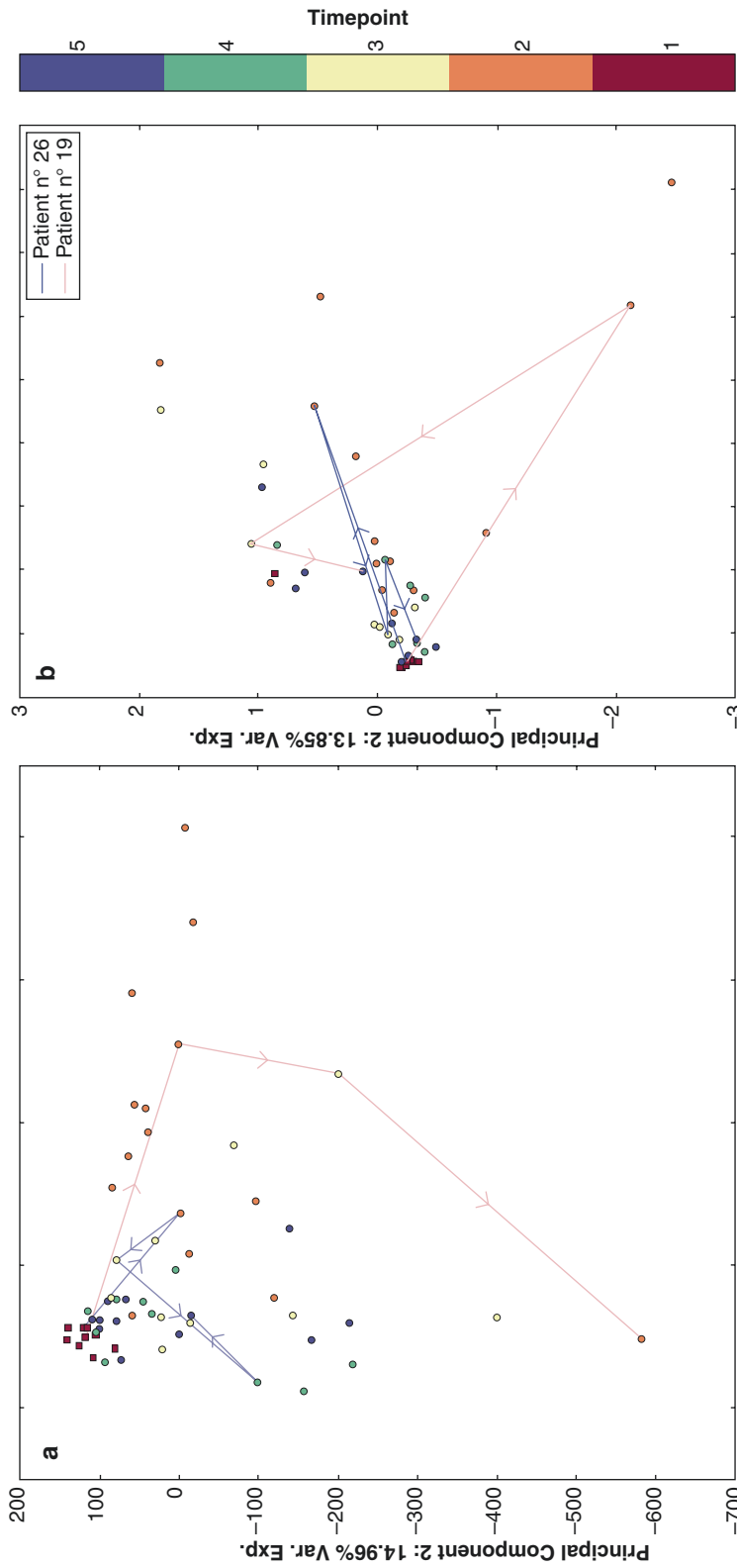

Fig. 4.4 Principal component score plots formed from (**a**) plasma NMR spectra and (**b**) cytokine data from children undergoing surgery for congenital heart disease. Samples were collected before the operation (red), at time of operation (orange), 6 h after the operation (yellow), 24 h after the operation (green), and 48 h after the operation (purple). The trajectories are shown for two patients: patient A, who underwent a more serious operation with a prolonged recovery period, and patient B, who had a less severe condition and a shorter operation and recovery period. The child with the more serious condition and prolonged recovery period had the larger trajectory. (From Ref. [67])

proteomic and targeted metabolomic analysis of human left ventricular myocardium to characterize, for the first time, the molecular differences between cardiomyopathy of ischemic (ICM) and non-ischemic (NICM) etiology [74]. A significant decrease in phosphorylation of PDHA1 was observed in ICM hearts compared to both NICM and non-failing samples, suggesting that PDH is most active in ICM. This corroborated with left ventricular levels of pyruvate being lowest (and lactate levels being highest) in ICM compared to the other groups and consistent with the current paradigm of a shift in myocardial fuel toward glucose in heart failure (HF). Intriguingly, PDH phosphorylation was unchanged in NICM hearts, suggesting this substrate shift could be HF etiology specific. Conversely, and reflecting the complexity of multiple metabolic defects present in human HF, a study by Gupte et al. identified a metabolomic pattern characterized by increased pyruvate concentrations, reduced TCA cycle intermediates, and short-chain acylcarnitines, suggesting a global impairment in mitochondrial substrate oxidation in heart failure (of mixed etiologies) compared to non-failing hearts [73]. Notably, HF samples had reduced levels of acetylcarnitine, a surrogate for acetyl-CoA and a product of glucose, amino acid, and fatty acid oxidation (FAO). Observed tissue metabolite changes were associated with decreased transcript levels for enzymes involved in FAO, pyruvate metabolism (including *PDHA1*), and key transcriptional regulators that orchestrate mitochondrial metabolism and biogenesis (*PGC1A*, *ERRA*, *ERRG*). Importantly, all metabolic and transcriptional defects were completely reversed by mechanical support with LVAD [73]. Thus, although most studies demonstrate that human HF involves metabolic reprogramming that limits FAO per se (both in absolute terms and as a fraction of myocardial oxygen consumption) [75], the overarching phenotype of HF is one of the energy starvation due to impaired oxidation of all major fuels [73, 76], as also shown by our group in cardiac surgical patients [70]. The pathophysiologic mechanisms underlying the substrate switch to glucose in HF, whether it occurs in all patients with HF, as a cause or consequence of the failing heart, and whether it represents a protective adaptive response or is deleterious to myocardial function, and its contribution to ventricular recovery remain poorly understood.

Consequently, an important cardiovascular application of metabolic phenotyping is in mechanistic understanding and prediction of ventricular recovery in patients with acute or advanced HF following unloading with mechanical circulatory support devices. Using targeted quantitative MS analysis of 60 plasma metabolites in a population of chronic HF patients, Ahmad et al. reported that circulating long-chain acylcarnitine levels (mitochondrial fatty acid metabolites) were independently associated with functional status and adverse clinical outcomes, including all-cause and cardiovascular mortality and hospitalization. Intriguingly, the specific metabolic abnormalities were significantly reduced following LVAD placement [77]. These findings have important translational relevance to monitor and possibly modify the mitochondrial dysfunction and metabolic inflexibility associated with advanced HF. Growing evidence suggests that ventricular remodeling and recovery in heart failure are preceded by characteristic molecular changes associated with mechanical circulatory support [78], which demonstrate substantial interindividual variability [79, 80]. At the metabolic level, mechanical unloading reduces myocardial levels of toxic lipid intermediates and improves cardiac insulin signaling [81], among many other changes in myocardial energetics [73, 82, 83].

Other applications revolve around prediction of organ injury following cardiac surgery. In a recent study, Elmariah et al. [84] performed MS-based metabolite profiling of plasma from patients undergoing transcatheter aortic valve replacement (TAVR) to predict acute kidney injury (AKI) occurrence using previously identified plasma metabolites predictive of incident chronic kidney disease. They have shown that, in an elderly population with severe aortic stenosis undergoing TAVR, metabolite profiling improves the prediction of AKI. Of 85 metabolites profiled, 5-adenosylhomocysteine successfully predicted AKI as well as all-cause mortality after TAVR.

Applications of Metabolic Phenotyping in Critically Ill Patients Requiring Extracorporeal Membrane Oxygenation (ECMO)

The metabolic consequences of cardiogenic shock, combined with tissue injury, hemorrhage, and host-ECMO interface are complex, and ECMO promotes a number of metabolic disturbances. Previous studies have shown that ECMO induces an inflammatory reaction, which increases insulin resistance, reduces glucose utilization, and promotes a general catabolic state [85]. Attempts to administer high-dose insulin however had minimal influence on protein turnover. Direct evidence of the importance of metabolic phenotyping in ECMO outcomes exists, particularly when assessed dynamically, with early lactate concentration and clearance being predictive of survival and successful weaning from ECMO in postcardiotomy shock patients [86–89], in addition to a number of preclinical reports (majority based on studies in immature animals) [85, 90–94]. Indirect evidence supporting metabolic phenotyping to assess injury and recovery trajectories following physical stressors, critical illness, and shock states comes from a large number of clinical [95–99] and preclinical reports [100–104]. Risk-benefit evaluation and optimal patient selection for ECMO support remain areas of uncertainty and active investigation, but there are currently no biomarkers to aid stratification of functional recovery in ECMO patients and identify modifiable recovery trajectories.

Applications in Trauma and Acute Care Surgery

As discussed above, metabolic phenotyping strategies are emerging as viable means for real-time metabolic assessment and optimization in critically ill patients [16, 50, 105, 106]. An important application of metabolomic approaches is in trauma-related critical illness and injury. Multivariate analysis of 43 quantitative metabolic parameters identified 3 lipid metabolites, triacylglycerol, glycerol heads of phospholipids, and monounsaturated fatty acids, as being the most discriminative markers to separate trauma survivors versus non-survivors at the time of admission. Glucose and glutamate were intermediate predictors, followed by lactate and hydroxybutyrate as two low-weight predictors [107].

Further examples include predicting early-onset systemic inflammatory responses (SIRS) and multiorgan dysfunction syndrome following major trauma [108]. Blaise et al. utilized NMR-based metabolic phenotyping of plasma obtained from a cohort of trauma patients upon admission to the ICU and identified eight metabolic hotspots (notably valine, citrate, aspartate, allantoin, and hydroxybutyrate) highly predictive of later development of sepsis [109]. Differentiating SIRS from sepsis is another important application of metabolic phenotyping in critical care. Schmerler et al. employed MS-based profiling of 186 metabolites and concluded that acylcarnitines and glycerophosphatidylcholines may be helpful for discriminating infectious from noninfectious systemic inflammation due to their significantly higher concentration in sepsis patients [110]. This is particularly relevant in the perioperative setting, where procalcitonin remains a controversial biomarker for differentiating SIRS from sepsis because it has been described to be elevated after major surgery, a common cause of SIRS without underlying infection. Considering the well-known pathophysiological relevance of lipid induction by bacterial components, metabolites as identified in this study are promising biomarker candidates in the differential diagnosis of SIRS and sepsis.

Peltz et al. identified trauma-dependent metabolic signatures, characterized by a state of hypercatabolism driven by glucose consumption, lipolysis and fatty acid utilization, accumulation of ketone bodies, and proteolysis and nucleoside breakdown [98]. Metabolites of bacterial origin were unexpectedly also found in plasma from trauma victims. These metabolic signatures could provide a method for assessing the efficacy of alternative resuscitative strategies. Moreover, serial metabolic characterization used to trend injury and recovery in critically ill trauma patients identified specific patterns of ongoing oxidative stress, impaired nucleotide synthesis, and initial suppression of protein metabolism followed by increased nitrogen turnover [99]. Importantly, this may provide new therapeutic and nutritional targets in critically injured patients. In a follow-up study from

the same group, Parent et al. used MS-based metabolomics to assess metabolic responses to enteral vs parenteral nutrition. They found that enteral nutrition was associated with amino acid repletion, urea cycle upregulation, restoration of antioxidants, and increasing RNA synthesis. Conversely, parenteral nutrition was associated with increased amino acid concentrations, but did not influence protein metabolism or antioxidant repletion [66]. The ability to identify differences between enteral and parenteral nutrition in surgical critically ill patients points to the sensitivity and power of this methodology, especially when evaluated dynamically and correlated with functional recovery.

Applications in Bariatric Surgery

A prime model to study surgical metabolism is provided by gastric bypass of the foregut, aptly named metabolic surgery, which is increasingly performed for the treatment of obesity and its metabolic complications. Preclinical models confirmed the co-dependence of mammalian and microbial metabolism, and bariatric surgery alters the host metabolic-microbial cross talk, fundamentally disrupting the distal gut microbiome and ultimately exerting global metabolic effects [111]. Intriguingly, bariatric surgery alters the myocardial metabolic phenotype, reflecting an enhancement of cardiac energy metabolism through TCA cycle intermediates, cardiorenal protective activity, and biochemical caloric restriction. Mechanistically, these metabolic shifts seem to mediate bariatric cardioprotection through changes in gut microbiota and an entero-cardiac axis [112]. A number of human studies have reported on the relationship between the metabolic shifts following bariatric surgery, changes in gut microbiota, and clinical outcomes (weight loss and relapse) [113–115] while also revealing metabolic benefits independent of the magnitude of weight loss [116].

Applications in Transplant Surgery

Time course trajectories of metabolic changes after kidney transplantation were one of the first published applications of longitudinal metabotyping [117] and shown to be superior to traditional clinical assessment in predicting graft failure and rejection. It has since been expanded to further refine prediction of kidney graft failure [118], end-organ drug toxicity [119], as well as intestinal [120] and liver transplant outcomes [121]. With the ever-increasing demand to expand the donor pool and donation after cardiovascular death, it is anticipated that metabolic phenotyping will become part of a suite of rapid molecular diagnostics to predict graft suitability for transplantation and survival.

Applications in Surgical Oncology

Using metabolic phenotyping (magic angle spinning NMR spectroscopy, MAS-NMR) to conduct chemical biopsies has been used in the analysis of brain tumors, shown to differentiate between malignant tumor types [122], and subsequently related to lower-resolution in vivo spectra obtained via MR spectroscopy [123]. Similar results have been reported for diagnosis, tumor typing, staging, and prognostication in prostate [124], breast [125], and colorectal cancer [126].

Metabolic Phenotyping for Intraoperative Patient Monitoring

Rapid metabolic phenotyping approaches are also emerging, enabling near real-time intraoperative tissue and tumor diagnosis by addressing surgical pathology at a multitude of scales. An example of such novel surgical technology that allows for near real-time metabolic analyses is the "intelligent surgical knife." Based on rapid evaporative ionization mass spectrometry, it provides real-time characterization of human tissue in vivo by analysis of the aerosol (smoke) released during electrosurgical dissection. This has significant implications for surgical oncology, and in preliminary studies, the approach differentiated accurately between tissue histopathologic subtypes, including distinct tumor types, and primary vs metastatic tumors" (Fig. 4.5) [127–130]. Furthermore, it can inform surgeons on tumor-free margins, in deciding on tissue viability in situations where resection of necrotic tissue is necessary and in assessing therapeutic efficacy after radiofrequency or laser

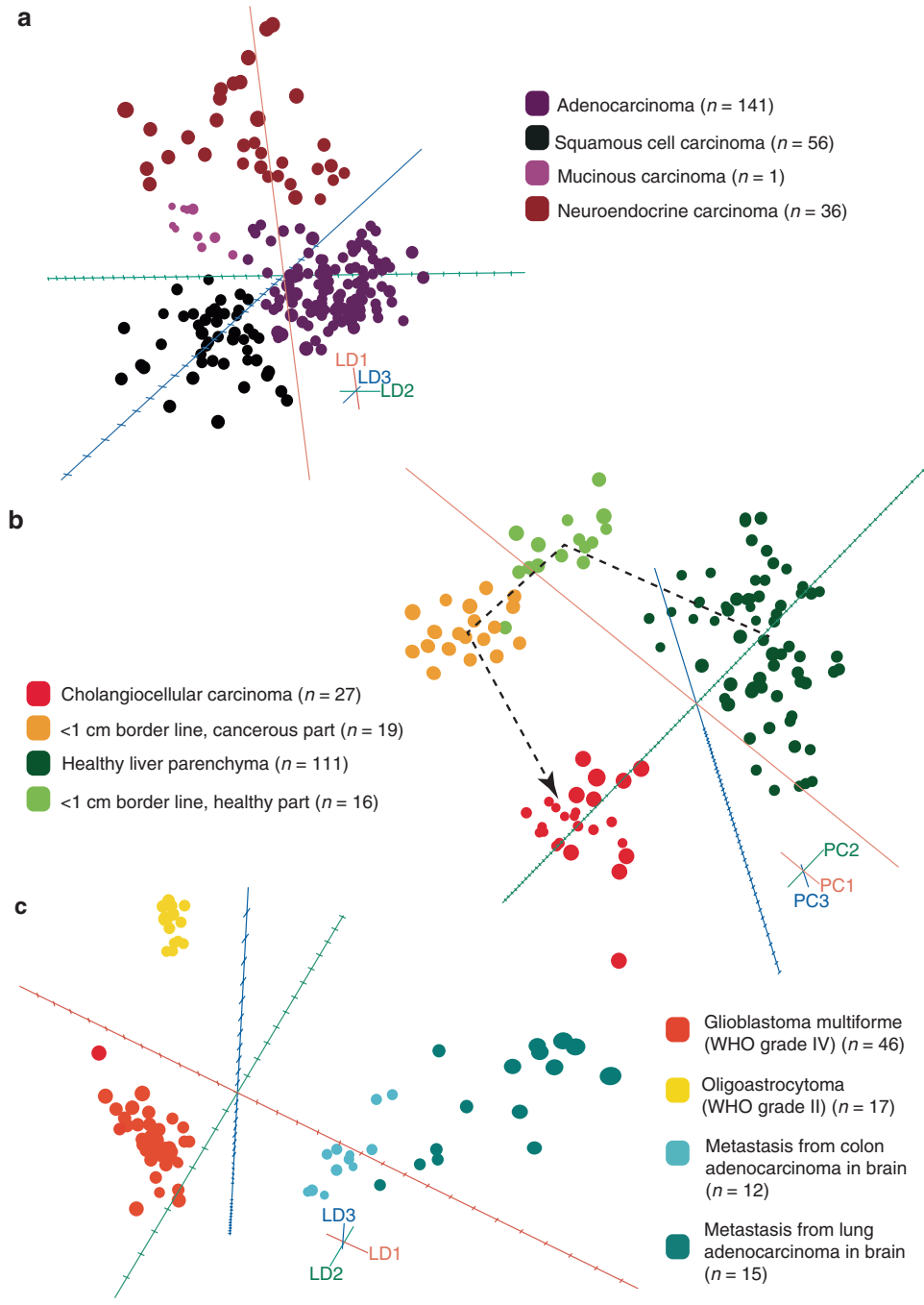

Fig. 4.5 Multivariate statistical analysis of malignant tumor data obtained ex vivo. n represents the number of spectra in the training set. (**a**) Pseudo–three-dimensional (3D) linear discriminant analysis (LDA) plot of different human lung tumors. (**b**) 3D principal component score plot of healthy liver parenchyma and hepatocellular carcinoma. Spectra obtained within 1 cm of the border lines are also depicted. The arrow demonstrates a shift from healthy liver parenchyma through tumor border into tumor tissue. (**c**) Pseudo-3D LDA plot of two different brain metastases and two different WHO-grade gliomas in the human brain. Numbers of patients were 40, 22, and 14 for (**a**), (**b**), and (**c**), respectively. (From Ref. [128])

ablation. The importance of this application in surgical oncology cannot be overemphasized, because surgical resection margin remains one of the most important prognostic factors in many cancers, and re-excision is not always possible.

Metabolic Adaptations: Metabolic Arrest, Hypometabolism, and Other Lessons Learned from Hibernation Biology

A number of animals employ metabolic arrest strategies to extend their hypoxia tolerance and more broadly as a defense against harsh environmental conditions or as a strategic retreat from them. Variable degrees of metabolic arrest down to fully ametabolic states are common strategies for dealing with desiccation, cold, and anoxia. The mechanisms invoked to turn down or turn off cell metabolism and cell functions, as well as the triggers and precise timing for activating such mechanisms to reversibly arrest of tissue and organ function, and then to switch them back on are the subject of intense investigation. Slowing down molecular or metabolic rate processes translates into extending biological time. In particular, *mammalian hibernation* is an integrative suite of natural molecular, cellular, and physiologic organismal adaptations used to survive extreme environmental conditions and avoid organ damage that would occur in nonhibernating species. These adaptations to physiologic extremes include regulated metabolic suppression (to ~2% of summer active levels), metabolic reprogramming (shifts in metabolic substrate utilization), supercooling, and immunosuppression, many of which have high translational potential [131]. Thus, hibernating mammals offer a naturally evolved model system of metabolic and immune adaptations, with successful and repeated returns to normal after *prolonged metabolic depression*, fasting, and ischemia-reperfusion – in other words, *a model of resilience to physical stressors*. Importantly, hibernation functions as an alternative discovery paradigm to understand the regulatory mechanisms controlling metabolic rate depression (independent of temperature), profound metabolic flexibility, transient reversible immune suppression, and cell preservation strategies that support long-term viability in a hypometabolic state. Having characterized for the first time in a comparative biology study the differences in heart responses of hibernators (arctic ground squirrels) and nonhibernators (rats) to experimental cardiac surgery and whole-body ischemia-reperfusion, which revealed robust ischemic tolerance and preservation of cardiac function in hibernators, we then conducted an integrated systems biology analysis of myocardial protein and metabolite abundance, identifying a series of endogenous metabolic adaptations in myocardial substrate utilization including the absence of mitochondrial substrate flux bottlenecks in the hibernator heart [132]. A remarkable finding was that hibernators increase expression and activity of the mitochondrial deacetylase sirtuin-3, opening a series of follow-up mechanistic studies focused on posttranslational modification regulators of the hibernator phenotype (i.e., Sirt3-mediated protein acetylation status) that could be amenable to pharmacological manipulation. Hibernation is a widely conserved behavior, including among primates (the fat tailed and the mouse lemurs), which may further inform strategies for inducing hibernation-like adaptive responses and recovery following surgical stress for human translation. This observation from nature has already informed the conduct of modern surgery, in particular cardiovascular and transplant surgery. By inducing partial metabolic arrest (through active cooling, chemical cardioplegia for cardiac arrest), surgeons gain many advantages, but the biggest gain is operating time. Strategies to "switch" metabolic and immune responses to resemble that naturally occurring in mammalian hibernators represent a transformative approach that could ultimately have a positive impact in patients undergoing major surgery, transplantation, coronary revascularization, victims of cardiac arrest, trauma, and hypothermia, in addition to fundamentally advancing cardiovascular aging biology.

Linking Metabolic with Immunophenotyping and Other "-Omics" Information

As outlined above, many fundamental biological processes predisposing to adverse perioperative outcomes and impaired recovery after surgery manifest themselves in all tissues, and thus quantitative assessment of circulating cell phenotypes, in particular high-content immune profiling, is transforming the field of predictive medicine. A detailed understanding of the complex inflammatory responses to surgery, trauma, and critical illness is crucial for identifying immunologic dysfunction predictive of organ injury, sepsis, and recovery. A novel deep immune profiling approach utilizes mass cytometry by time-of-flight (CyTOF), which enables longitudinal phenotypic and functional characterization of major innate and adaptive immune responses by simultaneously interrogating many parameters on a cell-by-cell basis [133]. The technology allows for concomitant quantification of both abundance of immune cell subsets and intracellular expression of various immune mediators and signaling proteins at the single-cell level.

Two recent studies employed high-dimensional mass cytometry to assess the role of immune responsiveness in predicting recovery after surgery. Using this novel immunophenotyping approach, Gaudilliere et al. identified a uniform surgical immune signature as well as novel predictors of specific aspects of recovery after orthopedic surgery such as functional impairment and pain [134]. Specifically, cell signaling responses, but not cell counts, were linked to recovery. Furthermore, the correlated signaling responses occurred most notably in $CD14^+$ monocytes and dendritic cells, with signaling induced by toll-like receptor 4 (TLR4) activation demonstrating very strong predictive ability for individual postoperative recovery trajectories. In a follow-up study from the same group, they demonstrated that the *preoperative* "immunophenotype" of individual patients, assessed in vitro as the strength of LPS-induced signaling in $CD14^+$ monocytes in samples collected before surgery, also predicts the speed of postoperative recovery in some domains [135]. This ability to interrogate patient-specific immune states before injury, specifically using ligand-evoked responses in myeloid and lymphoid cell subsets, highlights the importance of surgery as a useful model of traumatic injury and has high translational potential in assessing preoperative interventions that alter a patient's immune state and surgical recovery. In one such application, the immune-modifying effects of a preoperative nutritional intervention (arginine-enriched dietary supplements) were assessed using single-cell mass cytometry combined with multiplex analysis of plasma cytokines [136]. Enhanced adaptive mechanisms were found in lymphoid cell subsets postoperatively (increased STAT1 and STAT3 signaling), as well as an unexpected increased signaling (ERK and p38 MAPK) and pronounced expansion of monocytic myeloid-derived suppressor cells. These immune features modulated by arginine-enriched supplements may explain their context-dependent effects, protective in the setting of surgery (decreased infection rates) but potentially harmful in critically ill patients.

Contribution of Genomic Variation in Inflammatory and Metabolic Responses to Surgery

We and others have reported that a number of DNA sequence variants (polymorphisms) in genes encoding important pathways involved in the host response to injury confer a constitutional predisposition to adverse perioperative and long-term postoperative outcomes following surgery. One overarching theme is that genetic susceptibility for increased inflammatory response to surgery is associated with a number of postoperative complications, including myocardial infarction, atrial fibrillation, cognitive decline, stroke, and bleeding [21, 22, 24, 26, 27, 29, 137, 138]. The "static" view of DNA sequence variants potentially involved in the pathophysiology of perioperative complications can be complemented by a "dynamic" view that integrates their functionality. There is increasing evidence that variability in gene expression levels underlies

complex disease and is determined by regulatory DNA polymorphisms affecting transcription, splicing, and translation efficiency in a tissue- and stimulus-specific manner. Thus, analysis of RNA and protein expression at baseline and in response to the perioperative stress (*dynamic genomics*) using microarray, next-generation sequencing, and proteomic approaches provides a much-needed understanding of the overall regulatory networks involved in the pathophysiology of adverse postoperative outcomes. This information is complementary to the assessment of genetic variability at the DNA sequence level discussed above using various genotyping techniques as described in previous sections (*static genomics*). Such dynamic genomic markers can be incorporated in genomic classifiers and used clinically to improve perioperative risk stratification or to monitor postoperative recovery. To illustrate the complementary information conferred by static and dynamic genomic approaches to risk prediction, we use thoracic aortic disease as an example. Although surgical repair of thoracic aortic aneurysms is typically recommended when the aortic diameter reaches 5.0–5.5 cm, studies indicate that 60% of aortic dissections occur at aortic diameters smaller than 5.5 cm. DNA variants in specific genes (static genomics) can not only distinguish however patients at risk for thoracic aortic disease but predict the risk of early dissection at diameters smaller than 5.0 cm, thus potentially personalizing the timing of aortic surgery [139]. Furthermore, by combining genomic and proteomic analysis (dynamic genomics), expression patterns of 138 genes from peripheral blood leukocytes and the concentrations of 7 circulating plasma proteins were able to discriminate patients who developed multiple organ dysfunction syndrome (MODS) after thoracoabdominal aortic aneurysm repair from those who did not. Importantly, these patterns of genome-wide gene expression and plasma protein concentration were observed *before* surgical trauma and visceral ischemia-reperfusion injury, suggesting that patients who developed MODS differed preoperatively in either their genetic predisposition or pre-existing inflammatory state [140].

Similarly, linking variation in the human genome with variation in metabolic profiles (genome-wide association studies GWAS with metabolic phenotyping) allows the identification of genes and pathways associated with specific metabolite levels that are intermediate phenotypes for biological and clinical endpoints. One such study found that common genetic variation explained 12% of the observed metabolic variance [141].

The Relationship Between Gut Microbiome and Metabolic Phenotypes

An increasing number of clinical [142–146] and preclinical studies [147] have been characterizing the complex bi-directional relationships between alterations in gut microbiome (dysbiosis) and complications or recovery following surgical stress, sepsis, and critical illness. It is now well established that following acute insults such as surgery, trauma, myocardial infarction, or burn surgery, the intestinal microbiota decrease in abundance and function, and a virulent and resistant pathobiome emerges, rendering the stressed host more vulnerable to infection [148, 149]. Intervention or treatment-related effects also appear to interact with endogenous determinants such as age in the context of prolonged postoperative stress and systemic inflammatory response. Furthermore, age-related imbalances in gut microbiome composition appear to drive increased intestinal permeability, age-associated inflammation, and decreased macrophage function [150]. In this regard, the main goal of early enteral nutrition in the postoperative course and critical illness is to promote non-nutritional benefits such as gut integrity and modulation of immunity (*immunonutrition*) and only later on to address maintenance of lean muscle mass and avoidance of malnutrition. Given our better understanding of the gut microbiome and its implication of surgical stress response and outcomes, the role of perioperative probiotics and other acute nutritional interventions (such as fecal transplantation) to help preserve or restore

beneficial intestinal microbial communities is an active area of investigation. Meta-analyses found an approximately 40% reduction in operative site infections and postoperative sepsis with systematic probiotic use, as well as consistent reduction in incidence of multiple organ dysfunction syndrome after trauma, but convincing evidence for their therapeutic efficacy is lacking [151]. However, quantitative analysis of the microbiome is more complex that simply characterizes the microbiota and relies on using integrated metagenomics and metabolic phenotyping, along with metatranscriptomics and metaproteomics. Modeling the microbe-host metabolic connectivities is essential to characterize the cause-effect relationships between disease and changes in the microbiome. What is clear is that several known metabolic functions are encoded in the human gut microbiome and thus can modify downstream metabolic phenotypes, influencing not only the GI tract but also substrate utilization in the liver, muscles, brain, kidneys, and heart. It is clear that the biochemical output of the gut microbiome is changing systemic metabolic phenotypes. Specific examples include short-chain fatty acids and by-products of carbohydrate fermentation, products of proteolysis and amino acid metabolism, ammonia, branched-chain amino acids, bile acids, dietary methylamines, and polyphenols, which have been identified as biomarkers in many disease processes [152].

Pharmacogenomic and Pharmacometabonomics

Pharmacogenomics is emerging as an additional modifying component to perioperative and acute care management along with age, gender, comorbidities, and medication usage. Specific testing and treatment guidelines allowing clinicians to appropriately modify drug utilization (e.g., adjust dose or change drug) already exist for a few compounds [153] and will likely be expanded to all relevant therapeutic compounds, together with identification of novel therapeutic targets. According to a 2015 Nature review article, approximately 7% of FDA-approved medications are known to be affected by "actionable" inherited pharmacogenes [154]. While more than 150 drug labels include pharmacogenomic information, many do not translate the genetic test results into specific prescribing actions, which has limited physician uptake. The international Clinical Pharmacogenetics Implementation Consortium has written guidelines for gene-drug pairs that have sufficient evidence from randomized controlled trials and other clinical studies to influence prescribing. So far, the group, which focuses on inherited genetic variations, has released clinical practice guidelines for 13 genes affecting the response to more than 30 drugs [155]. It has been suggested that variation in pharmacology of beta-blockers (including the extent of metabolism by CYP2D6, pharmacogenomic variation in CYP2D6) may contribute to the heterogeneous trial results of perioperative beta-blockade [156]. However, the pharmacogenetic approach is limited because most complex diseases and responses to drugs involve an interaction between genetic and environmental factors, such as nutritional status, gut bacterial activities, and other drug uses. As discussed above, there is increased appreciation of the robust complex influence exerted by the gut microbiome over host metabolism and disease risk [157–159]. Furthermore, a phenomenon induced by co-administration of drugs termed *phenoconversion* (the conversion of genotypical extensive metabolizer into phenotypical poor metabolizer) can significantly confound pharmacogenomic analyses [160]. An alternative and complementary approach called *pharmacometabonomics* is used to predict variable drug metabolism in humans [161]. At its core, pharmacometabonomics uses *predose* metabolite profiles in biological fluids to characterize the physiologic and biochemical state of the subject prior to dosing (or preoperatively) and then develop a model to predict differential responses (e.g., responders vs nonresponders to drug treatment). Patient subgroups based on differences in *predose* metabolite profiles are analyzed with respect to observed *postdose* response differences (e.g., varying pharmacokinetics, metabolism, efficiency, or toxicity), thus enabling

prediction of drug responses [162]. An initial proof of principle study reported in humans that the metabolic fate of acetaminophen can be predicted from baseline urine samples, identified a human gut microbiome cometabolite that competes with acetaminophen metabolism was identified [163], and created the framework for prediction of acetaminophen-induced hepatotoxicity [164]. It further highlighted the limitations of pharmacogenomic approaches to predict drug effects in the presence of significant microbiome influences. Using the same concept, mortality in patients with septic shock receiving L-carnitine treatment could be predicted based on a unique metabolite profile indicative of L-carnitine responsiveness [165]. Patients with low pretreatment ketone levels showed a marked increase in survival after L-carnitine treatment and were superior to using the SOFA score in guiding L-carnitine therapy decisions, thus highlighting the application of pharmacometabonomic phenotyping to inform precision sepsis therapeutics. Using a combined pharmacogenomic and pharmacometabonomic approach, Shin et al. predicted clearance of midazolam based on predose urinary ratios of four metabolites and the CYP3A5 genotype [166].

Challenges to Creating a Dynamic Analytical Environment that Allows for Real Decisions in Real Time

While the ability of metabolic phenotypes to expose metabolically driven processes triggered by external factors such as drugs or the gut microbiota represents an advantage over other systems biology "-omics" tools, it also faces similar challenges to robust implementation in the perioperative period. Like other molecular phenomic strategies, these challenges revolve around the highly heterogeneous perioperative environment superimposed on interindividual variability in preoperative lifestyle and diet, degree of malnutrition and nutritional optimization strategies, gut microflora and its complex two-way biochemical interaction with the host, and perioperative drugs and their metabolites. Further challenges in longitudinal perioperative data analysis include nonuniform timing of sample collection (for practical reasons) and integration of data from different biofluids (urine and plasma) with other multi"-omic" datasets, clinical metrics, and metadata [167] to create a clinical decision-making environment along the perioperative continuum of care [106].

For both metabolic and immunophenotyping, it is imperative that longitudinal data is handled in a dynamic fashion, with models built to predict patient trajectories (outcome prediction related to baseline information) and implemented at the point of care. In this regard, metabolic and immunophenotypes become *endophenotypes* of postoperative recovery and critical illness. Supervised and unsupervised machine learning models have produced highly discriminative models predicting physiologic state transitions, treatment appropriateness, and clinical outcomes in critically ill patients. Such novel endophenotypes clustered according to specific clinical and biological characteristics (molecular, physiologic, and biochemical patterns) could represent a major step toward resolving heterogeneity of treatment effects and achieving precision in perioperative/intensive care medicine. It is important to refine the computational methodology for rigorously integrating and rapidly analyzing such longitudinal physiologic and molecular data in the perioperative period (*dynamic phenotyping*) [168] to identify temporal patterns of inflammation and metabolic dysregulation associated with adverse outcomes or a recovery trajectory (*dynamic network analysis*) [169–172]. Machine and deep learning algorithms that integrate multi-omic datasets are now being developed [173, 174], but their applications to perioperative settings are limited. Decision support is also necessary to guide clinicians on how to use pharmacogenomic information, and efforts are underway to standardize terms for clinical pharmacogenetic test results [175] and update existing guidelines to provide more computational tables that can be uploaded into EHR systems to facilitate implementation of genetic testing. Innovative data visualization strategies are required to aid clinicians with adoption of actionable molecular information along the perioperative continuum of care.

Summary and Future Directions

This chapter outlines a framework of surgical care that uses a systems-based multiscale approach and dynamic computational modeling to generate granular and precise stratifications of individual patients on the basis of their robustness and resilience to physical surgical stressors. At its core, it entails a rational, quantitative description of the dynamic patient state before and immediately following the stressor in the perioperative and critical care settings, by analyzing patterns in multiparameter physiologic time series data and in molecular "-omic" or biomarker profiles, with a particular focus on their *recovery trajectories*. Specifically, metabolic and immunophenotypes (in particular innate immune responses) in biofluids and circulating cells are required to understand the complex relationship between perioperative metabolic reprogramming, inflammation, and its resolution, with physical resilience to surgical stress. By focusing multiple metabolic measuring technologies on the patient at any one moment during their surgical pathway, unique phenotypic information can increase the quality and depth of prognostic and diagnostic processes.

The ultimate goal is to use these sensitive and specific molecular signatures to aid clinical decision-making and develop effective means to control biological processes that impact postoperative recovery by optimizing therapeutic strategies. However, this emphasis on collecting ever more detail about the biological processes involved may divert efforts from finding out how biological systems function and therefore should be complemented with follow-up molecular studies of mechanisms underlying physical resilience to surgical stress in experimental models of surgery.

The opportunities for developing and testing patient-centered prediction and treatment algorithms for perioperative care, including through machine learning analysis of metabolic trajectories, are numerous, but few rigorous studies and clinical validation exist. Medical databases incorporating metabolomics data have to be developed and populated with large-scale metabotyping data for various diseases. In the bioinformatics field, we foresee major improvement in real-time analysis of different layers of omics data sampled from patients and broad incorporation of machine learning and artificial intelligence systems to provide physicians with fully automated clinical analyzers capable in assisting in disease diagnosis, devising treatment strategy, and predicting prognosis. Smarter continuous monitoring systems in the postoperative and critical care environments will enable better pattern detection and early recognition of clinical deterioration, with a resulting decrease in failure to rescue. The promise of high-performance medicine is truly data-driven, decompressing our reliance on human resources, and ultimately going beyond the sum of the parts of human and machine intelligence [176]. Such comprehensive framework for data sharing and collaborative work to enable preoperative prevention and optimization, identification of patients at risk for perioperative adverse events, early diagnosis, and appropriate individualized treatment for a given surgical patient represents the necessary transformational step from *perioperative genomics* [15] to *perioperative intelligence* [177].

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008;372:139–44.
2. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. Lancet. 2012;380:1059–65.
3. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK. Perioperative organ injury. Anesthesiology. 2013;119:1474–89.
4. Dobson GP. Addressing the global burden of trauma in major surgery. Front Surg. 2015;2:43.
5. Lowry SF. The stressed host response to infection: the disruptive signals and rhythms of systemic inflammation. Surg Clin North Am. 2009;89:311–26, vii.
6. Speziale G, Nasso G, Barattoni MC, et al. Operative and middle-term results of cardiac surgery in nonagenarians: a bridge toward routine practice. Circulation. 2010;121:208–13.
7. Speziale G, Nasso G, Barattoni MC, et al. Short-term and long-term results of cardiac surgery in elderly and very elderly patients. J Thorac Cardiovasc Surg. 2011;141:725–31, 731.e1.

8. Rydingsward JE, Horkan CM, Mogensen KM, Quraishi SA, Amrein K, Christopher KB. Functional status in ICU survivors and out of hospital outcomes: a cohort study. Crit Care Med. 2016;44:869–79.
9. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA. 2010;303:849–56.
10. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: systematic review and development of an emerging construct. J Gerontol A Biol Sci Med Sci. 2016;71:489–95.
11. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation. 2009;16:300–17.
12. Ghini V, Saccenti E, Tenori L, Assfalg M, Luchinat C. Allostasis and resilience of the human individual metabolic phenotype. J Proteome Res. 2015;14:2951–62.
13. Turkson S, Kloster A, Hamilton PJ, Neigh GN. Neuroendocrine drivers of risk and resilience: the influence of metabolism & mitochondria. Front Neuroendocrinol. 2019;54:100770.
14. Brame AL, Singer M. Stressing the obvious? An allostatic look at critical illness. Crit Care Med. 2010;38:S600–7.
15. Podgoreanu MV, Schwinn DA. New paradigms in cardiovascular medicine: emerging technologies and practices: perioperative genomics. J Am Coll Cardiol. 2005;46:1965–77.
16. Kinross JM, Holmes E, Darzi AW, Nicholson JK. Metabolic phenotyping for monitoring surgical patients. Lancet. 2011;377:1817–9.
17. Iwashyna TJ. Trajectories of recovery and dysfunction after acute illness, with implications for clinical trial design. Am J Respir Crit Care Med. 2012;186:302–4.
18. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg. 2017;152:292–8.
19. Engelman DT, Ben Ali W, Williams JB, et al. Guidelines for perioperative care in cardiac surgery: enhanced recovery after surgery society recommendations. JAMA Surg. 2019;154:755.
20. Memtsoudis SG, Poeran J, Kehlet H. Enhanced recovery after surgery in the United States: from evidence-based practice to uncertain science. JAMA. 2019;321:1049–50.
21. Kertai MD, Li YJ, Ji Y, et al. Genome-wide association study of new-onset atrial fibrillation after coronary artery bypass grafting surgery. Am Heart J. 2015;170:580–90.e28.
22. Kertai MD, Li YJ, Li YW, et al. Genome-wide association study of perioperative myocardial infarction after coronary artery bypass surgery. BMJ Open. 2015;5:e006920.
23. Kertai MD, Qi W, Li YJ, et al. Gene signatures of postoperative atrial fibrillation in atrial tissue after coronary artery bypass grafting surgery in patients receiving β-blockers. J Mol Cell Cardiol. 2016;92:109–15.
24. Kertai MD, Ji Y, Li YJ, et al. Interleukin-1β gene variants are associated with QTc interval prolongation following cardiac surgery: a prospective observational study. Can J Anaesth. 2016;63:397–410.
25. Stafford-Smith M, Li YJ, Mathew JP, et al. Genome-wide association study of acute kidney injury after coronary bypass graft surgery identifies susceptibility loci. Kidney Int. 2015;88:823–32.
26. Grocott HP, White WD, Morris RW, et al. Genetic polymorphisms and the risk of stroke after cardiac surgery. Stroke. 2005;36:1854–8.
27. Mathew JP, Podgoreanu MV, Grocott HP, et al. Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. J Am Coll Cardiol. 2007;49:1934–42.
28. Podgoreanu MV, Michelotti GA, Sato Y, et al. Differential cardiac gene expression during cardiopulmonary bypass: ischemia-independent upregulation of proinflammatory genes. J Thorac Cardiovasc Surg. 2005;130:330–9.
29. Podgoreanu MV, White WD, Morris RW, et al. Inflammatory gene polymorphisms and risk of postoperative myocardial infarction after cardiac surgery. Circulation. 2006;114:I275–81.
30. Ashrafian H, Athanasiou T, Nicholson JK, Darzi AW. Unmet medical needs. In: Holmes E, Nicholson JK, Darzi AW, Lindon JC, editors. Metabolic phenotyping in personalized and public healthcare. Academic Press: San Diego; 2016. p. 1–13.
31. Gillman MW, Hammond RA. Precision treatment and precision prevention: integrating "below and above the skin". JAMA Pediatr. 2016;170:9–10.
32. Valente TW. Network interventions. Science. 2012;337:49–53.
33. Houle D, Govindaraju DR, Omholt S. Phenomics: the next challenge. Nat Rev Genet. 2010;11:855–66.
34. Dona AC, Jiménez B, Schäfer H, et al. Precision high-throughput proton NMR spectroscopy of human urine, serum, and plasma for large-scale metabolic phenotyping. Anal Chem. 2014;86:9887–94.
35. Semmar N. Metabotype concept: flexibility, usefulness and meaning in different biological populations. In: Metabolomics. Cambridge: Elsevier; 2012. p. 131–66.
36. Lindon JC, Nicholson JK, Holmes E, Everett JR. Metabonomics: metabolic processes studied by NMR spectroscopy of biofluids. Concept Magn Reson. 2000;12:289–320.
37. Nicholson JK, Holmes E, Kinross JM, Darzi AW, Takats Z, Lindon JC. Metabolic phenotyping in clinical and surgical environments. Nature. 2012;491:384–92.
38. Want EJ, Wilson ID, Gika H, et al. Global metabolic profiling procedures for urine using UPLC-MS. Nat Protoc. 2010;5:1005–18.
39. Naz S, García A, Barbas C. Multiplatform analytical methodology for metabolic fingerprinting of lung tissue. Anal Chem. 2013;85:10941–8.

40. Matheus N, Hansen S, Rozet E, et al. An easy, convenient cell and tissue extraction protocol for nuclear magnetic resonance metabolomics. Phytochem Anal. 2014;25:342–9.
41. Tilgner M, Vater TS, Habbel P, Cheng LL. High-Resolution Magic Angle Spinning (HRMAS) NMR methods in metabolomics. Methods Mol Biol. 2019;2037:49–67.
42. Beckonert O, Coen M, Keun HC, et al. High-resolution magic-angle-spinning NMR spectroscopy for metabolic profiling of intact tissues. Nat Protoc. 2010;5:1019–32.
43. Wallner-Liebmann S, Gralka E, Tenori L, et al. The impact of free or standardized lifestyle and urine sampling protocol on metabolome recognition accuracy. Genes Nutr. 2015;10:441.
44. Yin P, Peter A, Franken H, et al. Preanalytical aspects and sample quality assessment in metabolomics studies of human blood. Clin Chem. 2013;59:833–45.
45. Dunn WB, Lin W, Broadhurst D, et al. Molecular phenotyping of a UK population: defining the human serum metabolome. Metabolomics. 2015;11:9–26.
46. Bouatra S, Aziat F, Mandal R, et al. The human urine metabolome. PLoS One. 2013;8:e73076.
47. MSI BM, Sansone SA, Fan T, et al. The metabolomics standards initiative.[letter]. Nat Biotechnol. 2007;25(8):846–8.
48. Castro-Perez JM, Kamphorst J, DeGroot J, et al. Comprehensive LC-MS E lipidomic analysis using a shotgun approach and its application to biomarker detection and identification in osteoarthritis patients. J Proteome Res. 2010;9:2377–89.
49. Yamada M, Kita Y, Kohira T, et al. A comprehensive quantification method for eicosanoids and related compounds by using liquid chromatography/mass spectrometry with high speed continuous ionization polarity switching. J Chromatogr B Analyt Technol Biomed Life Sci. 2015;995–996:74–84.
50. The emergent role of metabolic phenotyping in dynamic patient stratification. [editorial]. Expert Opin Drug Metab Toxicol. 2014;10(7):915.
51. Würtz P, Havulinna AS, Soininen P, et al. Metabolite profiling and cardiovascular event risk: a prospective study of 3 population-based cohorts. Circulation. 2015;131:774–85.
52. Shah SH, Bain JR, Muehlbauer MJ, et al. Association of a peripheral blood metabolic profile with coronary artery disease and risk of subsequent cardiovascular events. Circ Cardiovasc Genet. Cambridge: Elsevier; 2010;3:207–14.
53. Shah SH, Sun JL, Stevens RD, et al. Baseline metabolomic profiles predict cardiovascular events in patients at risk for coronary artery disease. Am Heart J. 2012;163:844–850.e1.
54. Wang Z, Tang WH, Buffa JA, et al. Prognostic value of choline and betaine depends on intestinal microbiota-generated metabolite trimethylamine-N-oxide. Eur Heart J. 2014;35:904–10.
55. Zordoky BN, Sung MM, Ezekowitz J, et al. Metabolomic fingerprint of heart failure with preserved ejection fraction. PLoS One. 2015;10:e0124844.
56. Wang-Sattler R, Yu Z, Herder C, et al. Novel biomarkers for pre-diabetes identified by metabolomics. Mol Syst Biol. 2012;8:615.
57. Jové M, Mauri-Capdevila G, Suárez I, et al. Metabolomics predicts stroke recurrence after transient ischemic attack. Neurology. 2015;84:36–45.
58. Holmes E, Loo RL, Stamler J, et al. Human metabolic phenotype diversity and its association with diet and blood pressure. Nature. 2008;453:396–400.
59. Fischer K, Kettunen J, Würtz P, et al. Biomarker profiling by nuclear magnetic resonance spectroscopy for the prediction of all-cause mortality: an observational study of 17,345 persons. PLoS Med. 2014;11:e1001606.
60. Ussher JR, Elmariah S, Gerszten RE, Dyck JR. The emerging role of metabolomics in the diagnosis and prognosis of cardiovascular disease. J Am Coll Cardiol. 2016;68:2850–70.
61. McGarrah RW, Crown SB, Zhang GF, Shah SH, Newgard CB. Cardiovascular metabolomics. Circ Res. 2018;122:1238–58.
62. Everett JR. From metabonomics to pharmacometabonomics: the role of metabolic profiling in personalized medicine. Front Pharmacol. 2016;7:297.
63. Nicholson JK, Wilson ID, Lindon JC. Pharmacometabonomics as an effector for personalized medicine. Pharmacogenomics. 2011;12:103–11.
64. Everett JR. Pharmacometabonomics in humans: a new tool for personalized medicine. Pharmacogenomics. 2015;16:737–54.
65. Rinehart D, Johnson CH, Nguyen T, et al. Metabolomic data streaming for biology-dependent data acquisition.[letter]. Nat Biotechnol. 2014;32(6):524–7.
66. Parent BA, Seaton M, Djukovic D, et al. Parenteral and enteral nutrition in surgical critical-care: plasma metabolomics demonstrates divergent effects on nitrogen, fatty-acid, ribonucleotide and oxidative metabolism. J Trauma Acute Care Surg. 2017;82:704.
67. Correia GD, Wooi Ng K, Wijeyesekera A, et al. Metabolic profiling of children undergoing surgery for congenital heart disease. Crit Care Med. 2015;43:1467–76.
68. Davidson JA, Pfeifer Z, Frank B, et al. Metabolomic fingerprinting of infants undergoing cardiopulmonary bypass: changes in metabolic pathways and association with mortality and cardiac intensive care unit length of stay. J Am Heart Assoc. 2018;7:e010711.
69. Lewis GD, Wei R, Liu E, et al. Metabolite profiling of blood from individuals undergoing planned myocardial infarction reveals early markers of myocardial injury. J Clin Invest. 2008;118:3503–12.
70. Turer AT, Stevens RD, Bain JR, et al. Metabolomic profiling reveals distinct patterns of myocardial substrate use in humans with coronary artery disease or left ventricular dysfunction during surgical ischemia/reperfusion. Circulation. 2009;119:1736–46.

71. Mayr M, Yusuf S, Weir G, et al. Combined metabolomic and proteomic analysis of human atrial fibrillation. J Am Coll Cardiol. 2008;51:585–94.
72. Shah AA, Craig DM, Sebek JK, et al. Metabolic profiles predict adverse events after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2012;143:873–8.
73. Gupte AA, Hamilton DJ, Cordero-Reyes AM, et al. Mechanical unloading promotes myocardial energy recovery in human heart failure. Circ Cardiovasc Genet. 2014;7:266–76.
74. Schechter MA, Hsieh MK, Njoroge LW, et al. Phosphoproteomic profiling of human myocardial tissues distinguishes ischemic from non-ischemic end stage heart failure. PLoS One. 2014;9:e104157.
75. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol Rev. 2010;90:207–58.
76. Neubauer S. The failing heart–an engine out of fuel. N Engl J Med. 2007;356:1140–51.
77. Ahmad T, Kelly JP, McGarrah RW, et al. Prognostic implications of long-chain acylcarnitines in heart failure and reversibility with mechanical circulatory support. J Am Coll Cardiol. 2016;67:291–9.
78. Birks EJ. Molecular changes after left ventricular assist device support for heart failure. Circ Res. 2013;113:777–91.
79. Blaxall BC, Tschannen-Moran BM, Milano CA, Koch WJ. Differential gene expression and genomic patient stratification following left ventricular assist device support. J Am Coll Cardiol. 2003;41:1096–106.
80. Hall JL, Birks EJ, Grindle S, et al. Molecular signature of recovery following combination left ventricular assist device (LVAD) support and pharmacologic therapy. Eur Heart J. 2007;28:613–27.
81. Chokshi A, Drosatos K, Cheema FH, et al. Ventricular assist device implantation corrects myocardial lipotoxicity, reverses insulin resistance, and normalizes cardiac metabolism in patients with advanced heart failure. Circulation. 2012;125:2844–53.
82. Diakos NA, Navankasattusas S, Abel ED, et al. Evidence of glycolysis up-regulation and pyruvate mitochondrial oxidation mismatch during mechanical unloading of the failing human heart: implications for cardiac reloading and conditioning. JACC Basic Transl Sci. 2016;1:432–44.
83. Shahinian JH, Rog-Zielinska EA, Schlimpert M et al. Impact of left ventricular assist device therapy on the cardiac proteome and metabolome composition in ischemic cardiomyopathy. Artif Organs. 2019.
84. Elmariah S, Farrell LA, Daher M, et al. Metabolite profiles predict acute kidney injury and mortality in patients undergoing transcatheter aortic valve replacement. J Am Heart Assoc. 2016;5:e002712.
85. Priddy CM, Kajimoto M, Ledee DR, et al. Myocardial oxidative metabolism and protein synthesis during mechanical circulatory support by extracorporeal membrane oxygenation. Am J Physiol Heart Circ Physiol. 2013;304:H406–14.
86. Li CL, Wang H, Jia M, Ma N, Meng X, Hou XT. The early dynamic behavior of lactate is linked to mortality in postcardiotomy patients with extracorporeal membrane oxygenation support: a retrospective observational study. J Thorac Cardiovasc Surg. 2015;149:1445–50.
87. Slottosch I, Liakopoulos O, Kuhn E, et al. Lactate and lactate clearance as valuable tool to evaluate ECMO therapy in cardiogenic shock. J Crit Care. 2017;42:35–41.
88. Zhang L, Yu X, Cheypesh A, et al. Plasma fatty acid levels in children during extracorporeal membrane oxygenation support–a pilot study. J Extra Corpor Technol. 2013;45:242–7.
89. Li X, Yu X, Cheypesh A, Li J. Non-invasive measurements of energy expenditure and respiratory quotient by respiratory mass spectrometry in children on extracorporeal membrane oxygenation-a pilot study. Artif Organs. 2015;39:815–9.
90. Ledee DR, Kajimoto M, O'Kelly Priddy CM, et al. Pyruvate modifies metabolic flux and nutrient sensing during extracorporeal membrane oxygenation in an immature swine model. Am J Physiol Heart Circ Physiol. 2015;309:H137–46.
91. Kajimoto M, Ledee DR, Olson AK, Isern NG, Des Rosiers C, Portman MA. Differential effects of octanoate and heptanoate on myocardial metabolism during extracorporeal membrane oxygenation in an infant swine model. Am J Physiol Heart Circ Physiol. 2015;309:H1157–65.
92. Kajimoto M, Ledee DR, Isern NG, Portman MA. Right ventricular metabolism during venoarterial extracorporeal membrane oxygenation in immature swine heart in vivo. Am J Physiol Heart Circ Physiol. 2017;312:H721–7.
93. Files MD, Kajimoto M, O'Kelly Priddy CM, et al. Triiodothyronine facilitates weaning from extracorporeal membrane oxygenation by improved mitochondrial substrate utilization. J Am Heart Assoc. 2014;3:e000680.
94. Kajimoto M, O'Kelly Priddy CM, Ledee DR, et al. Extracorporeal membrane oxygenation promotes long chain fatty acid oxidation in the immature swine heart in vivo. J Mol Cell Cardiol. 2013;62:144–52.
95. D'Alessandro A, Moore HB, Moore EE, et al. Plasma succinate is a predictor of mortality in critically injured patients. J Trauma Acute Care Surg. 2017;83:491–5.
96. Banoei MM, Vogel HJ, Weljie AM, et al. Plasma metabolomics for the diagnosis and prognosis of H1N1 influenza pneumonia. Crit Care. 2017;21:97.
97. Lusczek ER, Muratore SL, Dubick MA, Beilman GJ. Assessment of key plasma metabolites in combat casualties. J Trauma Acute Care Surg. 2017;82:309–16.
98. Peltz ED, D'Alessandro A, Moore EE, et al. Pathologic metabolism: an exploratory study of the plasma metabolome of critical injury. J Trauma Acute Care Surg. 2015;78:742–51.
99. Parent BA, Seaton M, Sood RF, et al. Use of metabolomics to trend recovery and therapy after

injury in critically ill trauma patients. JAMA Surg. 2016;151:e160853.
100. Slaughter AL, Nunns GR, D'Alessandro A, et al. The metabolopathy of tissue injury, hemorrhagic shock and resuscitation in a rat model. Shock. 2018;49(5):580–90.
101. Clendenen N, Nunns GR, Moore EE, et al. Hemorrhagic shock and tissue injury drive distinct plasma metabolome derangements in swine. J Trauma Acute Care Surg. 2017;83:635–42.
102. D'Alessandro A, Slaughter AL, Peltz ED, et al. Trauma/hemorrhagic shock instigates aberrant metabolic flux through glycolytic pathways, as revealed by preliminary (13)C-glucose labeling metabolomics. J Transl Med. 2015;13:253.
103. D'Alessandro A, Moore HB, Moore EE, et al. Plasma first resuscitation reduces lactate acidosis, enhances redox homeostasis, amino acid and purine catabolism in a rat model of profound hemorrhagic shock. Shock. 2016;46:173–82.
104. D'Alessandro A, Moore HB, Moore EE, et al. Early hemorrhage triggers metabolic responses that build up during prolonged shock. Am J Physiol Regul Integr Comp Physiol. 2015;308:R1034–44.
105. Muirhead LJ, Kinross J, FitzMaurice TS, Takats Z, Darzi A, Nicholson JK. Surgical systems biology and personalized longitudinal phenotyping in critical care. Per Med. 2012;9:593–608.
106. Mirnezami R, Kinross JM, Vorkas PA, et al. Implementation of molecular phenotyping approaches in the personalized surgical patient journey. Ann Surg. 2012;255:881–9.
107. Cohen MJ, Serkova NJ, Wiener-Kronish J, Pittet JF, Niemann CU. 1H-NMR-based metabolic signatures of clinical outcomes in trauma patients-beyond lactate and base deficit. J Trauma. 2010;69:31–40.
108. Mao H, Wang H, Wang B, et al. Systemic metabolic changes of traumatic critically ill patients revealed by an NMR-based metabonomic approach. J Proteome Res. 2009;8:5423–30.
109. Blaise BJ, Gouel-Chéron A, Floccard B, Monneret G, Allaouchiche B. Metabolic phenotyping of traumatized patients reveals a susceptibility to sepsis. Anal Chem. 2013;85:10850–5.
110. Schmerler D, Neugebauer S, Ludewig K, Bremer-Streck S, Brunkhorst FM, Kiehntopf M. Targeted metabolomics for discrimination of systemic inflammatory disorders in critically ill patients. J Lipid Res. 2012;53:1369–75.
111. Li JV, Ashrafian H, Bueter M, et al. Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. Gut. 2011;60:1214–23.
112. Ashrafian H, Li JV, Spagou K, et al. Bariatric surgery modulates circulating and cardiac metabolites. J Proteome Res. 2014;13:570–80.
113. Samczuk P, Ciborowski M, Kretowski A. Application of metabolomics to study effects of bariatric surgery. J Diabetes Res. 2018;2018:6270875.
114. Mutch DM, Fuhrmann JC, Rein D, et al. Metabolite profiling identifies candidate markers reflecting the clinical adaptations associated with Roux-en-Y gastric bypass surgery. PLoS One. 2009;4:e7905.
115. Zhang H, DiBaise JK, Zuccolo A, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A. 2009;106:2365–70.
116. Palau-Rodriguez M, Tulipani S, Marco-Ramell A, et al. Metabotypes of response to bariatric surgery independent of the magnitude of weight loss. PLoS One. 2018;13:e0198214.
117. Foxall PJ, Mellotte GJ, Bending MR, Lindon JC, Nicholson JK. NMR spectroscopy as a novel approach to the monitoring of renal transplant function. Kidney Int. 1993;43:234–45.
118. Chen J, Wen H, Liu J, et al. Metabonomics study of the acute graft rejection in rat renal transplantation using reversed-phase liquid chromatography and hydrophilic interaction chromatography coupled with mass spectrometry. Mol BioSyst. 2012;8:871–8.
119. Kim CD, Kim EY, Yoo H, et al. Metabonomic analysis of serum metabolites in kidney transplant recipients with cyclosporine A- or tacrolimus-based immunosuppression. Transplantation. 2010;90:748–56.
120. Girlanda R, Cheema AK, Kaur P, et al. Metabolomics of human intestinal transplant rejection. Am J Transplant. 2012;12 Suppl 4:S18–26.
121. Legido-Quigley C, McDermott L, Vilca-Melendez H, et al. Bile UPLC-MS fingerprinting and bile acid fluxes during human liver transplantation. Electrophoresis. 2011;32:2063–70.
122. Opstad KS, Bell BA, Griffiths JR, Howe FA. Toward accurate quantification of metabolites, lipids, and macromolecules in HRMAS spectra of human brain tumor biopsies using LCModel. Magn Reson Med. 2008;60:1237–42.
123. Wright AJ, Fellows GA, Griffiths JR, Wilson M, Bell BA, Howe FA. Ex-vivo HRMAS of adult brain tumours: metabolite quantification and assignment of tumour biomarkers. Mol Cancer. 2010;9:66.
124. Wu CL, Jordan KW, Ratai EM, et al. Metabolomic imaging for human prostate cancer detection. Sci Transl Med. 2010;2:16ra8.
125. Bathen TF, Geurts B, Sitter B, et al. Feasibility of MR metabolomics for immediate analysis of resection margins during breast cancer surgery. PLoS One. 2013;8:e61578.
126. Mirnezami R, Jiménez B, Li JV, et al. Rapid diagnosis and staging of colorectal cancer via high-resolution magic angle spinning nuclear magnetic resonance (HR-MAS NMR) spectroscopy of intact tissue biopsies. Ann Surg. 2014;259:1138–49.
127. Balog J, Szaniszlo T, Schaefer KC, et al. Identification of biological tissues by rapid evaporative ionization mass spectrometry. Anal Chem. 2010;82:7343–50.
128. Balog J, Sasi-Szabó L, Kinross J, et al. Intraoperative tissue identification using rapid evaporative ionization mass spectrometry. Sci Transl Med. 2013;5:194ra93.
129. Phelps DL, Balog J, Gildea LF, et al. The surgical intelligent knife distinguishes normal, borderline

and malignant gynaecological tissues using rapid evaporative ionisation mass spectrometry (REIMS). Br J Cancer. 2018;118:1349–58.
130. Guenther S, Schäfer KC, Balog J, et al. Electrospray post-ionization mass spectrometry of electrosurgical aerosols. J Am Soc Mass Spectrom. 2011;22:2082–9.
131. Quinones QJ, Ma Q, Zhang Z, Barnes BM, Podgoreanu MV. Organ protective mechanisms common to extremes of physiology: a window through hibernation biology. Integr Comp Biol. 2014;54:497–515.
132. Quinones QJ, Zhang Z, Ma Q, et al. Proteomic profiling reveals adaptive responses to surgical myocardial ischemia-reperfusion in hibernating arctic ground squirrels compared to rats. Anesthesiology. 2016;124:1296–310.
133. Bendall SC, Nolan GP, Roederer M, Chattopadhyay PK. A deep profiler's guide to cytometry. Trends Immunol. 2012;33:323–32.
134. Gaudillière B, Fragiadakis GK, Bruggner RV, et al. Clinical recovery from surgery correlates with single-cell immune signatures. Sci Transl Med. 2014;6:255ra131.
135. Fragiadakis GK, Gaudillière B, Ganio EA, et al. Patient-specific immune states before surgery are strong correlates of surgical recovery. Anesthesiology. 2015;123:1241–55.
136. Aghaeepour N, Kin C, Ganio EA, et al. Deep immune profiling of an arginine-enriched nutritional intervention in patients undergoing surgery. J Immunol. 2017;199:2171.
137. Collard CD, Shernan SK, Fox AA, et al. The MBL2 'LYQA secretor' haplotype is an independent predictor of postoperative myocardial infarction in whites undergoing coronary artery bypass graft surgery. Circulation. 2007;116:I106–12.
138. Welsby IJ, Podgoreanu MV, Phillips-Bute B, et al. Association of the 98T ELAM-1 polymorphism with increased bleeding after cardiac surgery. J Cardiothorac Vasc Anesth. 2010;24:427–33.
139. Milewicz DM, Regalado ES. Use of genetics for personalized management of heritable thoracic aortic disease: how do we get there. J Thorac Cardiovasc Surg. 2015;149:S3–5.
140. Feezor RJ, Baker HV, Xiao W, et al. Genomic and proteomic determinants of outcome in patients undergoing thoracoabdominal aortic aneurysm repair. J Immunol. 2004;172:7103–9.
141. Gieger C, Geistlinger L, Altmaier E, et al. Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. PLoS Genet. 2008;4:e1000282.
142. Zheng S, Shao S, Qiao Z, et al. Clinical parameters and gut microbiome changes before and after surgery in thoracic aortic dissection in patients with gastrointestinal complications. Sci Rep. 2017;7:15228.
143. Lukovic E, Moitra VK, Freedberg DE. The microbiome: implications for perioperative and critical care. Curr Opin Anaesthesiol. 2019;32:412–20.
144. Lederer AK, Pisarski P, Kousoulas L, Fichtner-Feigl S, Hess C, Huber R. Postoperative changes of the microbiome: are surgical complications related to the gut flora? A systematic review. BMC Surg. 2017;17:125.
145. Stavrou G, Kotzampassi K. Gut microbiome, surgical complications and probiotics. Ann Gastroenterol. 2017;30:45–53.
146. McDonald D, Ackermann G, Khailova L et al. Extreme dysbiosis of the microbiome in critical illness. mSphere. 2016;1.
147. Kinross JM, Alkhamesi N, Barton RH, et al. Global metabolic phenotyping in an experimental laparotomy model of surgical trauma. J Proteome Res. 2010;10:277–87.
148. Alverdy JC, Luo JN. The influence of host stress on the mechanism of infection: lost microbiomes, emergent pathobiomes, and the role of interkingdom signaling. Front Microbiol. 2017;8:322.
149. Codner PA, Herron TJ. The shifting microbiome in surgical stress. Curr Surg Rep. 2017;5:9.
150. Thevaranjan N, Puchta A, Schulz C, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe. 2017;21:455–466.e4.
151. Morrow LE, Blurred Lines WP. Dysbiosis and probiotics in the ICU. Chest. 2017;151:492–9.
152. Hoyles L, Swann J. Influence of the human gut microbiome on the metabolic phenotype. In: Lindon JC, Nicholson JK, Holmes E, editors. The handbook of metabolic phenotyping. Rijeka: InTech; 2019. p. 535–60.
153. Bukaveckas BL, Valdes R, Linder MW. Pharmacogenetics as related to the practice of cardiothoracic and vascular anesthesia. J Cardiothorac Vasc Anesth. 2004;18:353–65.
154. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526:343–50.
155. Trescot AM. Genetics and implications in perioperative analgesia. Best Pract Res Clin Anaesthesiol. 2014;28:153–66.
156. Badgett RG, Lawrence VA, Cohn SL. Variations in pharmacology of beta-blockers may contribute to heterogeneous results in trials of perioperative beta-blockade. Anesthesiology. 2010;113:585–92.
157. Eloe-Fadrosh EA, Rasko DA. The human microbiome: from symbiosis to pathogenesis. Annu Rev Med. 2013;64:145–63.
158. Holmes E, Li JV, Marchesi JR, Nicholson JK. Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. Cell Metab. 2012;16:559–64.
159. Pflughoeft KJ, Versalovic J. Human microbiome in health and disease. Annu Rev Pathol. 2012;7:99–122.
160. Shah RR, Smith RL. Addressing phenoconversion: the Achilles' heel of personalized medicine. Br J Clin Pharmacol. 2015;79:222–40.

161. Clayton TA, Lindon JC, Cloarec O, et al. Pharmacometabonomic phenotyping and personalized drug treatment. Nature. 2006;440:1073–7.
162. Everett JR, Loo RL, Pullen FS. Pharmacometabonomics and personalized medicine. Ann Clin Biochem. 2013;50:523–45.
163. Clayton TA, Baker D, Lindon JC, Everett JR, Nicholson JK. Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. Proc Natl Acad Sci U S A. 2009;106:14728–33.
164. Winnike JH, Li Z, Wright FA, Macdonald JM, O'Connell TM, Watkins PB. Use of pharmacometabonomics for early prediction of acetaminophen-induced hepatotoxicity in humans. Clin Pharmacol Ther. 2010;88:45–51.
165. Puskarich MA, Finkel MA, Karnovsky A, et al. Pharmacometabolomics of l-carnitine treatment response phenotypes in patients with septic shock. Ann Am Thorac Soc. 2015;12:46–56.
166. Shin KH, Choi MH, Lim KS, Yu KS, Jang IJ, Cho JY. Evaluation of endogenous metabolic markers of hepatic CYP3A activity using metabolic profiling and midazolam clearance. Clin Pharmacol Ther. 2013;94:601–9.
167. Robinette SL, Holmes E, Nicholson JK, Dumas ME. Genetic determinants of metabolism in health and disease: from biochemical genetics to genome-wide associations. Genome Med. 2012;4:30.
168. Albers DJ, Elhadad N, Tabak E, Perotte A, Hripcsak G. Dynamical phenotyping: using temporal analysis of clinically collected physiologic data to stratify populations. PLoS One. 2014;9:e96443.
169. Namas RA, Vodovotz Y, Almahmoud K, et al. Temporal patterns of circulating inflammation biomarker networks differentiate susceptibility to nosocomial infection following blunt trauma in humans. Ann Surg. 2016;263:191–8.
170. Namas RA, Almahmoud K, Mi Q, et al. Individual-specific principal component analysis of circulating inflammatory mediators predicts early organ dysfunction in trauma patients. J Crit Care. 2016;36:146–53.
171. Almahmoud K, Namas RA, Abdul-Malak O, et al. Impact of injury severity on dynamic inflammation networks following blunt trauma. Shock. 2015;44:101–9.
172. Almahmoud K, Abboud A, Namas RA, et al. Computational evidence for an early, amplified systemic inflammation program in polytrauma patients with severe extremity injuries. PLoS One. 2019;14:e0217577.
173. Camacho DM, Collins KM, Powers RK, Costello JC, Collins JJ. Next-generation machine learning for biological networks. Cell. 2018;173:1581–92.
174. Zitnik M, Nguyen F, Wang B, Leskovec J, Goldenberg A, Hoffman MM. Machine learning for integrating data in biology and medicine: principles, practice, and opportunities. Inf Fusion. 2019;50:71–91.
175. Caudle KE, Dunnenberger HM, Freimuth RR, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017;19:215–23.
176. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25:44–56.
177. Maheshwari K, Ruetzler K, Saugel B. Perioperative intelligence: applications of artificial intelligence in perioperative medicine. J Clin Monit Comput. 2019.

Part II

Global Perturbations of Metabolism

Starvation

5

Charles Weissman and Rawhi Hashem

Starvation is a multifaceted condition commonly encountered by surgeons (Table 5.1). The inability to ingest sufficient calories and/or an appropriate mixture of nutrients causes changes in the underlying metabolic milieu that can affect the outcome of illnesses and their treatments. Therefore, surgeons and other clinicians must be acquainted with the consequences of starvation and take measures to reverse its detrimental effects.

Table 5.1 Definitions

Malnutrition — A state resulting from lack of ingestion or absorption of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass [1]
Starvation — The most extreme form of malnutrition, which involves severe deficiency in caloric (energy), nutrient, and vitamin intake. It is a pure deficit in food intake causing gradual loss of both fat and muscle mass [1]
Fasting — The act of refraining from food, drink, or both, for a finite time period
Postabsorptive State — After the complete absorption of a meal (3–5 h after a meal), the metabolism changes to that of a fasting state
Cachexia — Loss of weight, muscle atrophy, fatigue, weakness, and significant loss of appetite in someone who is not actively trying to lose weight, usually associated with underlying illness [1]
Sarcopenia — Degenerative loss of skeletal muscle mass usually related to aging [1]
Marasmus — Chronic undernourishment caused by a diet deficient in all forms of energy intake, including protein
Kwashiorkor — A condition where there is dietary protein deficiency but adequate energy intake
Wasting — Unintentional loss of weight, due to decreases in both fat and fat-free compartments. Surgical patients who suffer from decreased caloric and nutrient intake are described as patients who "should not, would not and/or could not eat"

Starvation and Surgery

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

C. Weissman (✉) · R. Hashem
Department of Anesthesiology and Critical Care Medicine, Hadassah—Hebrew University Medical Center, Hebrew University – Hadassah School of Medicine, Jerusalem, Israel

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_5

Insufficient caloric and nutrient intake can delay wound healing; weaken the immune system leading to vulnerability to infection; cause muscle weakness secondary to proteolysis; and weight loss due to lipolysis.

Short-Term Starvation: Metabolic Consequences

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

Major homeostatic changes occur soon after fasting begins. For example, in human skeletal muscle, more than 900 genes are altered after 24 h of fasting, representing about 7% of the genes expressed in this tissue. Twenty-three genes largely involved in metabolic process regulation are significantly affected by both early (10 h) and late (24 h) fasting [2].

Carbohydrate Metabolism

The postabsorptive state (Table 5.1), seen mainly during the late morning, late afternoon, and overnight, is characterized by metabolic changes aimed at preserving the body's blood glucose concentration within a range of 90–100 mg/dL. Maintaining blood glucose concentrations is particularly critical for brain and red blood cells which exclusively use glucose as their energy source. The postabsorptive state is triggered by falling blood glucose concentrations which result in declining insulin concentrations. As the glucose and insulin concentrations decrease, glucagon is secreted by pancreatic α-cells likely in response to intrinsic (within the α-cell itself) and paracrine (mediated by factors released by pancreatic β- and/or δ-cells) stimulation [3]. Among the latter is a reduction in intra-islet insulin-mediated suppression of glucagon secretion. Mitochondrial uncoupling protein-2 (UCP2) likely plays a role in α-cell glucose sensing and is upregulated by hypoglycemia [4]. Glucagon is synthesized as a 160-amino acid prohormone (proglucagon) from a gene on chromosome 2. Proglucagon undergoes cleavage by prohormone convertase-2 into four peptides including 29-amino acid glucagon. Much of the secreted glucagon is then transported to the liver where the high glucagon/insulin ratio triggers glycogenolysis and gluconeogenesis while inhibiting glycolysis and glycogenesis. Glucagon acts via a transmembrane G-protein-coupled receptor to increase intracellular c-AMP. The glucagon receptor is expressed not only in the liver but also in the kidney, intestinal smooth muscle, brain, adipose tissue, heart, pancreatic β-cells, and placenta [5]. Activation of the β-adrenergic system and increased cortisol further promotes glycogenolysis and gluconeogenesis and inhibits glycolysis and glycogenesis [6]. These glycolytic/gluconeogenic hormones alter the rate of enzyme synthesis at the transcriptional level by modulating key transcription factors and coactivators, including FOXO1, CREB/CRTC2 (cAMP-responsive element-binding protein/CREB-regulated transcriptional coactivator 2) nuclear receptors, hepatocyte nuclear factors, C/EBP-β (CCAAT-enhancer-binding protein-β), PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1 α), and CLOCK (circadian locomotor output cycles kaput) genes [7]. After 48 h of fasting, insulin concentrations are reduced by about 80% resulting in decreased insulin receptor activation which in turn leads to reduced protein kinase B/AKT activity (i.e., decreased AKT phosphorylation [8]). The lower plasma insulin concentrations decrease tissue glucose uptake, increase protein catabolism, and increase lipolysis. Interestingly, in skeletal muscle some investigators observed that after 48 h of fasting, there was no change in protein kinase B/AKT phosphorylation or insulin receptor substrates 1 and 2 compared to prefasting levels reflecting other functional alterations in metabolism. Yet, after 62 h of starvation, there was reduced protein kinase B/AKT phosphorylation [9, 10]. Conversely, other investigators found reduced phosphorylation of protein kinase B/AKT in skeletal muscle after just 24 hours of fasting [2]. The contribution of the adrenergic system is variable.

However, after a 72 h fast in normal subjects, 24 h urinary norepinephrine and dopamine concentrations and heart rate were increased, while cardiac vagal modulation decreased [11]. In addition, secretion of the incretins, glucagon-like peptide 1 (GLP-1, an insulinotropic hormone), and glucose-dependent insulinotropic polypeptide (GIP) by the small intestinal L and K cells is decreased during fasting resulting in reduced insulin secretion, upregulation of glycogen degradation, and greater endogenous glucose production [12]. The relative influence of the incretins on glucose metabolism is a highly familial trait [13].

During the initial few hours of fasting, blood glucose concentration is maintained by hepatic glycogenolysis—the conversion of glycogen stored in the liver to glucose. Higher glucagon concentrations and lower insulin concentrations are the triggers of hepatic glycogenolysis due in part to protein kinase A-dependent inactivation of glycogen synthase kinase and stimulation of the glycogen degradation enzymes, glycogen phosphorylase (GP), and glycogen debranching enzyme (GDE) [14, 15]. The purpose of glycogenolysis is release of glucose into the bloodstream for uptake by non-hepatic cells (Fig. 5.1). As these

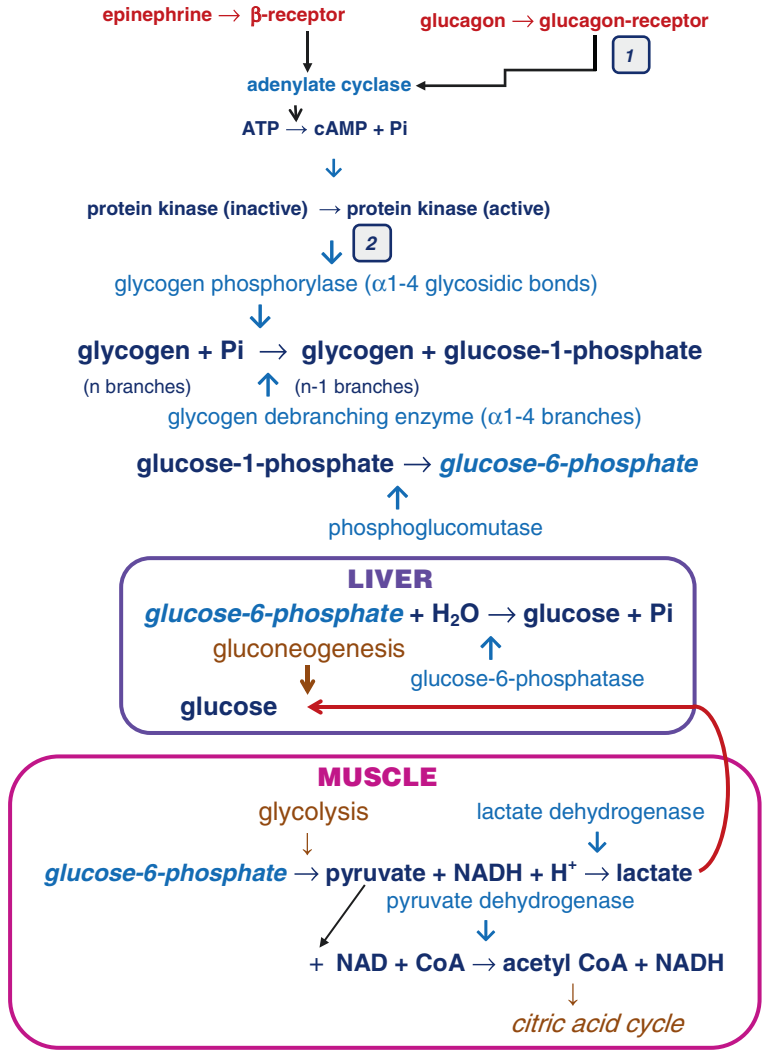

Fig. 5.1 Glycogenolysis is the initial source of glucose in the postabsorptive state and early starvation. However, the supply of hepatic and muscle glycogen is limited, lasting only a few hours. Muscle lacks glucose-6-phosphatase so that it cannot produce glucose directly but produces lactate which is transported to the liver where it undergoes gluconeogenesis. *Note 1*: Glucagon increases cAMP via its own G-protein-coupled receptors, i.e., a mechanism not requiring β-adrenergic receptors. Glucagon receptors are found mainly in the liver and kidney and less in adipose tissue. *Note 2*: Active protein kinase A catalyzes the transformation of inactive dephospho-phosphorylase kinase to active phospho-phosphorylase. Phospho-phosphorylase kinase then activates glycogen phosphorylase. *Pi* inorganic phosphate

hepatic stores become depleted, glycogenolysis can also occur within skeletal muscles (Fig. 5.1). However, muscle lacks glucose-6-phospatase so that intramuscular gluconeogenesis cannot occur, instead the glycogen is converted to lactate which is then transported to the liver and kidney to undergo gluconeogenesis. Gluconeogenesis occurs in parallel with the hepatic glycogenolysis, even when liver glycogen stores are still maximal. At this stage gluconeogenesis contributes approximately 50% of the endogenous glucose production [16]. After 24 h of no caloric or nutrient intake, blood glucose concentrations decrease to the low "normal" ranges. Concomitantly, plasma concentrations of free fatty acids and ketones increase, which differentiate the postabsorptive from the fasting state [17]. During starvation, hepatic glycogen stores remain very low, while those in skeletal muscle remain unchanged or even slightly increased.

The secreted glucagon binds to G-protein-coupled glucagon receptors located on hepatocytes and other cells activating adenylate cyclase and inhibiting cyclic AMP (cAMP) phosphodiesterase thus causing a rise in intracellular cAMP [18]. β-adrenergic stimulation also enhances cAMP formation. The increased cAMP activates protein kinase A leading to greater glycogen phosphorylation causing glycogenolysis. In addition there is upregulation of gluconeogenic enzymes leading to increased glucose production. Protein kinase A enters the nucleus to phosphorylate cAMP-responsive element-binding protein (CREB). Phosphorylated CREB is transcriptionally active and binds to cAMP-responsive element (CRE) located in the promotor region of the target genes. CREB binds to its coactivator to form CREB-regulated transcription coactivator 2 (CRTC2, also known as TORC2). This complex is a major regulator of gluconeogenesis promoting the synthesis of major enzymes such a glucose-6-phosphatase. Parallel decreases in insulin signaling augment this gluconeogenic gene expression through the dephosphorylation and nuclear shuttling of forkhead box protein 1 (FOXO1—a transcription factor involved in regulating gene expression) in concert with TORC2 [19, 20]. FOXO1 and the peroxisome proliferator-activated receptor-γ synergistically increase transcription of gluconeogenic genes [21]. Glucocorticoids also stimulate gluconeogenesis by increasing the transcription of the glucose-6-phosphatase and phosphoenolpyruvate carboxykinase genes. Glucocorticoids bind to glucocorticoid receptors (an intracellular receptor which is a ligand-inducible transcription factor belonging to the nuclear receptor superfamily), and the resulting complex translocates to the nucleus where it binds to glucocorticoid-responsive elements located on genes associated with gluconeogenesis. During fasting the effects of glucocorticoids and glucagon massively reorganize liver chromatin inducing many fasting-induced enhancers [22]. For example, glucocorticoids and glucagon induce Krüppel-like factor 15 (KLF15), a unique fasting-related transcription factor which supports gluconeogenesis by inducing gluconeogenic genes, as well as by inducing genes such as alanine aminotransferase, responsible for the catabolism of amino acids which serve as gluconeogenic precursors [23].

Gluconeogenesis is the key process for maintaining the body's glucose supply becoming the main mechanism for glucose production once glycogen stores have been depleted. After 42 h of fasting by healthy subjects, it provided practically all (93%) of the glucose production [24]. Gluconeogenesis takes place in the liver and kidney using the breakdown products of adipose and muscle tissues that supply glycerol and amino acids, respectively, as substrates for glucose production [25]. After 60 h of starvation, glycerol accounts for about 15% of glucose production. This proportion increases as starvation continues and proteolysis diminishes [26]. In addition, lactate from red blood cells, muscle activity, and renal medulla is used as a substrate [6]. The amino acid gluconeogenic substrate is mainly alanine in the liver and mainly glutamine in the kidney [27]. The liver produces about 60% of the glucose with the remainder produced by the renal cortex [28, 29]. As fasting progresses, the total hepatic glucose production decreases largely because of reduced glycogenolysis, with little change in gluconeogenesis [30]. As the period of starvation continues, the rate of gluconeogenesis begins to fall as the body tries to preserve muscle mass. Compared to overnight fast, endogenous glucose production falls by

about 12% after 38 h of starvation and by 30% after 62 h [26]. The reduction in hepatic glucose production after 64 h of fasting was greater in females than in males [31]. In its stead, both fat oxidation and ketone body formation increase [26]. This is reflected in a reduction of about 40% in insulin-mediated glucose uptake with an increase in non-insulin-mediated nonoxidative disposal [26]. After 40–48 h of starvation, the increase in muscle and liver concentrations of acetyl-CoA activates pyruvate dehydrogenase kinase isozyme 4 (PDK4), a phosphorylating mitochondrial enzyme that inhibits the pyruvate dehydrogenase complex. This inhibition reduces the conversion of pyruvate to acetyl-coenzyme A (CoA), resulting in decreased glucose oxidation [26]. In kidney, pyruvate dehydrogenase kinase isozyme 2 (PDK2) activity is also increased [32]. The mechanism of PDK2 and PDK4 activation includes reduced insulin signaling attributed to reduced insulin concentrations and/or insulin resistance. The reduced insulin stimulation leads to activation of transcription factors FOXO1 and FOXO3. FOXO1 in turn binds to the promoter region of the PDK4 gene [33]. Simultaneously, FOXO proteins are involved in the transcription of gluconeogenic genes responsible for glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities [32]. The latter enzyme, along with fructose-1,6-diphosphatase, regulates gluconeogenesis.

When nutrient intake resumes, glucagon production and gluconeogenesis decrease due to the direct inhibitory effect of glucose on pancreatic α-cells and by glucose-stimulated secretion of insulin and somatostatin from neighboring β and δ cells, respectively. Additionally, the satiety-promoting and insulinotropic gut hormone, glucagon-like peptide 1 (GLP-1) also inhibits pancreatic α-cell secretion thus decreasing plasma glucagon concentrations in a glucose-dependent manner [34].

Lipid Metabolism

Humans have limited stores of carbohydrates and protein, while it is the fat stores that possess the surplus calories that maintain body functions during fasting and starvation. Stored triglycerides are excellent sources of energy providing 9 kcal/g as opposed to 4 kcal/g for protein and carbohydrate. The dominant fuels for energy production during fasting are thus free fatty acids and ketones derived from stored triglycerides. Lipolysis, the breakdown of stored triglycerides to free fatty acids and glycerol, occurs in response to increased epinephrine, growth hormone, and glucagon stimulation plus decreased insulin stimulation [8, 35]. Not only is there a decrease in the serum insulin concentration but also reduced end-organ sensitivity [36]. Stimulation of β2-adrenergic receptors by epinephrine causes cAMP concentrations to rise thereby increasing the cAMP-dependent protein kinase A phosphorylation of the various lipolytic enzymes, especially hormone-sensitive lipase and perilipin (Fig. 5.2). Phosphorylation of perilipin, a lipid droplet surface protein, appears to increase translocation of hormone-sensitive lipase to the lipid droplet thus enhancing lipolysis [37]. Some lipolysis likely occurs via a form of chaperone-mediated autophagy, called lipophagy [38]. The rate of lipolysis, measured by palmitate turnover, doubles from postabsorptive levels after 84 h of fasting, releasing glycerol and free fatty acids [27]. The former is converted to glucose via gluconeogenesis and the latter undergoes β-oxidation and ketone body formation. This shift to lipid oxidation and ketogenesis is reflected by the decrease in respiratory quotient from 0.85 prior to fasting to 0.70 after 4 days of starvation [39].

In volunteers starved for 2–4 days, there were significant changes in the plasma metabolome, specifically increases in free fatty acids and various acylcarnitines, reflecting the lipolysis occurring during the mobilization of endogenous fat stores [40]. However, unlike the plasma, the metabolome of circulating leukocytes had minor changes demonstrating the maintenance of intracellular leukocyte homeostasis despite changing extracellular conditions [40]. The rate of free fatty acid appearance after 87 h of starvation is double that required to provide substrate for energy production. Many of the remaining free fatty acids are reesterified to triglycerides in adipose tissue and skeletal muscle and to a much lower extent

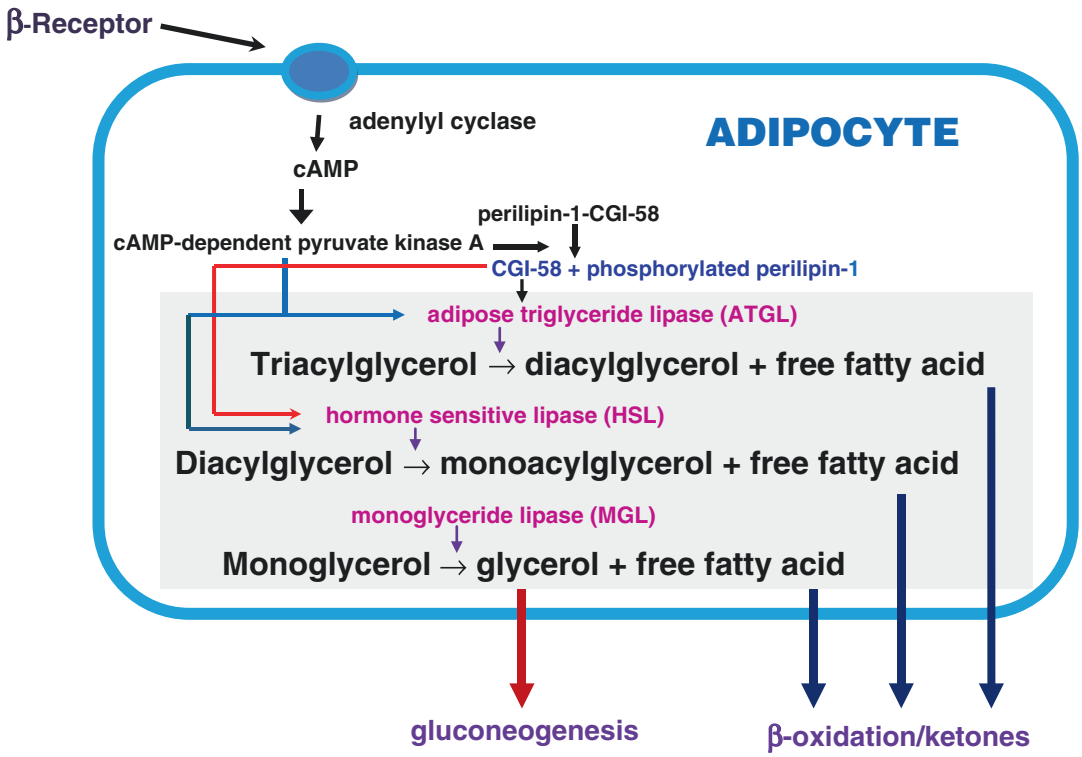

Fig. 5.2 Lipolysis—the breakdown of stored triglycerides into glycerol and fatty acids—is a key pathway in the adaptive response to starvation. During starvation it is triggered by β-adrenergic stimulation and also growth hormone, glucagon, and cortisol. Perilipin (also called lipid droplet-associated protein) coats lipid droplets located in adipocytes and forms a protective coating to protect the stored lipid from lipases. During lipolysis perilipin is phosphorylated by cAMP-dependent pyruvate kinase A and undergoes a change in conformation exposing the stored lipids to hormone-sensitive lipase. Although cAMP-dependent pyruvate kinase A also activates hormone-sensitive lipase, phosphorylated perilipin is more potent an activator

in the liver. Teleologically, the reesterification cycles permit rapid increases and decreases in the metabolism of lipolytic substrates. Some of the free fatty acids are converted to bioactive intermediates, e.g., ceramide and acylcarnitines [26].

Lipolysis occurs differentially among the body's fat stores. In the postabsorptive state, 80–90% of the lipolysis in lean subjects occurs within the upper body non-splanchnic (subcutaneous) fat. In individuals with larger visceral fat stores, a greater portion of the lipolysis occurs within the visceral adipose tissue. This situation is accentuated in women compared to men [41]. After 72 h of fasting, lipolysis occurs predominantly in skeletal muscle, upper body subcutaneous fat, and abdominal adipose tissue, while sparing peripheral adipose tissue [42]. In addition, 15–20% of glycerol turnover is attributable to intravascular hydrolysis of very low-density lipoprotein triglycerides [43].

Within 24 h of the onset of fasting, blood concentrations of glycerol and free fatty acids begin to increase. Average plasma free fatty acid concentrations were higher in women than men during 4–24 h of fasting, a difference not seen during 24–48 h of fasting due to the increases in free fatty acid concentrations being fourfold greater in males [17]. Free fatty acids are released into blood plasma where they bind to albumin and then are taken up by the liver, skeletal muscle, heart, and kidney where they undergo β-oxidation in the mitochondria to acetyl-CoA (Fig. 5.2). Cellular fatty acid uptake was long thought to be due to simple diffusion, but it is now estab-

lished that proteins such as fatty acid transport proteins (FATPs), fatty acid translocase (CD36), and plasma membrane fatty acid-binding protein (FABPpm, GOT2) also aid in this process [44]. The elevated fatty acid concentrations in hepatocytes (and monocytes) activate nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR-α), a ligand-activated transcription factor [45]. PPAR-α activation, along with the transcription factors FOXA2 (also known as hepatocyte nuclear factor 3-beta - HNF-3β) and Sp1 (specificity protein 1), promotes uptake, utilization, and metabolism of the fatty acids by upregulating genes involved in fatty acid transport, mitochondrial fatty acid β-oxidation, and ketogenesis. These genes code for enzymes such as pyruvate dehydrogenase and carnitine/acylcarnitine carrier. β-oxidation of fatty acids coupled with oxidative phosphorylation is the key pathway for producing energy during fasting. Fatty acid acyl groups are transported from the cytosol into the mitochondrial matrix by means of the carnitine shuttle system (Fig. 5.3). In the cytosol, fatty acid units are transferred from acyl-CoAs to carnitine by the action of carnitine palmitoyltransferase 1 located on the external surface of the outer mitochondrial membrane. The acylcarnitines are translocated through the inner mitochondrial membrane by the carnitine/acylcarnitine carrier in exchange for intramitochondrial-free carnitine. Therefore, metabolomic studies demonstrate an increase in cytosolic carnitine [46]. Within the mitochondrial matrix, fatty acid acyl units are transferred from carnitine to matrix CoA by carnitine palmitoyltransferase 2 (CPT2), and these mitochondrial acyl-CoAs are oxidized by the β-oxidation enzymes. The acetyl-CoA produced from the fatty acids enters either the Krebs cycle or is used to form ketone bodies [47]. As starvation persists, acetyl-CoA accumulates within the hepatic mito-

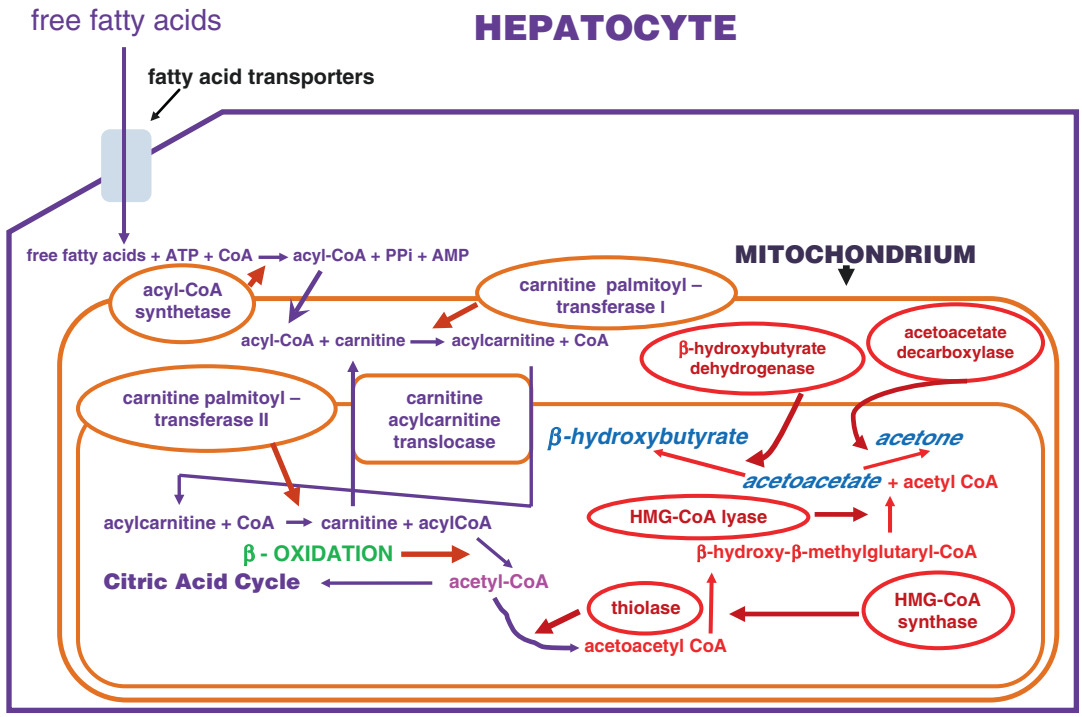

Fig. 5.3 Hepatocyte fatty acid β-oxidation and ketogenesis—fatty acids released by lipolysis undergo β-oxidation and ketogenesis within hepatocytes. The acetyl-CoA produced either enters the citric acid cycle (tricarboxylic acid cycle or Krebs cycle) where the NADH generated enters the oxidative phosphorylation pathway to produce ATP, or it is converted to ketone bodies (β-hydroxybutyrate and acetoacetate). The ketone bodies are transported to other organs to be used as energy substrate. Acetone, a waste product, is excreted by the kidneys and lungs

chondria leading to the increased formation of the three ketone molecules: acetone, acetoacetate, and β-hydroxybutyrate (Fig. 5.2). The latter two are synthesized from acetyl-CoA, in the mitochondria of liver cells, and can be used as a source of energy by the heart and brain. Acetone, formed by spontaneous decarboxylation of acetoacetate, is a waste product excreted in urine or breath.

As starvation persists, tissues begin to use ketones as energy sources and by weeks 5 and 6 of starvation they become the main energy substrate [48]. The brain, which under most circumstances is dependent on glucose for energy, adapts to using ketones as its major energy source. In the brain, acetoacetate and β-hydroxybutyrate are reconverted to acetyl-CoA and enter the citric acid cycle to produce energy. β-hydroxybutyrate is a good source of energy providing 4.7 kcal/g [28]. During starvation the brain can use ketones for up to 70% of its energy needs. This preservation of cerebral physiological functional capacity and brain mass plus the safeguarding of its own energy supply at the expense of sacrificing the energy requirements of other organ has been termed the "selfish brain" theory [49]. The concentrations of β-hydroxybutyrate observed during starvation are usually 1–2 mM/L during the initial period of fasting, reaching levels of 4–7 mM/L after 2 weeks of starvation. This is much below the concentrations of 15–25 mM/L seen in ketoacidosis [17, 28]. Breakdown of ketone bodies in peripheral tissues increases acetyl-CoA bringing about reduced insulin signaling thus decreasing cellular glucose uptake. Although neuronal glucose uptake and oxidation during starvation is reduced, its influx (transport) through the blood-brain barrier is upregulated although the absolute amount of transported glucose is reduced due to decreased blood glucose concentrations [48, 50]. The increase in the amount of ketone bodies transported across the blood-brain barrier appears to be passive and dependent on the greatly increased arterial concentrations seen during starvation. The increased capacity of the blood-brain barrier monocarboxylic acid transporters, including MCT1 in endothelial cells and MCT2 in neurons and glial cells, contributes only a small fraction of the transported ketones [48, 50].

The hyperketonemia is accompanied by hyperketonuria caused by a lack of renal tubular reabsorption of a significant proportion of the acetoacetate ($AcAc^-$) and β-hydroxybutyrate ($\beta\text{-}OHB^-$). To prevent systemic acidosis, near urinary electroneutrality is maintained by obligate isomolar excretion of cations, mainly NH_4^+. The NH_4^+ is obtained largely from renal deamination and deamidation of glutamine [17]. Persistent ketonuria, thus, results in the loss of valuable fuels derived from fat and also depletes protein stores to provide NH_4^+ [51]. Suppression of glucagon secretion by free fatty acids and ketone bodies may be part of a negative feedback system regulating ketogenesis.

In addition to its role as an energy substrate, β-hydroxybutyrate ($\beta\text{-}OHB^-$) has cellular signaling functions [52, 53]. It is an endogenous inhibitor of histone deacetylases (HDACs) and a ligand for at least two cell surface receptors. HDACs affect gene expression via chromatin modification, and their inhibition by β-hydroxybutyrate results in histone hyperacetylation and the induction of FOXO3 expression. These appear to be involved in regulation of autophagy, a process upregulated during starvation [54]. HCAR2 (hydroxycarboxylic acid receptor 2 also known as PUMA-G or Gpr109), when activated by β-OHB, decreases lipolysis in adipocytes through G(i)-protein-mediated inhibition of adenylyl cyclase. This is likely a feedback mechanism to regulate the availability of the fatty acid precursors of ketone body formation thus preventing ketoacidosis during starvation. HCAR2 also mediates the increased adiponectin secretion seen during starvation. β-OHB also binds and antagonizes free fatty acid receptor 3 (FFAR3, also known as Gpr41), present in sympathetic ganglions, suppressing sympathetic activity. This suppression of sympathetic activity likely contributes to the overall decrease in metabolic rate seen during fasting [52, 53].

After 7 days of fasting, normal-weight volunteers had increased serum concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B, while triglyceride and high-density lipoprotein (HDL) cholesterol concentrations were unchanged. The latter were found

by others to be decreased after 6 days of fasting, while triglyceride concentrations were increased [55]. The increasing LDL levels were associated with decreasing serum insulin growth factor-1 (IGF-1) concentrations which is in keeping with the inverse correlation between the two [56]. In another study of normal weight individuals, 3 days of fasting resulted in increases in plasma triglyceride, very low-density lipoprotein cholesterol, and apolipoprotein B concentrations [57].

Insulin Resistance

In addition to the low concentrations of insulin during fasting and starvation, there is end-organ insulin resistance that some have called "diabetes of starvation." This was demonstrated by the observations that 48–60 h of fasting led to a 50% reduction in insulin sensitivity likely attributable to increased free fatty acid concentrations and/or accumulation of triglycerides in peripheral tissues [30, 58]. The teleological explanation for this resistance insures minimal insulin effects thus assuring that gluconeogenesis and lipolysis are not inhibited by insulin. The insulin resistance also reduces peripheral glucose utilization thus decreasing the need for greater proteolysis to supply gluconeogenic substrate, while also assuring an adequate glucose supply for the brain and erythrocytes. Therefore, insulin resistance mainly decreases carbohydrate utilization by fat, muscle, and liver [59]. Lean subjects subjected to 6 days of fasting developed insulin intolerance [60]. Compared to lean subjects, obese subjects had less of a decrease in insulin action after a 48-h fast. The greater reduction in insulin action after 48 h of fasting in lean subjects was ascribed to greater increases in FFA and β-hydroxybutyrate concentrations [30]. Furthermore, oral glucose intake normally stimulates a biphasic insulin secretion response from pancreatic β cells. However, after a 72-h fast, there was inhibition of the first phase of insulin secretion, similar to that seen in type 2 diabetes [61]. The proposed mechanism of fasting-induced insulin resistance is mitochondrial production of reactive oxygen species caused by increased fatty acid oxidation thus impairing glucose transporter-4 [GLUT4] translocation to the cell surface. This reduced transporter translocation leads to less cellular glucose uptake [59]. The diminished whole-body insulin sensitivity manifests as decreased insulin-stimulated glucose disposal caused by reduced insulin stimulation of both glucose oxidation and nonoxidative glucose disposal [62]. However, insulin-induced suppression of endogenous glucose production, reflecting hepatic insulin sensitivity, was only marginally affected by 60 h of fasting [62]. Furthermore, one exercise session increased mitochondrial fatty acid oxidation and reverses starvation-induced insulin resistance [63]. However, other investigators observed that after a 3-day fast, intramyocellular lipid content was increased over prefasting levels in subjects who did not exercise, but did not accumulate in those who did moderate-intensity exercise. However, exercise did not change the concentration of free fatty acid or insulin sensitivity [64].

Protein Metabolism

The postabsorptive and initial fasting periods are characterized by the release into the blood stream of amino acids derived from the breakdown of muscle tissue. These amino acids are used for protein synthesis or endogenous glucose production. About 1.75 g of muscle protein must be broken down to produce 1 g of glucose [65–68]. The carbon skeletons of the amino acids are substrates for gluconeogenesis and/or enter the citric acid cycle. The greater amount of nitrogenous waste, urea, uric acid (urate), creatinine, and ammonium (NH_4^+) manifests as increased urinary nitrogen excretion. With the enhanced proteolysis, plasma concentrations of branched-chain amino acids (leucine, isoleucine, valine) are increased. However, as the fasting continues past its initial few days, nitrogen excretion decreases as the body begins to utilize stored fat to produce energy. Some have ascribed this decreased nitrogen excretion to also being due to the total body reduction in metabolic rate [66]. This protein-sparing phenomenon can continue for much time, during which adipose tissue

becomes the main source of energy substrate. The greater the adipose tissue stores, the longer the time that the organism can survive. The etiology for this decreased proteolysis is unclear and has been ascribed to the reduced T3 concentrations and increased growth hormone concentrations which stimulate lipolysis [67].

Nitrogen balance is always negative during starvation due to the lack of protein and amino acid intake. During the initial 1–3 weeks of starvation, there is significant excretion of nitrogen occasioned by accelerated proteolysis of skeletal muscle (myofibrillar protein). This accelerated protein catabolism subsides thereafter, as evidenced by the pattern of 3-methylhistidine (an index of myofibrillar proteolysis) excretion. The excretion of 3-methylhistidine increases after 2–3 days of starvation and decreases substantially by the third week. The amino acids released by proteolysis are utilized as gluconeogenic substrates by the liver (alanine) and kidney (glutamine). Alanine transported to the liver is converted to pyruvate which enters the gluconeogenic pathway to be synthesized to glucose [69]. The decline in proteolysis is accompanied by an increase in lipid oxidation, enhanced ketone production, increased use of glycerol as a gluconeogenic substrate, and reduced demand for glucose by various tissues such as the brain. With prolonged fasting up to 100% of the glycerol turnover is diverted to glucose production in healthy humans [69]. The rate of protein catabolism remains low until the supply of lipid substrates is exhausted at which point protein catabolism again increases. This resumption of high levels of proteolysis is associated with impending death.

The triggers for proteolysis are unclear but might include decreased insulin concentrations along with increased cortisol and glucagon concentrations, but not growth hormone [8]. Furthermore, the mechanisms of proteolysis in myocytes are thought to be a combination of autophagic (lysosomal) and ubiquitin-proteasomic protein breakdown associated with a reduction in mTORC1 (mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1), although their relative contributions are still unclear [8, 70]. However, in many other tissues (except the brain), lysosomal proteolysis pathways are stimulated during fasting [68]. It appears that short-term starvation activates macroautophagy, a nonselective mechanism, while as starvation progresses, there is a switch to chaperone-mediated autophagy, which is more selective in identifying cellular components for degradation. Autophagy is a lysosomal-based degradation process that permits cells to adapt to stress, mobilize energetic reserves, and degrade potentially harmful and dysfunctional substances.

Macroautophagy involves the formation of vesicles called autophagosomes that incorporate many types of cytoplasmic materials. These autophagosomes then fuse with lysosomes where the material is degraded. The trigger for autophagy is the dissociation of the ULK1 (Unc-51-like autophagy-activating kinase 1, an autophagy related gene [atg])—mTORC1 (mammalian target of rapamycin complex 1) complex which is promoted by adenosine monophosphate-activated protein kinase (AMPK) [71, 72]. The latter in turn is activated by increased cytosolic AMP (a sign of energy depletion) or amino acid depletion. AMPK directly regulates autophagic activity through phosphorylation of ULK1 [73]. ULK1 then phosphorylates Beclin 1 complex (Beclin-1 bound to class III phosphoinositide 3-kinase (PI3K;Vps34)) giving rise to autophagosome membranes that engulf proteins, organelles, and other cytosolic material (lipids, nucleosides) to form vesicles that fuse with lysosomes (called autolysosomes). Lysosomal enzymes then metabolize this material which is subsequently released into the cytosol as amino acids, fatty acids (macrolipophagy), and ribose-phosphate. The latter can be converted to glucose via the nonoxidative pentose phosphate pathway. The activity of the lysosomes to sequester or release the amino acids freed by protein proteolysis is affected by mTORC1 activity, which in early starvation is inhibited thus preventing the release of essential amino acids from the lysosome [74, 75]. Later in starvation mTORC1 activity reactivates permitting the release of the amino acids [74]. In humans, increased skeletal

muscle phenylalanine release following a 72-h fast was associated with decreased in mTORC1 activity, as well as ULK1 phosphorylation. This was associated with increased muscle proteolysis and reduced downstream signaling of muscle cell growth [76].

Chaperone-mediated autophagy increases the selectivity of the autophagy-lysosomal pathway since proteins with the exposed peptide sequence KFERQ (sequences biochemically related to Lys–Phe–Glu–Arg–Gln) are selectively broken down. This sequence targets cytosolic proteins, such as ribonuclease A, for lysosomal degradation. The targeted protein is initially recognized by heat-shock cognate 70 kDa (hsc-70). Multiple co-chaperones (e.g., heat-shock protein 90) interact with the protein-chaperone complex which attaches to the receptor, lysosome-associated membrane protein 2 (LAMP2), on the lysosomal membrane. The substrate proteins then translocate across the lysosomal membrane of lysosomes containing hsc-70. During starvation the number of hsc-70 rich lysosomes may double, facilitating chaperone-mediated autophagy. Among the proteins degraded are those involved with glycolysis, an enzyme pathway not particularly active during starvation [77]. Chaperone-mediated autophagy is also implicated in controlling lipolysis [78].

The ubiquitin-proteasome system (UPS) is another proteolytic mechanism active during starvation. Markedly reduced nutrient intake results in the upregulation of UPS-associated gene expression, with increased mRNA expression of the atrogenes muscle RING-finger protein-1 (MuRF1, an E3 ubiquitin ligase found in skeletal and cardiac muscle) and atrogin-1, another E3 ubiquitin ligase [79]. Proteins are tagged for degradation with a 76 amino acid protein called ubiquitin. This reaction is catalyzed by a group of enzymes: ubiquitin-activating enzymes, ubiquitin-conjugating enzymes, and ubiquitin ligases. An example of the latter is atrogin-1 which increases proteolysis and reduces protein synthesis by mechanisms independent of decreased phosphorylation of AKT and forkhead transcription factors (FOXO). A protein tagged with an ubiquitin molecule is a target for other ligases to attach additional ubiquitin molecules. The resulting polyubiquitin chain is bound by a cytosolic 26S proteasome which then cleaves the chain via a threonine-dependent nucleophilic attack to very short peptide fragments. These fragments are then further cleaved to individual amino acids.

Hepatic protein synthesis is also affected by starvation. After a 3-day fast, the albumin concentration significantly increased, while the concentration of retinal binding protein fell by 16%, unrelated to changes in hydration state [80]. A systematic review revealed that in healthy subjects, serum albumin and prealbumin concentrations remained normal in the face of starvation. They only fell with extremes of starvation, BMI <12 or more than 6 weeks of starvation [81]. During short-term (3 days) fasting, the overall protein synthetic rate decreases as much as 13%, although overall protein turnover is increased [8, 82]. However, with a 5% weight loss after 6 days of starvation in lean individuals, whole-body protein oxidation increased, while the fractional synthetic rates of specific hepatic export proteins increased (high-density lipoprotein apolipoprotein A1, retinol-binding protein, α1-antitrypsin). However, the plasma concentrations of binding proteins, such as retinol, retinol-binding protein, and transthyretin, were decreased [83]. Four days of starvation produced marked reductions (approximately 30%) in the circulating concentrations of retinol-binding protein, but did not significantly affect the plasma concentration of immunoglobulins (Ig) G, A, and M or other proteins (orosomucoid, haptoglobin, alpha(1) antitrypsin), albumin, and total protein [84]. In ten healthy volunteers starved for 4.5 days, daily measurements showed a rapid reduction in plasma fibronectin, no alteration in either C3 or plasma transferrin, and, at the end of the starvation period, an elevated serum albumin [85]. Proteomic analysis of murine small intestines revealed that during the first 12 h of starvation, there was a decline in proteins associated with energy production and glycolysis, while after 24 h, substances related to protein synthesis and amino acids were also decreased. Additionally, after 24 h, extracellular enzymes that reduce oxidative stress were increased [86]. Furthermore, to support starvation-mediated autophagy, there

is de novo synthesis of proteins involved in this process. Proteomic analysis revealed 711 such proteins [87].

Bone Metabolism

Starvation also affects bone formation with increased urinary calcium and phosphorous excretion, increased serum calcium concentrations, and decreased concentrations of serum osteocalcin and procollagen carboxyl-terminal propeptide. The former indicate enhanced bone resorption, while the latter two substances are markers of bone formation. Fasting-induced metabolic acidosis appears to play an important role in bone resorption [88]. Autopsies of adult starvation victims showed severe cortical demineralization and matrix decomposition. Starvation has also been conjectured to play a role in the development of osteopenia and osteoporosis [89].

Energy Expenditure

Among the adaptive responses to starvation (Fig. 5.4) is a decrease in total body energy expenditure, attributed to reduced basal energy expenditure and decreased physical activity. However, at the onset of fasting, resting energy expenditure increased significantly, in some, but not all studies, from day 1 to day 3 associated with more than a doubling of norepinephrine concentrations from day 1 to day 4 [90, 91]. In some studies epinephrine concentrations did not increase concomitantly, leading to the conclusion that the increased norepinephrine was due to sympathetic nervous system stimulation. However, some investigators found that during 24-h fasts, higher urinary epinephrine concentrations correlated with smaller reductions in energy expenditure [92]. As the lack of caloric and nutrient intake continues, the resting energy expenditure has been reported by most, but not all, investigators to decrease [93]. This decreased energy expenditure is accompanied by diminished catecholamine and thyroid hormone stimulation as well as decreased insulin secretion, reduced heart rate, lower creatinine clearance, negative fluid balance, and lower free water clearance [91, 94]. The decrease in basal energy expenditure is greater than can be accounted for by changes in body weight or composition. This reduction in basal energy expenditure increases metabolic efficiency thus reducing the rate of tissue depletion [95]. In addition, total daily energy expenditure is also decreased because of reduced activity and exercise on the part of the weakened starving individual. Furthermore, starvation can effect thermoregulation as demonstrated by a reduced thermoregulatory response to a cooling stimulus in normal weight young females after 48 h of starvation [96].**

As starvation progresses, there is continuous loss of lean body mass, along with decreases in both basal energy expenditure and protein oxidation. Lean subjects, who have less lean body mass than obese subjects, maintain higher daily nitrogen excretion in absolute terms, in relation to weight loss and in relation to energy expenditure. Moreover, in lean subjects the contribution of protein oxidation to basal energy expenditure does not decrease as starvation progresses (up to 45 weeks), while in obese individuals, it decreases reaching values more than twofold lower than observed in lean subjects [97]. Therefore, pre-starvation conditions play an important role in the energy expenditure response to starvation.

Hydration

Starvation due to the lack of ingestion of nutrients should be differentiated from dehydration, the lack of water ingestion. Death from the lack of any food and water intake occurs within a week to 10 days depending on the rate of external water loss, e.g., sweating, and the body's intrinsic water supply [98]. A 15% loss of body water after acute dehydration and a >20% loss after longer dehydration are fatal [99]. The continuum of dehydration is characterized by headaches, orthostatic hypotension, decreased resting blood pressure, reduced or no urine output, delirium, unconsciousness, and, eventually, death. In studies of starvation, subjects are routinely provided

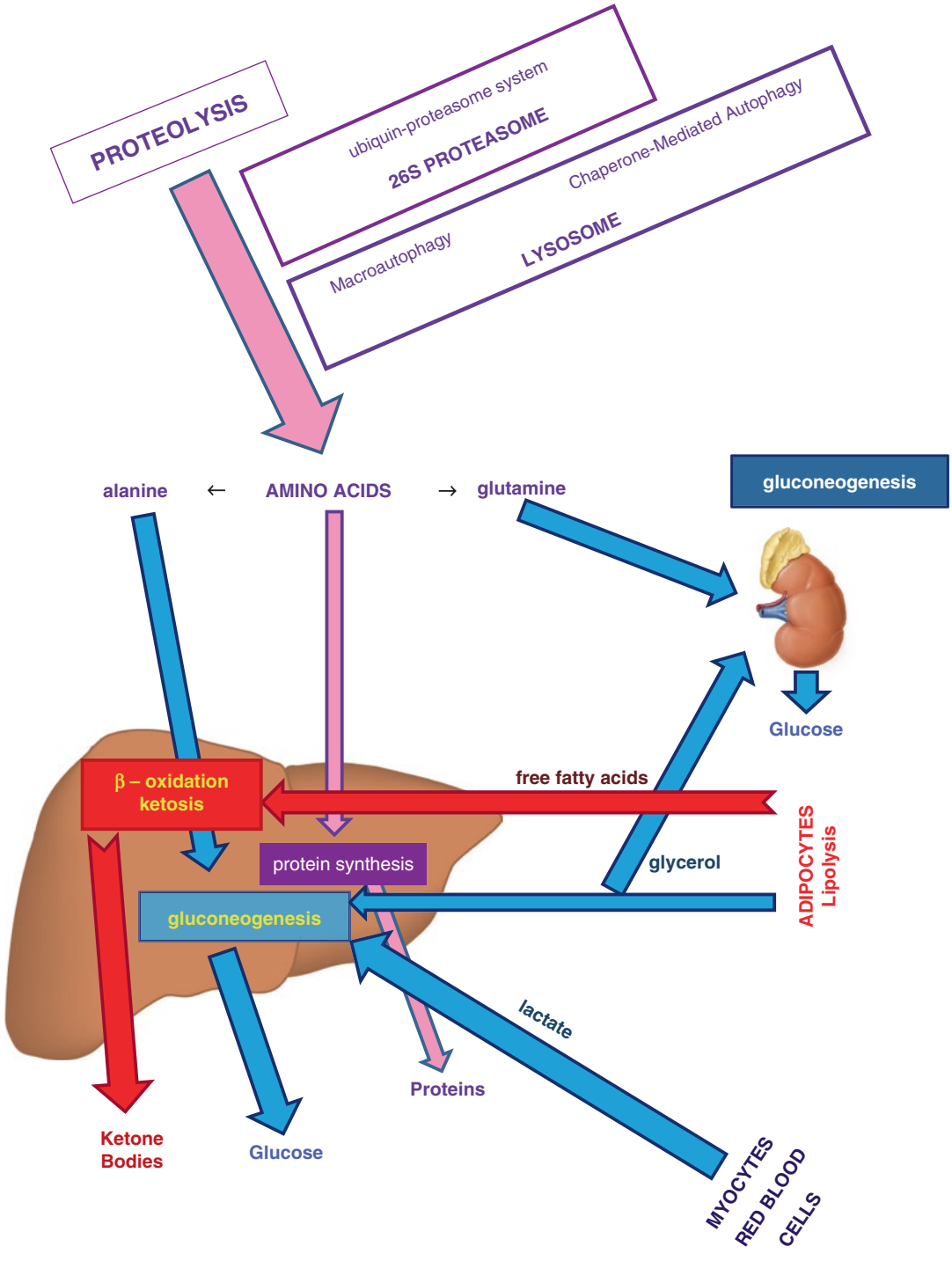

Fig. 5.4 The adaptive response to starvation—gluconeogenesis uses glycerol from fat stores, amino acids from muscles, and lactate from red blood cells and muscle activity to produce glucose. Lipolysis of adipose tissue triglycerides releases free fatty acids for β-oxidation and ketone body formation. Endogenous glucose production via gluconeogenesis occurs in the kidney and liver. Hepatic protein synthesis occurs but at a reduced rate

with oral or intravenous solutions containing water and electrolytes to prevent dehydration and electrolyte disturbances. Hunger strikers are generally provided with such solutions and, in prolonged starvation, also with vitamins to prevent vitamin deficiencies.

Weight Loss

Total cessation of nutrient intake results in substantial weight loss. Early in fasting weight loss is rapid, averaging 0.9 kg/day during the first week due to negative water and sodium balance. The losses slow to about 0.3 kg/day by the third week [100]. During a 10-day fast, a 54-year-old male lost 0.25 kg/day [101], while hunger strikers had lost 18% of their prefast body weight by days 28–35 [102]. Some of the weight loss during the initial period of fasting is due to loss of water in association with glycogenolysis [26]. With a 5% weight loss secondary to starvation, the fraction of fat-free mass to total weight loss was 46% indicating much loss of muscle tissue. In obese individuals subject to total starvation, weight loss was biphasic, with more rapid losses observed during the first 14 days followed by slower more linear losses from day 15 to days 30. Over the first 14 days, males lost significantly more weight (8%) than females (7%) [103].

Hormonal Changes

Starvation is accompanied by substantial changes in the hormonal milieu that helps organisms to adapt their metabolism to reduced nutrient intake. Plasma concentrations of thyroid hormones are decreased, while glucagon, catecholamine, and growth hormone concentrations increase [104]. There are increases in serum cortisol and urinary free cortisol concentrations but without changes in adrenocorticotropic hormone (ACTH) levels. These hormonal changes suppress energy-consuming activities, such as growth and reproduction, while preserving basal metabolic functions. There are thus substantial reductions in serum testosterone concentrations caused by alterations in the pulsatility of luteinizing hormone (LH) secretion likely mediated by reduced hypothalamic GnRH pulses. This situation appears related to the decrease in leptin concentrations [105]. Among premenopausal women, amenorrhea occurs while fertility is reduced in males.

Short-term fasting results in a drop in thyroid-stimulating hormone (TSH) pulse amplitude, a decrease in serum T3 levels with an increase in rT3 (reverse T3), a reduced TSH response to thyrotropin-releasing hormone (TRH), and little change in thyroid-binding globulin (TBG). T4 concentrations are unchanged due to its longer half-life. It has been proposed that the decreased T3 and thyroid receptor protein concentrations are involved in the reduced energy expenditure during fasting. As starvation continues, TBG concentrations begin to decrease so that after a 10-day fast, free T4 levels were still normal [101, 105].

Adipose tissue is an endocrine organ that secrets cytokines and unique substances dubbed adipocytokines or adipokines which have both metabolic and immunological effects. After 72 h of fasting, leptin (a satiety factor regulating body weight by appetite suppression and stimulation of energy expenditure) decreased by 21% of baseline values [106–110]. This rapid decrease in serum leptin concentrations results in concentrations that are disproportionately lower than would be expected for a given fat mass [111]. This causes decreased energy expenditure at the same time that appetite is stimulated [112]. Furthermore, these diminished leptin concentrations are associated with T cell dysfunction [113]. Alternately, the concentration of adiponectin (enhances insulin sensitivity, reduces energy expenditure, and negatively regulates hematopoiesis) is increased. This increase is partially due to the effects of greater concentrations of FGF21 (fibroblast growth factor 21) [114]. It has been hypothesized that adiponectin ("the starvation gene") evolved to help organisms survive malnutrition [115]. The serum concentrations of the adipokines vaspin (an endogenous insulin sensitizer) and visfatin (which has insulin-mimetic effects) were unchanged after 72 h of fasting [109]. Asprosin is a fasting-induced

protein hormone secreted by white adipose tissue that modulates hepatic glucose production and release. It is the C-terminal cleavage product of profibrillin that circulates at nanomolar concentrations. In the liver it activates the G-protein-cAMP-PKA pathway resulting in glucose release into the circulation [116].

Growth hormone (GH) is secreted by the somatotropic cells of the anterior pituitary gland. Its secretion is enhanced by hypothalamic growth hormone-releasing hormone (GHRH) and ghrelin (an orexigenic hormone produced by stomach neuroendocrine cells). Growth hormone secretion is reduced by somatostatin and circulating insulin growth factor-1 (IGF-1) concentrations. Growth hormone secretion is increased after 24 h of fasting, with both free and total growth hormone concentrations increasing since there is little change in concentrations of growth hormone-binding protein [107]. There is some tissue level resistance to growth hormone's effects associated with reduced insulin growth factor-1 (IGF-1) concentrations. The reduced IGF-1 effects are due to both reduced IGF-1 production and increased IGF-specific binding protein concentrations thus reducing the amount of circulating IGF-1 [67]. This situation appears to reduce the anabolic effects of IGF-1, while permitting the lipolytic effects of growth hormone in adipose tissue and lipid oxidation, especially in skeletal muscle [117]. By stimulating lipolysis, growth hormone preserves muscle tissue by reducing the need for proteolysis to supply gluconeogenic substrate. However, in prolonged starvation, there is a drastic increase in plasma GH mediated by ghrelin. When adipose tissue is depleted, increased GH is essential for survival by upregulating hepatic and renal gluconeogenesis to maintain blood glucose [114].

During fasting, circulating ghrelin has been reported to be increased by some, but not all, investigators [67]. Ghrelin secretion is likely increased secondary to the increased adrenergic stimulation present during fasting [108]. The effects of ghrelin include enhancing olfactory sensitivity, promoting food intake, increasing GH secretion, enhancing lipolysis, reducing peripheral glucose uptake, and restraining insulin secretion to prevent hypoglycemia. These effects can all be considered protective mechanisms in the face of starvation [118]. During short-term fasting, increased ghrelin secretion indirectly reduces insulin secretion from β-cells by stimulating somatostatin release from the δ-cells within the pancreatic islet [118].

The central control of energy balance involves the complex interaction of a variety of substances and neuronal centers including α-melanocyte-stimulating hormone (α-MSH—an anorexigenic substance) and its antagonism at the melanocortin-4 receptor by agouti-related protein (AgRP—an orexigenic or appetite-stimulating substance that increases food intake and decreases energy expenditure in times of negative energy balance). During a 6-day fast in lean subjects, coincident with a decrease in plasma leptin concentrations, there was increased AgRP but no change in α-MSH. This increase in AgRP, along with increased neuropeptide Y (another orexigenic substance), appears to inhibit the thyroid axis at the level of the pituitary gland [119]. The increase in AgRP is also implicated in the infertility associated with starvation [120].

Another substance active during starvation is FGF21 (fibroblast growth factor 21), whose plasma concentrations initially drop and then increase after a 7–10 day fast [121, 122]. It is thus a mediator of the late stages of the adaptation to starvation [122]. FGF21 is secreted by the liver, pancreas, and white adipose tissue [123]. Activation of PPARα stimulates greater hepatic FGF21 gene transcription, while glucagon also plays a role in increased FGF21 secretion [124]. In the liver, FGF21 stimulates metabolic changes characteristic of fasting including gluconeogenesis, fatty acid oxidation, and ketogenesis, but does not stimulate glycogenolysis [123]. Additionally it induces growth hormone resistance (which prevents expenditure of energy on growth) and disruption of the hypothalamic-pituitary-ovarian axis (which minimizes the expenditure of energy on reproduction). However, in humans ketogenesis increased before FGF21 concentrations rose questioning the influence of FGF21s on starvation-induced ketogenesis [122].

Prolonged Starvation: Metabolic Consequences

Starvation for over 30 days is considered long-term starvation, with serious complications and death occurring from the 40th day. Although, such prolonged starvation is a rare event, hunger strikes have provided information on the metabolic and other effects of such extended food deprivation. Among Northern Ireland hunger strikers, death occurred between days 57 and 73 and after the loss of 40–50% of body weight [125]. A male subject who fasted for 44 days lost 25% of his weight, 24% of his fat-free body mass (20% of total body protein), and 33% of his fat mass [126, 127]. To survive for over a month requires the oral ingestion and/or intravenous infusion of water, electrolytes, and vitamins. The most common cause of death in these extreme cases of starvation is myocardial infarction, pneumonia, or organ failure. It occurs almost inevitably when the body mass index reaches about 12.5 kg/m^2. Obese individuals can survive longer than the 60–70-day survival times seen in lean individuals. Survivals of 200–300 days have been seen in obese individuals ascribed to their greater fat stores and thus lower need to derive energy from protein [128, 129]. Starting mass appears to be a key variable in surviving an extreme fast and not the amount of mass lost, as shown by a loss of 20.7% of body mass without substantial loss of function after a 50-day fast in a patient who began fasting with a weight of 96.8 kg (BMI = 30.2 kg/m^2) [130]. Upon forensic postmortem examination, mild increases in blood, vitreous, pericardial fluid, and urinary β-hydroxybutyrate concentrations provided evidence of starvation in individuals without other probable causes for ketosis [131].

Substrate Metabolism

During prolonged fasting, hormonal and metabolic changes reduce protein and muscle breakdown so that protein catabolism produces only about 10% of total energy. Muscle and other tissues use ketone bodies and fatty acids as their main energy source. Therefore, the human brain derives energy from fat stores, permitting survival in starving normal weight persons for up to 2–2.5 months. After 44 days of starvation, a 30-year-old subject had normal plasma glucose, cholesterol, and triacylglycerol but substantially elevated free fatty acid and 3-hydroxybutyrate concentrations [126]. Only 13–17% of total energy expenditure was from protein oxidation [127]. In starving patients, ketonemia can often be detected by the characteristic ketone "smell of apples" as they are eliminated through the respiratory system [132]. Once fat stores are depleted, catastrophic protein catabolism of all organs, including the heart, develops leading to death [129].

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

Vitamin Deficiencies

The neurological problems encountered during long-term starvation are often secondary to vitamin deficiencies. For example, thiamine (vitamin B_1) deficiency (beriberi—distal motor and sensory neuropathy plus heart failure and Wernicke-Korsakoff syndrome) occurs when fasting is accompanied by the exclusive intake of sugar and liquids or during prolonged starvation [133, 134]. Of 25 hunger strikers admitted to hospital after more than 153 days of fasting, one third had ophthalmoparesis (paresis of the lateral rectus muscle), about half had some form of paresis, and a quarter had truncal ataxia. At discharge, 16% had persistent ophthalmoparesis and 36% had nystagmus. Only four patients (16%) could walk

independently [135]. In half the patients, nystagmus and ataxia had not resolved after 1 year. Since glucose oxidation is a thiamin-dependent process, thiamin supplementation should be provided prior to glucose (dextrose) or carbohydrate administration [136].

Semistarvation

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

Metabolic and Hormonal Changes

Many of the metabolic and hormonal changes observed during total starvation are also seen during semistarvation. However, the magnitude of these changes is smaller and depends on the caloric intake and its composition. Studies performed with very low caloric intakes (450 kcal/day for 16 weeks) in obese patients showed that in adipocytes, there was decreased expression of genes encoding leptin, adiponectin, de novo lipogenesis, and rate-limiting enzymes for fatty acid β-oxidation and carnitine palmitoyltransferase 1B. This pattern reflects increased adipocyte fatty acid oxidation [137]. Furthermore, genes associated with protein synthesis were downregulated [137]. The 1950 Minnesota semistarvation study of Keys and colleagues [138] demonstrated that normal lean subjects who had lost 25% of their body weight over 24 weeks and had little measureable fat remaining (i.e., <5% of body weight) were catabolizing substantial amounts of their lean mass. Other studies which examined serum concentrations of proteins, fatty acids, hematologic parameters, liver function tests, electrolytes, and vitamins showed little or no change from pre-semistarvation levels [138]. However, despite these normal results, T3 declined significantly, while the changes in T4 and T4/TBG were smaller but demonstrated statistically significant declines that paralleled the changes in T3. TSH was elevated over baseline through most of the course. However, a meta-analysis found that long-term low-calorie diets, unlike short-term fasting, did not significantly increase serum cortisol concentrations [139]. However, in some studies cortisol concentrations increased significantly and testosterone declined to levels well below the normal range for men. A large rise in sex hormone-binding globulin (SHBG) to outside of the normal male range paralleled similar changes in TBG. This increase in SHBG further reduced bioavailable testosterone to 10% of pre-semistarvation levels. LH also decreased significantly. Similarly, among female victims of famine, menstrual irregularities were observed secondary to impaired gonadotropin secretion [140]. Semistarvation with weight loss is associated with decreased resting energy expenditure and adaptive thermogenesis. The reduction in the basal metabolic rate during semistarvation is highly associated with the loss of body fat [95]. Adaptive thermogenesis involves a decrease in resting energy expenditure greater than the decreases attributable to decreases in fat-free mass (FFM) and fat mass (FM) [91].

Substrate Metabolism

A computational model used a simulated semistarvation diet averaging 1100 kcal/day of carbohydrates, 290 kcal/day of fat, and 195 kcal/day of protein for 24 weeks. After the first week of this diet, the simulated carbohydrate oxidation dropped by 35% and accounted for ~42% of the total energy expenditure [141]. The simulated protein oxidation decreased by 12% after the first week of semistarvation and remained suppressed, while the simulated fat oxidation increased by 12% during the initial days of semistarvation due to enhanced lipolysis associated with the reduced

carbohydrate intake. After a week of semistarvation, fat oxidation was 46% of the total energy expenditure. This led to a negative fat balance of more than 1000 kcal/day that slowly became less negative as the semistarvation progressed and body fat was catabolized. At the end of the semistarvation period, all three macronutrient oxidation rates were roughly equal to their respective dietary intakes [141].

Both the total caloric intake and composition of the semistarvation diet are important in determining the composition of tissue loss. After a 5% weight loss, the fraction of fat-free mass to total weight loss was 30% and 18% for a very low-calorie diet (600 kcal/day) and low-calorie diet (1200 kcal/day), respectively, indicating that slower weight loss with a higher caloric intake results in greater loss of fat than muscle [125]. Meta-regression analysis of patients on weight loss diets showed that higher protein intakes (>1.05 g/kg) reduce the loss of lean body mass [142]. This conclusion was confirmed on subsequent studies, which also showed higher concentrations of the anabolic substance IGF-1 with higher protein intakes [143, 144].

Long-Term Consequences of Semistarvation

Semistarvation can have especially detrimental long-term effects. Early gestation appeared to be the most vulnerable period. People who were conceived during famine were at increased risk of schizophrenia and depression, had a more atherogenic plasma lipid profile, were more responsive to stress, and had double the rate of coronary heart disease, obesity, and hypertension [145, 146]. They also performed worse on cognitive tasks which may be a sign of accelerated aging. However, at age 68 Dutch citizens with prenatal exposure to famine did not have shortening of telomeres in peripheral blood leukocytes, although another study of exposure to famine hinted at shortening [147, 148]. People exposed during any period of semistarvation during gestation had more type 2 diabetes [149].

Marasmus

Chronic malnutrition caused by deficient and insufficient dietary intakes results in major changes in body composition and homeostasis. Any form of illness in such patients is frequently life-threatening because of altered metabolism, lack of glycogen and adipose tissue reserves, and immune deficiency. Marasmus is derived from the Greek *marasmos*, which means withering or wasting. Marasmus is one of the three forms of serious chronic protein-energy malnutrition (PEM). The other two forms are kwashiorkor and marasmic kwashiorkor. Marasmus involves insufficient intake of both protein and calories and is characterized by emaciation, whereas kwashiorkor is due to protein deficiency, resulting in an edematous appearance [4]. Marasmic kwashiorkor indicates the often encountered difficulty in separating these entities and indicates that features of both marasmus and kwashiorkor are present. These forms of serious PEM represent a group of pathologic conditions that occur mainly in young children from developing countries. They are classically observed around time of weaning from their mother's milk. However, more recently there has been the realization that PEM also occurs among home-dwelling older adults, particularly in the context of aging, with a greater incidence in developing countries, among women and in rural areas [150]. PEM occurs in about 50% of hospitalized old people due to reduced nutrient intake and increased catabolism secondary to acute diseases such as sepsis [151]. Renal insufficiency is strongly associated with malnutrition, especially when end-stage renal disease (ESRD) is present [151]. The prevalence of PEM is high (16–54%) in ESRD, and its presence is a predictor of morbidity such as poor wound healing, susceptibility to infection, fatigue, and poor rehabilitation plus increased mortality [151]. The reasons why a nutritional deficit progresses to marasmus rather than kwashiorkor are unclear and cannot be solely explained by the composition of the deficient diet (i.e., a diet deficient in energy for marasmus and a diet deficient in protein for kwashiorkor). The

study of these entities is considerably limited by the lack of appropriate animal models.

Body Composition in Marasmus

Marasmus results from negative energy balance secondary to a decreased energy intake, loss of ingested calories (via emesis and diarrhea), increased energy expenditure (due to infections, burns), or combinations of these factors. Marasmatic individuals display adaptive energy-conserving behavior by reducing physical activity and growth. The basal energy metabolism is associated with lethargy which also conserves energy. In patients with marasmus, body mass is significantly reduced, and fat stores can decline to as low as 5% of total body weight [152]. The proportion of total body water content increases as the magnitude of the protein-energy malnutrition (marasmus or kwashiorkor) increases and is associated with loss of fat mass, which is poor in water. Protein mass can decrease as much as 30% in the most serious forms of marasmus. Marasmus malnutrition does not substantially change concentrations of albumin, but levels of transport proteins with very short half-lives, such as prealbumin, transferrin, or transcortin, are reduced. Muscle fibers are thin and lose their striations. Muscle cells are atrophic, and muscle tissue is infiltrated with fat and fibrous tissue. Serum leptin concentration is low [151]. The brain, skeleton, and kidneys are preserved, whereas the liver, heart, pancreas, and digestive tract are the first to be affected. The loss of fat and muscle mass can be evaluated by measuring arm circumference and triceps skinfold thickness.

The gut microbiome is also affected by protein-energy malnutrition. Such malnutrition results in reduced fecal microbial community richness, i.e., there are fewer unique bacterial taxa. Furthermore, there are alterations in the proportions of certain bacterial groups. For example, in malnourished Bangladeshi and Indian children, there was an overabundance of *Proteobacteria*, such as *Enterobacter*, *Klebsiella*, *Escherichia*, and *Shigella* [153].

Minerals and Vitamins

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

Kwashiorkor

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

Carbohydrate Metabolism

Blood glucose concentrations are regulated by the fine balance between gluconeogenesis and glucose clearance. In kwashiorkor, an inability to maintain sufficient gluconeogenic glucose production can result in hypoglycemia. Glucose clearance rates correlated with plasma albumin concentrations in both marasmus and kwashiorkor. The reduced glucose clearance in both conditions appears related to impaired insulin availability as demonstrated by impaired insulin responses to a glucose load. Among the potential mechanisms of disturbed insulin secretion in these two conditions is pancreatic dysfunction [154, 155]. Pancreatic atrophy and fibrosis, as well as fatty infiltration, have been consistent autopsy features in kwashiorkor [156, 157]. Pancreatic β-cells are vulnerable to oxidative stress which is increased in kwashiorkor and

might explain the pancreatic changes [158–161]. However, there was no indication of peripheral or hepatic insulin resistance. Another cause of the hypoglycemia in kwashiorkor is impaired glucose absorption possibly related to intestinal villous atrophy [162, 163]. Lower disaccharidase activity was found in kwashiorkor compared with marasmus [164–166]. Another possible factor contributing to impaired glucose absorption could be decreased expression of the sodium-dependent hexose transporter or the glucose transporter 2, which transports glucose across the luminal membranes. A third cause of reduced glucose absorption could be a decreased gut motility and consumption of carbohydrates by small bowel bacterial overgrowth [167].

Lipid Metabolism

Lipolysis is elevated in kwashiorkor more than in marasmus, while both lipolysis and fatty acid β-oxidation are less efficient in kwashiorkor [168]. The latter was demonstrated by slower palmitate oxidation and the former by reduced release of free fatty acids from adipose tissue. Additionally, there are reduced plasma concentrations of carnitine in kwashiorkor which might be part of the reason there is slower fatty acid oxidation. This was confirmed on metabolomic studies where compared with marasmus, children with kwashiorkor had lower 2-acylcarnitine concentrations and lower ratios of acetylcarnitine to free carnitine, a marker of β-oxidation. This may indicate decreased fatty acid transport into the mitochondria via the carnitine shuttle, thus limiting β-oxidation [169].

Protein Metabolism

Unlike marasmus, kwashiorkor is characterized by low serum albumin concentrations and slow protein breakdown and turnover. For example, there is slower methionine production in kwashiorkor than marasmus because of a slower rate of release from protein breakdown [170, 171]. This slower protein breakdown in kwashiorkor might be among the reason for poorer survival in these patients [170, 171]. Metabolomic studies showed that the availability of amino acids, especially essential amino acids, was decreased more in kwashiorkor than marasmus. Additionally, aspartic acid, tryptophan, and its derivative kynurenine were more depleted in patients with kwashiorkor. The low tryptophan availability might also be related to the albumin depletion seen with kwashiorkor, since albumin binds 80–90% of tryptophan in the circulation [169]. In addition, damaged hepatic mitochondria cause greater production of reactive oxygen species leading to reduced glutathione concentrations.

Anorexia Nervosa

Anorexia nervosa is an eating disorder where people lose more weight than is healthy for their age and height. It is far more common in females than males. Those suffering from this disorder may greatly fear weight gain, even when underweight with neurobehavioral mechanisms underlying the perception of food and emotion likely part of the pathophysiology [172]. Anorectics may diet excessively, taking in only a few hundred calories a day or just water (restricting type), or eat and then purge, either by vomiting or by taking laxatives (binge/purging type). This chapter will focus on the restricting type.

Hormonal Responses

The hormonal responses observed with anorexia nervosa are similar to those seen in starved and semistarved individuals. However, in anorexia these responses may continue for years at varying intensities resulting in major changes in body composition and homeostasis even during periods of reasonable caloric and nutrient intake. Surgeons may encounter patients during these various phases.

Anorexia nervosa is characterized by hypothalamic-pituitary-adrenal axis hyperactivity as evidenced by increased corticotropin-releasing hormone secretion [173]. This leads

to increased free plasma, salivary, urinary, and 24-h mean plasma cortisol concentrations. The elevated cortisol concentrations are ascribed to prolonged cortisol half-life along with decreased metabolic clearance with normal cortisol production. Cortisol concentrations are higher in anorectics with lower BMI, fat mass, insulin, leptin, and IGF-1 signifying an adaptive response to maintain euglycaemia in a low-energy setting [174]. With refeeding, the enhanced cortisol salivary responses to awakening were reduced [175]. Dexamethasone suppression tests performed in untreated anorexia nervosa patients showed reduced cortisol suppression. Although anorexics have elevated central corticotropin-releasing hormone (CRH) concentrations, underweight anorexics showed low CSF ACTH levels but normal plasma ACTH concentrations [174]. Circadian cortisol rhythms are normal although nocturnal spikes can occur [176]. Anorexia nervosa is characterized by adrenal sympathetic overactivity and neural sympathetic underactivity as demonstrated by a predominance of circulating epinephrine over norepinephrine levels [177]. Markedly increased subcutaneous abdominal adipose tissue norepinephrine concentrations in anorectics compared to control subjects reflect increased sympathetic nervous system activity [178, 179]. However, not all studies have reached similar conclusions, with some reporting reduced sympathetic activity.

Growth hormone concentrations are increased, but due to relative hepatic resistance, insulin-like growth factor-1 levels are reduced. Thyroid function studies show a "sick-euthyroid" (non-thyroidal illness syndrome) pattern with normal TSH, low to normal total and free T4, and low T3. There is increased conversion of T4 to reverse T3. Additionally there is hypogonadotropic hypogonadism. Hypothalamic gonadotropin-releasing hormone (GnRH) secretion is decreased leading to reduced pituitary gonadotropin secretion [180]. Therefore, LH, FSH, estradiol, and androgen concentrations are significantly lower in anorexia nervosa than in controls, while SHBG concentrations are increased [181, 182]. This constellation leads to amenorrhea in female anorectics [183]. Serum leptin concentrations are also low which likely contributes to the appearance of amenorrhea [180].

Anorectics suffer from bone loss leading in the long-term to low bone mass (bone mineral density, bone microarchitecture). They are thus particularly vulnerable to fractures [184]. The low bone density is a consequence of hormonal alterations including hypoestrogenism, hypoandrogenemia, hypoleptinemia, hypercortisolism, and decreased IGF-1 levels [185].

Adipokines are also affected by anorexia nervosa with circulating adiponectin levels inversely related to body mass index (BMI) [186]. When adiponectin isoforms were examined, there were decreases in the percentage of those with high molecular weights, while there were increases in the percentage of low molecular weight isoforms that correlated with BMI [186]. Serum leptin concentrations are significantly decreased, while serum soluble leptin receptor levels are increased [186]. This receptor increase might be a protective mechanism that decreases free leptin bioavailability thus facilitating energy conservation [186]. Concentrations of serum resistin (adipose tissue-specific secretory factor; increases hepatocyte LDL production and degrades hepatic LDL receptors) were significantly lower in anorexics when compared to controls, in some but not all studies. Furthermore, serum concentrations of visfatin, a peptide regulating adipocyte differentiation, were decreased in anorectics [181].

Some evidence points to anorexia patients being in a state of inflammation. In one study anorectic patients had increased TNF-α and IL-6 mRNA expression, while another study found plasma TNF-α to be significantly higher in patients than controls [187–189]. Both TNF-R55 and TNF-R75 (receptors) were higher in those suffering from anorexia for longer than a year as compared to controls and patients with shorter disease duration [187]. However, increased TNF and IL-1 activity was not seen in all studies [190]. Plasma concentrations of IL-1β, s-TNF-α-R-I and s-TNF-α-R-II, TGF-β, and sIL-1β-RA did not differ significantly in anorexia nervosa compared with controls [189, 191]. However, serum IL-6 was higher in anorexic women in comparison with a control group. Serum sIL-6R (soluble

IL-6 receptor) was lower, and serum sgp130 (an inhibitor of the IL-6 trans-signaling pathway) was higher in anorexics compared with controls [192]. This constellation appears directed at inhibiting IL-6 action [192].

Ghrelin, a peptide hormone secreted by stomach endocrine cells, is a peripherally produced and centrally acting peptide that stimulates food intake. In anorexia nervosa ghrelin concentrations were elevated but decreased after BMI increased with refeeding resulting in a negative relationship between BMI and ghrelin. In addition to increased ghrelin expression, there is impaired ghrelin signaling and modulation as demonstrated by delayed or absent postprandial decrease of ghrelin attributed to ghrelin resistance [193]. The increased ghrelin secretion might also stimulate corticotropin-releasing hormone (CRH) thus stimulating plasma cortisol secretion [180].

Serum fibroblast growth factor 21 (FGF21) concentrations were decreased in anorectics and thus might be involved in maintaining normal blood glucose through adjustment of insulin levels and insulin sensitivity [194]. The decreased FGF21 concentrations were also associated with impaired radial trabecular bone microarchitecture and diminished radial bone strength [195]. Betatrophin, a hormone primarily secreted by hepatic and adipose tissue which promotes pancreatic β-cell proliferation and β-cell mass thus improving glucose tolerance, was found to be increased in anorectic patients. This increase in betatrophin is secondary to reduced plasma glucose and insulin concentrations [196].

Carbohydrate Metabolism

In chronic anorectic starvation, regulation of substrates depends mainly on decreased serum insulin concentrations and increased growth hormone secretion [197]. These low plasma insulin levels are the result of greater insulin clearance rather than depressed insulin secretion [198]. Following an overnight fast, anorexics maintained normal fasting plasma glucose concentrations which were not related to body weight or BMI thus demonstrating that endogenous glucose production remains a priority, providing glucose to the central nervous system [199]. Since anorectics consume some carbohydrates, they do not generally develop ketosis. The role of glucagon seems to be of minor importance in this situation, although impaired recovery of plasma glucose after insulin-induced hypoglycemia in anorexia nervosa is primarily attributable to impaired pancreatic glucagon (α-cell) secretory capability [200]. Furthermore, pancreatic β-cell dysfunction as evidenced by reduced insulin secretion was seen following glucagon administration to anorectic patients [201].

Insulin-stimulated glucose disposal is normal in anorexia nervosa patients, a finding that contrasts with previously reported increases in erythrocyte insulin receptors [202]. Other studies agree with the latter one by revealing that insulin-stimulated glucose disposal and nonoxidative glucose metabolism were significantly reduced in anorexia nervosa. Nonoxidative glucose metabolism reflects skeletal muscle storage of glucose as glycogen as evidenced by lower glycogen concentrations in muscles of anorectic patients. Therefore, in anorexia nervosa the nonoxidative pathway of glucose metabolism is resistant to the action of insulin (i.e., insulin stimulates glucose oxidation more than glucose storage), a situation similar to that commonly observed during prolonged starvation [203]. Furthermore, insulin sensitivity is not systemically increased, and glucose effectiveness is unchanged in anorectic women when compared to normal weight controls [198].

Both albumin and prealbumin concentrations are usually within the normal range and are thus unsuitable nutritional markers in anorectic adults and adolescents [204].

Lipid Metabolism

Anorexia nervosa is characterized by the marked loss of adipose tissue. Therefore, it is not surprising that these individuals have increased lipolysis as evidenced by an inverse linear relationship

between the rate of glycerol production and weight after an overnight fast [199]. Interestingly, concentrations of serum free fatty acid are either not or only mildly elevated in anorexia nervosa [205]. Furthermore, during exercise, but not at rest, there was a local increase in both adipose tissue norepinephrine and glycerol concentrations in anorectic patients in comparison with controls, indicating accelerated lipolysis [179].

Anorexia nervosa patients display a complex membrane fatty acid profile without characteristics of nutritional essential free fatty acid deficiency but with a deficiency in long-chain polyunsaturated fatty acids [206]. The phospholipid profile showed significantly lower (*n*-6) and (*n*-3) elongation and desaturation products with elevated short-chain saturated, short-chain monounsaturated, branched-chain, and odd-chain fatty acids. This latter pattern indicates enhanced biosynthesis of alternative fatty acids that only partially compensate for the loss of polyunsaturated fatty acids in providing membrane "fluidity" [207]. The most consistent finding in the fatty acid pattern is decreased content of linoleic acid and increased content of palmitoleic acid in all lipid classes. The alteration in plasma lipids and lipoproteins in anorexia nervosa is the result of complex mechanisms including decreased catabolism of triglyceride-rich lipoproteins, normal rate of cholesterol synthesis, and increased resorption of exogenous cholesterol [208]. Mean serum levels of total cholesterol; low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol; apolipoproteins (apo) A1, B, C2, C3, and E; and cholesterol ester transfer protein (CETP) activity were significantly higher in anorexic compared to controls [209]. The elevated cholesterol concentrations in anorexia are generally attributed to increased LDL cholesterol secondary to the severe loss of body fat, changes in thyroid hormones, increased lipolysis, and decreased endogenous cholesterol synthesis with resultant decrease in LDL removal. CETP activity increases cholesterol turnover as an adaptation to its low intake thus maintaining elevated cholesterol concentrations. In severe anorexia this mechanism can fail resulting in the fall of cholesterol concentrations [210].

Energy Expenditure

Metabolic rate slows in patients with anorexia nervosa, with resting energy expenditures (REE) decreasing to as low as 50–70% of predicted values [211, 212]. REE adjusted for both fat-free mass and fat mass was significantly lower than predicted indicating significant downregulation of cellular metabolism in the fat free mass. The low resting energy expenditure (REE) is thus not only attributable to the absolute loss of lean body mass (skeletal muscle) but also an adaptive decrease in the energy expenditure of the remaining tissue [213]. This appears to be due to some extent to the effects of reduced thyroid hormones and leptin. Schebendach et al. [214] studied 21 anorexic adolescents and found that mean measured resting energy expenditures were 62 ± 18% of that predicted by the Harris–Benedict equation. The authors proposed a corrective formula for predicting resting energy expenditures in anorexia nervosa for use when indirect calorimetry is not available [214]. Marra et al. [215] performed indirect calorimetry on 237 females with anorexia nervosa and confirmed that both the Harris–Benedict equation and the World Health Organization equations overestimate REE in patients with anorexia nervosa. The Schebendach correction accurately predicted measured REE in the adolescents, but not in the adults, in a follow-up prospective study of 50 patients with anorexia nervosa.

The Elderly: Cachexia and Sarcopenia

Weight loss, often coinciding with frailty, is commonly observed in the elderly. It is frequently preceded by sarcopenia—the involuntary loss of skeletal muscle mass and, consequently, loss of strength and a decline in functional quality—which occurs even in "successfully" aging adults [216, 217]. In fact, after the age of 50 years, individuals lose muscle mass at the rate of about 1–2% per year, with losses of 40% not uncommon in octogenarians. Sarcopenia is associated with dynapenia—the loss of muscle strength secondary to reduced neural activation and reduced

contractility quality [218]. The cause of sarcopenia is unknown but might be due to a combination of decreased physical activity; loss of spinal motor neurons due to apoptosis; reduced endogenous growth hormone and other growth factors; decreased estrogen and androgen production; insufficient protein intake; infiltration of fat into muscle; and a chronic low-grade inflammatory response (i.e., elevated cytokines IL-1, TNF, and IL-6 [217, 219]). The age-related loss of spinal motor neurons decreases muscle fiber number and size causing impaired mechanical muscle performance [217]. Sarcopenia is aggravated by a complex interaction of several factors among them aging, disuse, immobilization, disease, and malnutrition. Another possible mechanism is an insufficient synthetic response to protein ingestion possibly due to reduced production and/or reduced responses to the anabolic effects of anabolic hormones such as androgens, growth hormone (GH), and IGF-1. The concentrations of these anabolic hormones decrease progressively during aging. Transcriptomic studies showed older males (63–79 years) to be less responsive to anabolic stimuli and more responsive to catabolic conditions (i.e., greater proteolysis with a low-protein diet) than younger males (21–43 years) [220]. The elderly have reduced numbers and sizes of type II muscle fibers apparently due to skeletal myocyte apoptosis [221]. Type I fibers are spared. When compared to tissue from young individuals, the mitochondrial respiration of muscle fibers from elderly individuals was reduced 41%. This reduction was associated with a 30% decline in cytochrome c oxidase activity and 50% reductions in the levels of the metabolic regulators, SIRT3 (silent mating-type information regulator number 3), and PGC-1α (peroxisome proliferation-activated receptor gamma coactivator 1-α). Some, but not all, studies found reduced ATP concentrations in aging muscle [222]. These observations suggest that aging is associated with impaired skeletal muscle mitochondrial function [223]. Weight lifting, resistance training, and endurance exercise regimens may improve both muscle mass and function. Increased protein intake is also being explored as a possible way to reduce muscle loss [224, 225]. Paradoxically, caloric restriction might reduce the development of sarcopenia.

The elderly not only lose muscle mass but many also lose weight. Age-related reduction in energy intake is a physiologic effect of healthy aging. However, harmful anorectic effects can intervene. The "anorexia of aging" is a physiologic decrease in food intake which gradually results in weight loss accompanied by age-related changes in body composition [226]. This "anorexia" is associated with increased frailty and disability [227]. Reduced food intake can be caused by appetite loss attributed to reduced caloric requirements or because of more rapid and stronger satiety signals. Early satiation is often due to a decrease in adaptive relaxation of the stomach fundus resulting in early antral filling. Increased concentrations and effectiveness of cholecystokinin may play a role. The central feeding drive (opioid and the neuropeptide Y effects) appears to decline with age. Physical factors such as poor dentition, ill-fitting dentures, or age-associated changes in taste and smell may influence food choice and limit the type and quantity of food eaten by older people [223]. In demented patients, weight loss was associated with total energy expenditures exceeding caloric intake [227]. High total energy expenditures were observed in those patients who required less sleep and/or spent less time lying down [228]. This weight loss and concomitant loss of muscle mass and strength are frequently observed in individuals suffering from dementia. It is associated with an increased risk of falls, functional dependence, and reduced quality of life.

The frailty syndrome is defined as unintentional weight and muscle loss accompanied by exhaustion along with declines in grip strength, gait speed, and activity [229]. In the United States, the prevalence of frailty in adults 65 years and older is 12% and 25% in those 85 years and older [230]. Frail individuals can rapidly progress to a disabled state when another stressor such as surgery or illness ensues. This situation frequently causes a domino effect that increases mortality [229]. A systemic review and meta-analysis revealed that frailty in patients undergoing surgery is associated with poorer outcomes as regard to mortality and return to independence [231].

The cause of frailty is thought to be an imbalance between inflammatory and anti-inflammatory networks, resulting in a low-grade chronic pro-inflammatory status, dubbed, "inflammaging." [232]. This pro-inflammatory state is linked to immunosenescence. Plasma concentrations of circulating noncoding RNAs (miRNAs), such as miR-21, were higher among fragile patients, while there was an association between miR-483 with frailty and the inflammatory cytokine IL-8. Additionally, the TNFα/IL-10 ratio was higher in the fragile group indicating that the cytokine balance favored inflammation [233]. Genotype also plays a role, with centenarians having a high level of anti-inflammatory cytokines together with a protective genotype [234]. Poor nutritional status has been implicated in the development and progression of chronic diseases affecting the elderly. Poor nutritional status along with chronic illnesses and conditions such as impaired muscle function, decreased bone mass, immune dysfunction, anemia, reduced cognitive function, poor wound healing, and delayed recovery from surgery ultimately lead to greater morbidity and mortality.

The Refeeding Syndrome

Refeeding syndrome describes the biochemical changes, clinical signs and symptoms, and complications that can occur secondary to feeding a malnourished and often catabolic individual. This syndrome usually begins within 72 hours of starting nutritional support and can cause serious harm and even death [235, 236]. Initial descriptions of the syndrome were from malnourished prisoners of war who developed cardiac and neurological symptoms soon after they resumed eating [237, 238]. Because of the potential for significant morbidity and mortality, healthcare professionals must be aware of its possible appearance and effects among at-risk populations. The syndrome's presentation ranges from simple nausea, vomiting, and lethargy to respiratory insufficiency, cardiac failure, hypotension, arrhythmias, delirium, coma, and death. Peripheral edema and fluid overload leading to pulmonary edema can also occur [239]. Clinical deterioration may occur rapidly if the cause is not established and appropriate measures not instituted.

Refeeding a starved individual rapidly decreases gluconeogenesis and anaerobic metabolism mediated by a rapid rise in serum insulin concentrations [240, 241]. The elevated insulin stimulates the intracellular movement of extracellular potassium, phosphate, and magnesium. During prolonged starvation, intracellular stores of these minerals can become severely depleted, while their serum concentrations often remain normal. The latter is due to the contraction of the extracellular compartment during starvation despite reduced renal excretion of sodium and water. Refeeding can potentially lead to expansion of the extracellular compartment resulting in the possibility of fluid overload and dilution of extracellular potassium, magnesium, and phosphate concentrations. Additionally, because the intracellular stores are depleted, there is a large extra-intracellular concentration gradient resulting in further decline in the extracellular concentrations of these ions often leading to marked hypokalemia, hypomagnesemia, and hypophosphatemia [242, 243]. To maintain osmotic neutrality, sodium and water are retained intracellularly [244]. Simultaneously, reactivation of carbohydrate-dependent metabolic pathways increases the demand for thiamine which can become rapidly deficient if not replaced [245, 246]. The increased in insulin also stimulates protein and ATP synthesis. Protein phosphorylation and generation of ATP further reduce extracellular and intracellular phosphate concentrations further contributing to the development of hypophosphatemia. Furthermore, magnesium is a key component of ATP stabilization and various enzymatic processes, further depleting intracellular and extracellular magnesium concentrations. In addition, the sodium-potassium membrane gradient is important for proper membrane excitation, transport processes, and signal transduction, so that hypokalemia can have multiple detrimental effects on muscle and neural functions [247]. During refeeding, phosphate, magnesium, potassium, and thiamine deficiencies occur to varying degrees and have different effects in different patients [248].

Some individuals, such as chronic alcohol abusers or those suffering from long-term starvation, are extremely vulnerable to the consequences of electrolyte and vitamin deficiencies [249–255]. Therefore it might be prudent to slowly increasing glucose intake to allow sufficient opportunity to replace serum electrolyte and thiamine deficiencies. Furthermore, excessive fluid intake is to be avoided to prevent further reductions in phosphate, magnesium, and potassium concentrations and increases in the intravascular fluid load.

Hypophosphatemia is among the markers used to diagnose the refeeding syndrome, although low serum phosphate is not pathognomonic [256]. A prospective study of 62 intensive care unit patients refed after 48 h of starvation found that 21 (34%) experienced hypophosphatemia associated with low prealbumin concentrations [239]. Low serum albumin concentrations may be an important predictor of hypophosphatemia [239]. Another study of 106 refed patients with histologically confirmed cancer noted an incidence of hypophosphatemia of 25% [257].

The optimum timing for correcting the biochemical and fluid abnormalities during refeeding has been the source of debate. Some investigators advocate correcting electrolyte abnormalities before beginning the refeeding. This approach has been rethought, and recent National Institute of Health and Clinical Excellence Guidelines (United Kingdom) recommend that careful refeeding and correction of electrolyte abnormalities can occur simultaneously without deleterious effects. There are no randomized trial data to support either approach. The currently recommended approach to refeeding is to increase the caloric intake in a stepwise fashion while closely monitoring electrolytes. A recent randomized trial of a caloric-restricted versus full nutritional support regimen among ICU patients who developed refeeding syndrome found better survival in the restricted group [258].

The National Institute of Health and Clinical Excellence Guidelines also include risk factors for developing the refeeding syndrome among patients beginning nutritional therapy. These risk factors include low body mass index, large unintentional weight loss over a short time period, little or no nutritional intake for 5–10 days, and/or a history of alcohol or drug abuse (including insulin, chemotherapy, antacids, or diuretics) [236]. Others have included as risk factors: starvation, older age, low prealbumin or albumin concentrations, enteral nutrition, low plasma potassium, phosphate and/or magnesium concentrations before feeding, severe catabolic disease, and high nutritional intake during initial nutritional therapy [236, 247, 259].

Conclusions

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

References

1. Ter Beek L, Vanhauwaert E, Slinde F, Orrevall Y, Henriksen C, Johansson M, Vereecken C, Rothenberg E, Jager-Wittenaar H. Unsatisfactory knowledge and use of terminology regarding malnutrition, starvation, cachexia and sarcopenia among dietitians. Clin Nutr. 2016;35:1450–6.
2. Wijngaarden MA, Bakker LE, van der Zon GC, 't Hoen PA, van Dijk KW, Jazet IM, Pijl H, Guigas B. Regulation of skeletal muscle energy/nutrient-sensing pathways during metabolic adaptation to fasting in healthy humans. Am J Physiol Endocrinol Metab. 2014;307:E885–95.
3. González-Vélez V, Dupont G, Gil A, González A, Quesada I. Model for glucagon secretion by pancreatic α-cells. PLoS One. 2012;7:e32282.
4. Allister EM, Robson-Doucette CA, Prentice KJ, Hardy AB, Sultan S, Gaisano HY, Kong D, Gilon P,

Herrera PL, Lowell BB, Wheeler MB. UCP2 regulates the glucagon response to fasting and starvation. Diabetes. 2013;62:1623–33.
5. Gastaldelli A, Gaggini M, DeFronzo R. Glucose kinetics: an update and novel insights into its regulation by glucagon and GLP-1. Curr Opin Clin Nutr Metab Care. 2017;20:300–9.
6. Meyer C, Stumvoll M, Dostou J, Welle S, Haymond M, Gerich J. Renal substrate exchange and gluconeogenesis in normal postabsorptive humans. Am J Physiol Endocrinol Metab. 2002;282:E428–34.
7. Anyamaneeratch K, Rojvirat P, Sukjoi W, Jitrapakdee S. Insights into transcriptional regulation of hepatic glucose production. Int Rev Cell Mol Biol. 2015;318:203–53.
8. Sakharova AA, Horowitz JF, Surya S, Goldenberg N, Harber MP, Symons K, Barkan A. Role of growth hormone in regulating lipolysis, proteolysis, and hepatic glucose production during fasting. J Clin Endocrinol Metab. 2008;93:2755–9.
9. Tsintzas K, Jewell K, Kamran M, Laithwaite D, Boonsong T, Littlewood J, Macdonald I, Bennett A. Differential regulation of metabolic genes in skeletal muscle during starvation and refeeding in humans. J Physiol. 2006;575(1):291–303.
10. Soeters MR, Sauerwein HP, Dubbelhuis PF, Groener JE, Ackermans MT, Fliers E, Aerts JM, Serlie MJ. Muscle adaptation to short-term fasting in healthy lean humans. J Clin Endocrinol Metab. 2008;93:2900–3.
11. Chan JL, Mietus JE, Raciti PM, Goldberger AL, Mantzoros CS. Short-term fasting-induced autonomic activation and changes in catecholamine levels are not mediated by changes in leptin levels in healthy humans. Clin Endocrinol. 2007;66:49–57.
12. Engelbrechtsen L, Mahendran Y, Jonsson A, Gjesing AP, Weeke PE, Jørgensen ME, Færch K, Witte DR, Holst JJ, Jørgensen T, Grarup N, Pedersen O, Vestergaard H, Torekov S, Kanters JK, Hansen T. Common variants in the hERG (KCNH2) voltage-gated potassium channel are associated with altered fasting and glucose-stimulated plasma incretin and glucagon responses. BMC Genet. 2018;19:15.
13. Gjesing AP, Ekstrøm CT, Eiberg H, Urhammer SA, Holst JJ, Pedersen O, Hansen T. Fasting and oral glucose-stimulated levels of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are highly familial traits. Diabetologia. 2012;55:1338–45.
14. Oh KJ, Han HS, Kim MJ, Koo SH. Transcriptional regulators of hepatic gluconeogenesis. Arch Pharm Res. 2013;36:189–200.
15. Prats C, Graham TE, Shearer J. The dynamic life of the glycogen granule. J Biol Chem. 2018;293:7089–98.
16. Petersen KF, Price T, Cline GW, Rothman DL, Shulman GI. Contribution of net hepatic glycogenolysis to glucose production during the early postprandial period. Am J Phys. 1996;270(1 Pt 1):E186–91.
17. Browning JD, Baxter J, Santhosh S, Burgess SC. The effects of short-term fasting on liver and skeletal muscle lipid, glucose and energy metabolism in healthy women and men. J Lipid Res. 2012;53:577–86.
18. Robles-Flores M, Allende G, Pinat E, Garcia-Sainz JA. Cross-talk between glucagon- and adenosine-mediated signalling systems in rat hepatocytes: effects on cyclic AMP-phosphodiesterase activity. Biochem J. 1995;312:763–7.
19. Liu Y, Dentin R, Chen D, Hedrick S, Ravnskjaer K, Schenk S, Milne J, Meyers DJ, Cole P, Yates J 3rd, Olefsky J, Guarente L, Montminy M. A fasting inducible switch modulates gluconeogenesis via activator/coactivator exchange. Nature. 2008;456:269–723.
20. Dentin R, Liu Y, Koo SH, Hedrick S, Vargas T, Heredia J, Yates J 3rd, Montminy M. Insulin modulates gluconeogenesis by inhibition of the coactivator TORC2. Nature. 2007;449:366–9.
21. Jitrapakdee S. Transcription factors and coactivators controlling nutrient and hormonal regulation of hepatic gluconeogenesis. Int J Biochem Cell Biol. 2012;44:33–45.
22. Goldstein I, Baek S, Presman DM, Paakinaho V, Swinstead EE, Hager GL. Transcription factor assisted loading and enhancer dynamics dictate the hepatic fasting response. Genome Res. 2017;27:427–39.
23. Goldstein I, Hager GL. Transcriptional and chromatin regulation during fasting – the genomic era. Trends Endocrinol Metab. 2015;26:699–710.
24. Landau BR, Wahren J, Chandramouli V, Schumann WC, Ekberg K, Kalhan SC. Contributions of gluconeogenesis to glucose production in the fasted state. J Clin Invest. 1996;98:378–85.
25. Marsenic O. Glucose control by the kidney: an emerging target in diabetes. Am J Kidney Dis. 2009;53:875–83.
26. Soeters MR, Soeters PB, Schooneman MG, Houten SM, Romijin JA. Adaptive reciprocity of lipid and glucose metabolism in human short-term starvation. Am J Physiol Endocrinol Metab. 2012;303:E1397–407.
27. Stumvoll M, Meyer C, Perriello G, Kreider M, Welle S, Gerich J. Human kidney and liver gluconeogenesis: evidence for organ substrate selectivity. Am J Phys. 1998;274:E817–26.
28. Cahill GF. Fuel metabolism in starvation. Annu Rev Nutr. 2006;26:1–22.
29. Alsahli M, Gerich JE. Renal glucose metabolism in normal physiological conditions and in diabetes. Diabetes Res Clin Pract. 2017;133:1–9.
30. Bergman BC, Cornier MA, Horton TJ, Bessesen DH. Effects of fasting on insulin action and glucose kinetics in lean and obese men and women. Am J Physiol Endocrinol Metab. 2007;293:E1103–11.
31. Clore JN, Glickman PS, Helm ST, Nestler JE, Blackard WG. Accelerated decline in hepatic glucose production during fasting in normal women compared with men. Metabolism. 1989;38:1103–7.
32. Jeong JY, Jeung NH, Park KG, Lee IK. Transcriptional regulation of pyruvate dehydrogenase kinase. Diabetes Metab J. 2012;36:328–35.
33. Tia N, Singh AK, Pandey P, Azad CS, Chaudhary P, Gambhir IS. Role of Forkhead Box O (FOXO)

transcription factor in aging and diseases. Gene. 2018;648:97–105.
34. Knop FK. EJE PRIZE 2018: a gut feeling about glucagon. Eur J Endocrinol. 2018;178:R267–80.
35. Young SG, Zechner R. Biochemistry and pathophysiology of intravascular and intracellular lipolysis. Genes Dev. 2013;27:459–84.
36. Horton TJ, Hill JO. Prolonged fasting significantly changes nutrient oxidation and glucose tolerance after a normal mixed meal. J Appl Physiol. 2001;90:155–63.
37. Frühbeck G, Méndez-Giménez L, Fernández-Formoso JA, Fernández S, Rodríguez A. Regulation of adipocyte lipolysis. Nutr Res Rev. 2014;27:63–93.
38. Kaushik S, Cuervo AM. AMPK-dependent phosphorylation of lipid droplet protein PLIN2 triggers its degradation by CMA. Autophagy. 2016;12:432–8.
39. Elia M, Lammert O, Zed C, Neale G. Energy metabolism during exercise in normal subjects undergoing total starvation. Hum Nutr Clin Nutr. 1984;38:355–62.
40. Pietrocola F, Demont Y, Castoldi F, Enot D, Durand S, Semeraro M, Baracco EE, Pol J, Bravo-San Pedro JM, Bordenave C, Levesque S, Humeau J, Chery A, Métivier D, Madeo F, Maiuri MC, Kroemer G. Metabolic effects of fasting on human and mouse blood in vivo. Autophagy. 2017;13:567–78.
41. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest. 2004;113:1582–8.
42. Gjedsted J, Gormsen LC, Nielsen S, Schmitz O, Djuhuus CB, Keiding S, Orskov H, Tonesen E, Moller N. Effects of a 3-day fast on regional lipid and glucose metabolism in human skeletal muscle and adipose tissue. Acta Physiol. 2007;191:205–16.
43. Jensen MD, Chandramouli V, Schumann WC, Ekberg K, Previs SF, Gupta S, Landau BR. Sources of blood glycerol during fasting. Am J Physiol Endocrinol Metab. 2001;281:E998–1004.
44. Houten SM, Violante S, Ventura FV, Wanders RJ. The biochemistry and physiology of mitochondrial fatty acid β-oxidation and its genetic disorders. Annu Rev Physiol. 2016;78:23–44.
45. Bouwens M, Afman LA, Müller M. Fasting induces changes in peripheral blood mononuclear cell gene expression profiles related to increases in fatty acid beta-oxidation: functional role of peroxisome proliferator activated receptor alpha in human peripheral blood mononuclear cells. Am J Clin Nutr. 2007;86:1515–23.
46. Krug S, Kastenmüller G, Stückler F, Rist MJ, Skurk T, Sailer M, Raffler J, Römisch-Margl W, Adamski J, Prehn C, Frank T, Engel KH, Hofmann T, Luy B, Zimmermann R, Moritz F, Schmitt-Kopplin P, Krumsiek J, Kremer W, Huber F, Oeh U, Theis FJ, Szymczak W, Hauner H, Suhre K, Daniel H. The dynamic range of the human metabolome revealed by challenges. FASEB J. 2012;26:2607–19.
47. Indiveri C, Iacobazzi V, Tonazzi A, Giangregorio N, Infantino V, Convertini P, Console L, Palmieri F. The mitochondrial carnitine/acylcarnitine carrier: function, structure and physiopathology. Mol Asp Med. 2011;32:223–33.
48. Hasselbalch SG, Knudsen GM, Jakobsen J, Hageman LP, Holm S, Paulson OB. Blood-brain barrier permeability of glucose and ketone bodies during short-term starvation in humans. Am J Physiol Endocrinol Metab. 1995;268:E1161–6.
49. Ye Q, Wu Y, Gao Y, Li Z, Li W, Zhang C. The 'selfish brain' is regulated by aquaporins and autophagy under nutrient deprivation. Mol Med Rep. 2016;13:3842–8.
50. Bouteldja N, Andersen LT, Møller N, Gormsen LC. Using positron emission tomography to study human ketone body metabolism: a review. Metabolism. 2014;63:1375–84.
51. Owen OE, Smalley KJ, D'Alessio DA, Mozzoli MA, Dawson EK. Protein, fat, and carbohydrate requirements during starvation: anaplerosis and cataplerosis. Am J Clin Nutr. 1998;68:12–34.
52. Newman JC, Verdin E. β-hydroxybutyrate: much more than a metabolite. Diabetes Res Clin Pract. 2014;106:173–81.
53. Newman JC, Verdin E. Ketone bodies as signaling metabolites. Trends Endocrinol Metab. 2014;25:42–52.
54. Bánréti Á, Sass M, Graba Y. The emerging role of acetylation in the regulation of autophagy. Autophagy. 2013;9:819–29.
55. Markel A, Brook JG, Aviram M. Increased plasma triglycerides, cholesterol and apolipoprotein E during prolonged fasting in normal subjects. Postgrad Med J. 1985;61:395–400.
56. Sävendahl L, Underwood LE. Fasting increases serum total cholesterol, LDL cholesterol and apolipoprotein B in healthy, nonobese humans. J Nutr. 1999;129:2005–8.
57. Fainaru M, Schafer Z. Effect of prolonged fasting on plasma lipids, lipoproteins and apolipoprotein B in 12 physicians participating in a hunger strike: an observational study. Isr Med Assoc J. 2000;2:215–9.
58. Hanssen MJ, Wierts R, Hoeks J, Gemmink A, Brans B, Mottaghy FM, Schrauwen P, van Marken Lichtenbelt WD. Glucose uptake in human brown adipose tissue is impaired upon fasting-induced insulin resistance. Diabetologia. 2015;58:586–95.
59. Fazakerley DJ, Krycer JR, Kearney AL, Hocking SL, James DE. Muscle and adipose tissue insulin resistance: malady without mechanism? J Lipid Res. 2018;60(10):1720–32.. [Epub ahead of print].
60. Göschke H. Mechanism of glucose intolerance during fasting: differences between lean and obese subjects. Metabolism. 1977;26:1147–53.
61. Kume S, Kondo M, Maeda S, Nishio Y, Yanagimachi T, Fujita Y, Haneda M, Kondo K, Sekine A, Araki SI, Araki H, Chin-Kanasaki M, Ugi S, Koya D, Kitahara S, Maeda K, Kashiwagi A, Uzu T, Maegawa H. Hypothalamic AMP-activated protein kinase regulates biphasic insulin secretion from pancreatic β cells during fasting and in type 2 diabetes. EBioMedicine. 2016;13:168–80.

62. Hoeks J, van Herpen NA, Mensink M, Moonen-Kornips E, van Beurden D, Hesselink MK, Schrauwen P. Prolonged fasting identifies skeletal muscle mitochondrial dysfunction as consequence rather than cause of human insulin resistance. Diabetes. 2010;59:2117–25.
63. Frank P, Katz A, Andersson E, Sahlin K. Acute exercise reverses starvation-mediated insulin resistance in humans. Am J Physiol Endocrinol Metab. 2013;15(304):E436–43.
64. Green JG, Johnson NA, Sachinwalla T, Cunningham CW, Thompson MW, Stannard SR. Moderate-intensity endurance exercise prevents short-term starvation-induced intramyocellular lipid accumulation but not insulin resistance. Metabolism. 2011;60:1051–7.
65. Awad S, Consantin-Teodosiu D, Macdonald IA, Lobo DN. Short-term starvation and mitochondrial dysfunction – a possible mechanism leading to postoperative insulin resistance. Clin Nutr. 2009;28:497–509.
66. Henry CJ, Rivers JP, Payne PR. Protein and energy metabolism in starvation reconsidered. Eur J Clin Nutr. 1988;42:543–9.
67. Norrelund H. The metabolic role of growth hormone in humans with particular reference to fasting. Growth Horm IGR Res. 2005;15:95–122.
68. Dice JF, Finn PF. Proteolytic and lipolytic responses to starvation. Nutrition. 2006;22:830–44.
69. Adeva-Andany MM, Pérez-Felpete N, Fernández-Fernández C, Donapetry-García C, Pazos-García C. Liver glucose metabolism in humans. Biosci Rep. 2016;29(36):6.
70. Zhao J, Goldberg AL. Coordinate regulation of autophagy and the ubiquitin proteasome system by MTOR. Autophagy. 2016;12:1967–70.
71. Rabinowitz JD, White E. Autophagy and metabolism. Science. 2010;330:1344–8.
72. Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation. Essays Biochem. 2017;61:585–96.
73. Allavena G, Boyd C, Oo KS, Maellaro E, Zhivotovsky B, Kaminskyy VO. Suppressed translation and ULK1 degradation as potential mechanisms of autophagy limitation under prolonged starvation. Autophagy. 2016;12:2085–97.
74. Abu-Remaileh M, Wyant GA, Kim C, Laqtom NN, Abbasi M, Chan SH, Freinkman E, Sabatini DM. Lysosomal metabolomics reveals V-ATPase- and mTOR-dependent regulation of amino acid efflux from lysosomes. Science. 2017;358:807–13.
75. Wyant GA, Abu-Remaileh M, Frenkel EM, Laqtom NN, Dharamdasani V, Lewis CA, Chan SH, Heinze I, Ori A, Sabatini DM. NUFIP1 is a ribosome receptor for starvation-induced ribophagy. Science. 2018;360:751–8.
76. Vendelbo MH, Møller AB, Christensen B, Nellemann B, Clasen BF, Nair KS, Jørgensen JO, Jessen N, Møller N. Fasting increases human skeletal muscle net phenylalanine release and this is associated with decreased mTOR signaling. PLoS One. 2014;9:e102031.
77. Bejarano E, Cuervo AM. Chaperone-medicated autophagy. Proc Am Thorac Soc. 2010;7:29–39.
78. Kaushik S, Cuervo AM. Degradation of lipid droplet-associated proteins by chaperone-mediated autophagy facilitates lipolysis. Nat Cell Biol. 2015;17:759–70.
79. Carbone JW, Margolis LM, McClung JP, Cao JJ, Murphy NE, Sauter ER, Combs GF Jr, Young AJ, Pasiakos SM. Effects of energy deficit, dietary protein, and feeding on intracellular regulators of skeletal muscle proteolysis. FASEB J. 2013;27:5104–11.
80. Broom J, Fraser MH, McKenzie K, Miller JD, Fleck A. The protein metabolic response to short-term starvation in man. Clin Nutr. 1986;5:63–5.
81. Lee JL, Oh ES, Lee RW, Finucane TE. Serum albumin and prealbumin in calorically restricted, nondiseased individuals: a systematic review. Am J Med. 2015;128:1023.e1–22.
82. Elia M, Stubbs RJ, Henry CJ. Differences in fat, carbohydrate, and protein metabolism between lean and obese subjects undergoing total starvation. Obes Res. 1999;7:597–604.
83. Afolabi PR, Jahoor F, Jackson AA, Stubbs J, Johnstone AM, Faber P, Lobley G, Gibney E, Elia M. The effect of total starvation and very low energy diet in lean men on kinetics of whole body protein and five hepatic secretory proteins. Am J Physiol Endocrinol Metab. 2007;293:E1580–9.
84. Elia M, Martin S, Price C, Hallworth MJ, Neale G. Effect of starvation and elective surgery on hand dynamometry and circulating concentration of various proteins. Clin Nutr. 1984;2:173–9.
85. Chadwick SJ, Sim AJ, Dudley HA. Changes in plasma fibronectin during acute nutritional deprivation in healthy human subjects. Br J Nutr. 1986;55:7–12.
86. Cottingham K. Proteomics of starvation. J Proteome Res. 2006;5:2075.
87. Wang J, Zhang J, Lee YM, Koh PL, Ng S, Bao F, Lin Q, Shen HM. Quantitative chemical proteomics profiling of de novo protein synthesis during starvation-mediated autophagy. Autophagy. 2016;12:1931–44.
88. Grinspoon SK, Baum HBA, Kim V, Coggiins C, Kilbansmi A. Decreased bone formation and increased mineral dissolution during acute fasting in young women. J Clin Endocrinol Metab. 1995;80:3628–33.
89. Kueper J, Beyth S, Liebergall M, Kaplan L, Schroeder JE. Evidence for the adverse effect of starvation on bone quality: a review of the literature. Int J Endocrinol. 2015;2015:628740.
90. Zauner C, Schneeweiss B, Kranz A, Madl C, Ratheiser K, Kramer L, Roth E, Schneider B, Lenz K. Resting energy expenditure in short-term starvation is increased as a result of an increase in serum norepinephrine. Am J Clin Nutr. 2000;71:1511–5.
91. Müller MJ, Enderle J, Pourhassan M, Braun W, Eggeling B, Lagerpusch M, Glüer CC, Kehayias JJ, Kiosz D, Bosy-Westphal A. Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. Am J Clin Nutr. 2015;102:807–19.

92. Vinales KL, Schlögl M, Piaggi P, Hohenadel M, Graham A, Bonfiglio S, Krakoff J, Thearle MS. The consistency in macronutrient oxidation and the role for epinephrine in the response to fasting and overfeeding. J Clin Endocrinol Metab. 2017;102:279–89.
93. Leibel RL, Rosenbaum M, Hirsch JH. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332:621–8.
94. Silva JE, Bianco SD. Thyroid-adrenergic interactions: physiological and clinical implications. Thyroid. 2008;18:157–65.
95. Dulloo AG, Jacquet J. Adaptive reduction in basal metabolic rate in response to food deprivation in humans: a role for feedback signals from fat stores. Am J Clin Nutr. 1998;68:599–606.
96. Mansell PI, Macdonald IA. Effects of underfeeding and of starvation on thermoregulatory responses to cooling in women. Clin Sci (Lond). 1989;77:245–52.
97. Elia M. Effect of starvation and very low calorie diets on protein-energy interrelationships in lean and obese subjects lean and obese subjects. http://www.unu.edu/unupress/food2/UID07E/UID07E11.HTM. Accessed 13 May 2013.
98. Malpas PJ. Dying is much more difficult than you'd think: a death by dehydration. Perm J. 2017;21:16–148.
99. Madea B, Ortmann J, Doberentz E. Forensic aspects of starvation. Forensic Sci Med Pathol. 2016;12:276–98.
100. Kerndt PR, Naughton JL, Driscoll CE, Loxterkamp DA. Fasting: the history, pathophysiology and complications. West J Med. 1982;137:379–99.
101. Heusser P, Wolf U, Vonwiller HM, Messerli N, Laederach-Hofmann K. Nutrition with 'light and water'? In strict isolation for 10 days without food – a critical case study. Forsch Komplementmed. 2008;15:203–9.
102. Frommel D, Gautier M, Questiaux E, Schwarzenberg L. Voluntary total fasting: a challenge for the medical community. Lancet. 1984;1(8392):1451–2.
103. Runcie J, Hilditch TE. Energy provision, tissue utilization, and weight loss in prolonged starvation. Br Med J. 1974;2:352–6.
104. Wassif WS, McLoughlin DM, Vincent RP, Conroy S, Russell GF, Taylor NF. Steroid metabolism and excretion in severe anorexia nervosa: effects of refeeding. Am J Clin Nutr. 2011;93:911–7.
105. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest. 2003;111:1409–21.
106. Komaki G, Tamai H, Mori T, Nakagawa T, Mori S. Changes in serum angiotensin-converting enzyme in acutely starved non-obese patients. A possible dissociation between angiotensin-converting enzyme and the thyroid state. Acta Endocrinol. 1988;118:45–50.
107. Salgin B, Marcovecchio ML, Hill N, Dunger DB, Frystyk J. The effects of prolonged fasting on levels of growth hormone-binding protein and free growth hormone. Growth Horm IGR Res. 2012;22:76–81.
108. Goldstein JL, Zhao T-j, Li RL. Surviving starvation: essential role of the ghrelin-growth hormone axis. Cold Spring Harb Symp Quant Biol. 2011;76:121–7.
109. Kang ES, Magkos F, Sienkiewicz E, Mantzoros CS. Circulating vaspin and visfatin are not affected by acute or chronic energy deficiency or leptin administration in humans. Eur J Endocrinol. 2011;164:911–7.
110. Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul. 2009;43:157–68.
111. Mancuso P. The role of adipokines in chronic inflammation. Immunotargets Ther. 2016;23(5):47–56.
112. Friedman J. The long road to leptin. J Clin Invest. 2016;26:4727–34.
113. Cohen S, Danzaki K, MacIver NJ. Nutritional effects on T-cell immunometabolism. Eur J Immunol. 2017;47:225–35.
114. Nakamura MT, Yudell BE, Loor JJ. Regulation of energy metabolism by long-chain fatty acids. Prog Lipid Res. 2014;53:124–44.
115. Behre CJ. Adiponectin: saving the starved and the overfed. Med Hypotheses. 2007;69:1290–2.
116. Romere C, Duerrschmid C, Bournat J, Constable P, Jain M, Xia F, Saha PK, Del Solar M, Zhu B, York B, Sarkar P, Rendon DA, Gaber MW, LeMaire SA, Coselli JS, Milewicz DM, Sutton VR, Butte NF, Moore DD, Chopra AR. Asprosin, a fasting-induced glucogenic protein hormone. Cell. 2016;165:566–679.
117. Thankamony A, Capalbo D, Marcovecchio ML, Sleigh A, Jørgensen SW, Hill NR, Mooslehner K, Yeo GS, Bluck L, Juul A, Vaag A, Dunger DB. Low circulating levels of IGF-1 in healthy adults are associated with reduced β-cell function, increased intramyocellular lipid, and enhanced fat utilization during fasting. J Clin Endocrinol Metab. 2014;99:2198–207.
118. Page LC, Gastaldelli A, Gray SM, D'Alessio DA, Tong J. Interaction of GLP-1 and ghrelin on glucose tolerance in healthy humans. Diabetes. 2018;67(10):1976–85.. [Epub ahead of print].
119. Sainsbury A, Zhang L. Role of the hypothalamus in the neuroendocrine regulation of body weight and composition during energy deficit. Obes Rev. 2012;13:234–57.
120. Padilla SL, Qiu J, Nestor CC, Zhang C, Smith AW, Whiddon BB, Rønnekleiv OK, Kelly MJ, Palmiter RD. AgRP to Kiss1 neuron signaling links nutritional state and fertility. Proc Natl Acad Sci U S A. 2017;114:2413–8.
121. Galman C, Lundasen T, Kharitonenkov A, et al. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARalpha. Activation in man. Cell Metab. 2008;8:169–74.
122. Fazeli PK, Lun M, Kim SM, Bredella MA, Wright S, Zhang Y, Lee H, Catana C, Klibanski A, Patwari P, Steinhauser ML. FGF21 and the late adaptive

response to starvation in humans. J Clin Invest. 2015;125:4601–11.
123. Kliewer SA, Mangelsdorf DJ. Fibroblast growth factor 21: from pharmacology to physiology. Am J Clin Nutr. 2010;91:254S–7.
124. Cyphert HA, Alonge KM, Ippagunta SM, Hillgartner FB. Glucagon stimulates hepatic FGF21 secretion through a PKA- and EPAC-dependent posttranscriptional mechanism. PLoS One. 2014;9:e94996.
125. Johnstone AM. Fasting – the ultimate diet? Obes Rev. 2007;8:211–22.
126. Korbonits M, Blaine D, Elia M, Powell-Tuck J. Metabolic and hormonal changes during the refeeding period of prolonged fasting. Eur J Endocrinol. 2007;157:157–66.
127. Jackson JM, Blaine D, Powell-Tuck J, Korbonits M, Carey A, Elia M. Macro- and micronutrient losses and nutritional status resulting from 44 days of total fasting in a non-obese man. Nutrition. 2006;22:889–97.
128. Elia M. Effect of starvation and very low calorie diets on protein-energy interrelationships in lean and obese subjects. In: Scrimshaw N, Schurch B, editors. Protein-energy interactions. International dietary energy consultancy group, proceedings of an IDECG workshop. Lausanne: Nestle Foundation; 1991. p. 249–84.
129. Chalela JA, Lopez JI. Medical management of hunger strikers. Nutr Clin Pract. 2013;28:128–35.
130. Elliott B, Mina M, Ferrier C. Complete and voluntary starvation of 50 days. Clin Med Insights Case Rep. 2016;9:67–70.
131. Palmiere C, Tettamanti C, Augsburger M, Burkhardt S, Sabatasso S, Lardi C, Werner D. Postmortem biochemistry in suspected starvation-induced ketoacidosis. J Forensic Legal Med. 2016;42:51–5.
132. García-Guerrero J, Vera-Remartínez EJ, Hunger Strike in Prison Study Group. Collaborators episodes of voluntary total fasting (hunger strike) in Spanish prisons: a descriptive analysis. J Forensic Legal Med. 2015;34:182–6.
133. Gétaz L, Rieder JP, Nyffenegger L, Eytan A, Gaspoz JM, Wolff H. Hunger strike among detainees: guidance for good medical practice. Swiss Med Wkly. 2012;142:w13675.
134. Hutcheon DA. Malnutrition-induced Wernicke's encephalopathy following a water-only fasting diet. Nutr Clin Pract. 2015;30:92–9.
135. Kirbas D, Sutlas N, Kuscu DY, Karagoz N, Tecer O, Altun U. The impact of prolonged hunger strike: clinical and laboratory aspects of twenty-five hunger strikers. Ideggyogy Sz. 2008;61:317–24.
136. Frank LL. Thiamin in clinical practice. JPEN J Parenter Enteral Nutr. 2015;39:503–20.
137. Franck N, Gummesson A, Jernås M, Glad C, Svensson PA, Guillot G, Rudemo M, Nyström FH, Carlsson LM, Olsson B. Identification of adipocyte genes regulated by caloric intake. J Clin Endocrinol Metab. 2011;96:E413–8.
138. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. Minneapolis: University of Minnesota Press; 1950.
139. Nakamura Y, Walker BR, Ikuta T. Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction. Stress. 2016;19:151–7.
140. Elias SG, van Noord PA, Peeters PH, den Tonkelaar I, Kaaks R, Grobbee DE. Menstruation during and after caloric restriction: the 1944-1945 Dutch famine. Fertil Steril. 2007;88(4 Suppl):1101–10.
141. Hall KD. Computational model of in vivo human energy metabolism during semistarvation and refeeding. Am J Physiol Endocrinol Metab. 2006;291:E23–37.
142. Kreiger JW, Sitren HS, Daniels MJ, Langkemp-Henken B. Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta regression. Am J Clin Nutr. 2006;83:260–74.
143. Bopp MJ, Houston DK, Lenchik L, Easter L, Kritchevsky SB, Nicklas BJ. Lean mass loss is associated with low protein intake during dietary-induced weight loss in postmenopausal women. J Am Diet Assoc. 2008;108:1216–20.
144. Sukumar D, Ambia-Sobhan H, Zurfluh R, Schlussel Y, Stahl TJ, Gordon CL, Shapses SA. Areal and volumetric bone mineral density and geometry at two levels of protein intake during caloric restriction: a randomized, controlled trial. J Bone Miner Res. 2011;26:1339–48.
145. Zhou J, Zhang L, Xuan P, Fan Y, Yang L, Hu C, Bo Q, Wang G, Sheng J, Wang S. The relationship between famine exposure during early life and body mass index in adulthood: a systematic review and meta-analysis. PLoS One. 2018;13:e0192212.
146. Liu L, Xu X, Zeng H, Zhang Y, Shi Z, Zhang F, Cao X, Xie YJ, Reis C, Zhao Y. Increase in the prevalence of hypertension among adults exposed to the great Chinese famine during early life. Environ Health Prev Med. 2017;22:64.
147. de Rooij SR, van Pelt AM, Ozanne SE, Korver CM, van Daalen SK, Painter RC, Schwab M, Viegas MH, Roseboom TJ. Prenatal undernutrition and leukocyte telomere length in late adulthood: the Dutch famine birth cohort study. Am J Clin Nutr. 2015;102:655–60.
148. Kobyliansky E, Torchinsky D, Kalichman L, Karasik D. Leukocyte telomere length pattern in a Chuvash population that experienced mass famine in 1922-1923: a retrospective cohort study. Am J Clin Nutr. 2016;104:1410–5.
149. Roseboom TJ, Painter RC, van Abeelen AF, Veenendaal MV, de Rooij SR. Hungry in the womb: what are the consequences? Lessons from the Dutch famine. Maturitas. 2011;70:141–5.
150. Crichton M, Craven D, Mackay H, Marx W, de van der Schueren M, Marshall S. A systematic review, meta-analysis and meta-regression of the prevalence of protein-energy malnutrition: associations

with geographical region and sex. Age Ageing. 2019;48(1):38–48. [Epub ahead of print].
151. Batool R, Butt MS, Sultan MT, Saeed F, Naz R. Protein-energy malnutrition: a risk factor for various ailments. Crit Rev Food Sci Nutr. 2015;55:242–53.
152. Buchanan N, Moodley G, Eyberg C, Bloom SR, Hansen JD. Hypoglycemia associated with severe kwashiorkor. S Afr Med J. 1976;50:1442–6.
153. Velly H, Britton RA, Preidis GA. Mechanisms of cross-talk between the diet, the intestinal microbiome, and the undernourished host. Gut Microbes. 2017;8:98–112.
154. Becker DJ, Pimstone BL, Hansen JD, et al. Patterns of insulin response to glucose in protein- calorie malnutrition. Am J Clin Nutr. 1972;25:499–505.
155. Das BK, Ramesh J, Agarwal JK, et al. Blood sugar and serum insulin response in protein-energy malnutrition. J Trop Pediatr. 1998;44:139–41.
156. Brooks SE, Golden MH. The exocrine pancreas in kwashiorkor and marasmus. Light and electron microscopy. West Indian Med J. 1992;41:56–60.
157. Campbell JA. The morbid anatomy of infantile malnutrition in Cape Town. Arch Dis Child. 1956;31:310–3104.
158. Golden MH, Ramadath D. Free radicals in pathogenesis of kwashiorkor. Proc Nutr Soc. 1987;46:53–68.
159. Manary MJ, Leeuwenburgh C, Heinecke JW. Increased oxidative stress in kwashiorkor. J Pediatr. 2000;137:421–4.
160. Fechner A, Bohme C, Gromer S, et al. Antioxidant status and nitric oxide in the malnutrition syndrome kwashiorkor. Pediatr Res. 2001;49:237–43.
161. Tiedge M, Lortz S, Drinkgern J, et al. Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin- producing cells. Diabetes. 1997;46:1733–42.
162. Robert HJ, Geert TH, et al. Impaired glucose absorption in children with severe malnutrition. J Pediatr. 2011;158:282–7.
163. Stanfield JP, Hutt MS, Tunnicliffe R. Intestinal biopsy in kwashiorkor. Lancet. 1965;2:519–23.
164. Sullivan PB, Marsh MN, Mirkian R, Hill SM, Milla PJ, Neale G. Chronic diarrhea and malnutrition-histology of the small intestinal lesion. J Pediatr Gastroenterol Nutr. 1991;12:195–203.
165. James WP. Jejunal disaccharidase activities in children with marasmus and kwashiorkor. Response to treatment. Arch Dis Child. 1971;46:218–20.
166. James WP. Intestinal absorption in protein-calorie malnutrition. Lancet. 1968;1:333–5.
167. Gracey M, SuharjonoSunotoStone DE. Microbial contamination of the gut: another feature of malnutrition. Am J Clin Nutr. 1973;26:1170–4.
168. Badaloo AV, Forrester T, Reid M, Jahorr F. Lipid kinetic differences between children with kwashiorkor and those with marasmus. Am J Clin Nutr. 2006;83:1283–8.
169. Di Giovanni V, Bourdon C, Wang DX, Seshadri S, Senga E, Versloot CJ, Voskuijl W, Semba RD, Trehan I, Moaddel R, Ordiz MI, Zhang L, Parkinson J, Manary MJ, Bandsma RH. Metabolomic changes in serum of children with different clinical diagnoses of malnutrition. J Nutr. 2016;146:2436–44.
170. Jahoor F, Badaloo A, Reid M, Forrester T. Protein kinetic differences between children with edematous and nonedematous severe childhood undernutrition in the fed and postabsorptive states. Am J Clin Nutr. 2005;82:792–800.
171. Jahoor F, Badaloo A, Reid M, Forrester T. Sulfur amino acid metabolism in children with severe childhood undernutrition: methionine kinetics. Am J Clin Nutr. 2006;84:1400–5.
172. Horndasch S, Roesch J, Forster C, Dörfler A, Lindsiepe S, Heinrich H, Graap H, Moll GH, Kratz O. Neural processing of food and emotional stimuli in adolescent and adult anorexia nervosa patients. PLoS One. 2018;13(3):e0191059.
173. Amitani H, Asakawa A, Ogiso K, Nakahara T, Ushikai M, Haruta I, Koyama K, Amitani M, Cheng KC, Inui A. The role of adiponectin multimers in anorexia nervosa. Nutrition. 2013;29:203–6.
174. Liyanarachchi K, Ross R, Debono M. Human studies on hypothalamo-pituitary-adrenal (HPA) axis. Best Pract Res Clin Endocrinol Metab. 2017;31:459–73.
175. Monteleone AM, Monteleone P, Serino I, Amodio R, Monaco F, Maj M. Underweight subjects with anorexia nervosa have an enhanced salivary cortisol response not seen in weight restored subjects with anorexia nervosa. Psychoneuroendocrinology. 2016;70:118–21.
176. Boyar RM, Hellman LD, Roffwarg H, Katz J, Zumoff B, O'Connor J, Bradlow HL, Fukushima DK. Cortisol secretion and metabolism in anorexia nervosa. N Engl J Med. 1977;296:190–3.
177. Lechin F, van der Dijs B, Pardey-Maldonado B, Rivera JE, Baez S, Lechin ME. Anorexia nervosa depends on adrenal sympathetic hyperactivity: opposite neuroautonomic profile of hyperinsulinism syndrome. Diabetes Metab Syndr Obes. 2010;3:311–7.
178. Nedvídková J, Dostálová I, Barták V, Papezov H, Pacák K. Increased subcutaneous abdominal tissue norepinephrine levels in patients with anorexia nervosa: an in vivo microdialysis study. Physiol Res. 2004;53:409–13.
179. Bartak V, Vybiral S, Papezova H, Dostalova I, Pacak K, Nedvidkova J. Basal and exercise-induced sympathetic nervous activity and lipolysis in adipose tissue of patients with anorexia nervosa. Eur J Clin Investig. 2004;34:371–7.
180. Schorr M, Miller KK. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol. 2017;13:174–86.
181. Ziora K, Oświęcimska J, Swiętochowska E, Ziora D, Stojewska M, Suwała A, Ostrowska Z, Gorczyca P, Klimacka-Nawrot E, Lukas W, Błońska-Fajfrowska B. Assessment of serum visfatin levels in girls with anorexia nervosa. Clin Endocrinol. 2012;76:514–9.
182. Estour B, Germain N, Diconne E, Frere D, Cottet-Emard JM, Carrot G, Lang F, Galusca B. Hormonal

profile heterogeneity and short-term physical risk in restrictive anorexia nervosa. J Clin Endocrinol Metab. 2010;95:2203–10.
183. Tomasik PJ, Sztefko K, Starzyk J, Rogatko I, Szafran Z. Entero-insular axis in children with anorexia nervosa. Psychoneuroendocrinology. 2005;30:364–72.
184. Fazeli PK, Klibanski A. Effects of anorexia nervosa on bone metabolism. Endocr Rev. 2018;39(6):895–910.. [Epub ahead of print].
185. Fernández-Soto ML, González-Jiménez A, Chamorro-Fernández M, Leyva-Martínez S. Clinical and hormonal variables related to bone mass loss in anorexia nervosa patients. Vitam Horm. 2013;92:259–69.
186. Housova J, Anderlova K, Krizová J, Haluzikova D, Kremen J, Kumstyrová T, Papezová H, Haluzik M. Serum adiponectin and resistin concentrations in patients with restrictive and binge/purge form of anorexia nervosa and bulimia nervosa. J Clin Endocrinol Metab. 2005;90:1366–70.
187. Agnello E, Malfi G, Costantino AM, Massarenti P, Pugliese M, Fortunati N, Catalano MG, Palmo A. Tumour necrosis factor alpha and oxidative stress as maintaining factors in the evolution of anorexia nervosa. Eat Weight Disord. 2012;17:e194–9.
188. Kahl KG, Kruse N, Rieckmann P, Schmidt MH. Cytokine mRNA expression patterns in the disease course of female adolescents with anorexia nervosa. Psychoneuroendocrinology. 2004;29:13–20.
189. Dalton B, Bartholdy S, Robinson L, Solmi M, Ibrahim MAA, Breen G, Schmidt U, Himmerich H. A meta-analysis of cytokine concentrations in eating disorders. J Psychiatr Res. 2018;103:252–64.
190. Shimizu T, Satoh Y, Kaneko N, Suzuki M, Lee T, Tanaka K, Iijima M, Yamashiro Y. Factors involved in the regulation of plasma leptin levels in children and adolescents with anorexia nervosa. Pediatr Int. 2005;47:154–8.
191. Brambilla F, Monti D, Franceschi C. Plasma concentrations of interleukin-1-beta, interleukin-6 and tumor necrosis factor-alpha, and of their soluble receptors and receptor antagonist in anorexia nervosa. Psychiatry Res. 2001;103(2–3):107–14.
192. Karczewska-Kupczewska M, Adamska A, Nikołajuk A, Otziomek E, Górska M, Kowalska I, Strączkowski M. Circulating interleukin 6 and soluble forms of its receptors in relation to resting energy expenditure in women with anorexia nervosa. Clin Endocrinol. 2013;79(6):812–6.
193. Schalla MA, Stengel A. The role of ghrelin in anorexia nervosa. Int J Mol Sci. 2018;19(7):E2117.
194. Mikolajczak A, Oswiecimska JM, Swietochowska E, Roczniak W, Ziora KT. Serum FGF21 in girls with anorexia nervosa - comparison to normal weight and obese female adolescents. Neuro Endocrinol Lett. 2017;38:173–81.
195. Fazeli PK, Faje AT, Cross EJ, Lee H, Rosen CJ, Bouxsein ML, Klibanski A. Serum FGF-21 levels are associated with worsened radial trabecular bone microarchitecture and decreased radial bone strength in women with anorexia nervosa. Bone. 2015;77:6–11.
196. Barja-Fernández S, Folgueira C, Seoane LM, Casanueva FF, Dieguez C, Castelao C, Agüera Z, Baños R, Botella C, de la Torre R, Fernández-García J, Fernández-Real JM, Frühbeck G, Gómez-Ambrosi J, Jiménez-Murcia S, Tinahones FJ, Estivill X, Fernández-Aranda F, Nogueiras R. Circulating Betatrophin levels are increased in anorexia and decreased in morbidly obese women. J Clin Endocrinol Metab. 2015;100:E1188–96.
197. Blickle JF, Reville P, Stephan F, Meyer P, Demangeat C, Sapin R. The role of insulin, glucagon and growth hormone in the regulation of plasma glucose and free fatty acid levels in anorexia nervosa. Horm Metab Res. 1984;16:336–40.
198. Letiexhe MR, Scheen AJ, Lefèbvre PJ. Plasma leptin levels, insulin secretion, clearance and action on glucose metabolism in anorexia nervosa. Eat Weight Disord. 1997;2:79–86.
199. Swenne I, Gustafsson J. Endogenous glucose production and lipolysis in anorexia nervosa–a study using stable isotope-labelled compounds. Acta Paediatr. 2004;93:1446–8.
200. Fujii S, Tamai H, Kumai M, Takaichi Y, Nakagawa T, Aoki TT. Impaired glucagon secretion to insulin-induced hypoglycemia in anorexia nervosa. Acta Endocrinol. 1989;120:610–5.
201. Kobayashi N, Tamai H, Takii M, Matsubayashi S, Nakagawa T. Pancreatic B-cell functioning after intravenous glucagon administration in anorexia nervosa. Acta Psychiatr Scand. 1992;85:6–10.
202. Castillo M, Scheen A, Lefebvre PJ, Luyckx AS. Insulin-stimulated glucose disposal is not increased in anorexia nervosa. J Clin Endocrinol Metab. 1985;60:311–4.
203. Pannacciulli N, Vettor R, Milan G, Granzotto M, Catucci A, Federspil G, De Giacomo P, Giorgino R, De Pergola GJ. Anorexia nervosa is characterized by increased adiponectin plasma levels and reduced nonoxidative glucose metabolism. Clin Endocrinol Metab. 2003;88:1748–52.
204. Huysentruyt K, De Schepper J, Vanbesien J, Vandenplas Y. Albumin and pre-albumin levels do not reflect the nutritional status of female adolescents with restrictive eating disorders. Acta Paediatr. 2016;105:e167–9.
205. Ohwada R, Hotta M, Oikawa S, Takano K. Etiology of hypercholesterolemia in patients with anorexia nervosa. Int J Eat Disord. 2006;39:598–601.
206. Caspar-Bauguil S, Montastier E, Galinon F, Frisch-Benarous D, Salvayre R, Ritz P. Anorexia nervosa patients display a deficit in membrane long chain polyunsaturated fatty acids. Clin Nutr. 2012;31:386–90.
207. Holman RT, Adams CE, Nelson RA, Grater SJ, Jaskiewicz JA, Johnson SB, Erdman JW Jr. Patients with anorexia nervosa demonstrate deficiencies of selected essential fatty acids, compensatory changes in nonessential fatty acids and decreased fluidity of plasma lipids. J Nutr. 1995;125:901–7.

208. Zák A, Vecka M, Tvrzická E, Hrubý M, Novák F, Papezová H, Lubanda H, Veselá L, Stanková B. Composition of plasma fatty acids and non-cholesterol sterols in anorexia nervosa. Physiol Res. 2005;54:443–51.
209. Matzkin VB, Geissler C, Coniglio R, Selles J, Bello M. Cholesterol concentrations in patients with anorexia nervosa and in healthy controls. Int J Psychiatr Nurs Res. 2006;11:1283–93.
210. Rigaud D, Tallonneau I, Vergès B. Hypercholesterolaemia in anorexia nervosa: frequency and changes during refeeding. Diabetes Metab. 2009;35:57–63.
211. Schebendach J, Golden NH, Jacobson MS, Arden M, Pettei M, Hardoff D, Bauman N, Reichert P, Copperman N, Hertz S. Indirect calorimetry in the nutritional management of eating disorders. Int J Eat Disord. 1995;17:59–66.
212. Vaisman N, Rossi MF, Goldberg E, Dibden LJ, Wykes LJ, Pencharz PB. Energy expenditure and body composition in patients with anorexia nervosa. J Pediatr. 1988;113:919–24.
213. Kosmiski L, Schmiege SJ, Mascolo M, Gaudiani J, Mehler PS. Chronic starvation secondary to anorexia nervosa is associated with an adaptive suppression of resting energy expenditure. J Clin Endocrinol Metab. 2014;99:908–14.
214. Schebendach JE, Golden NH, Jacobson MS, Hertz S, Shenker IR. The metabolic responses to starvation and refeeding in adolescents with anorexia nervosa. Ann N Y Acad Sci. 1997;817:110–9.
215. Marra M, Polito A, De Filippo E, Cuzzolaro M, Ciarapica D, Contaldo F, Scalfi L. Are the general equations to predict BMR applicable to patients with anorexia nervosa? Eat Weight Disord. 2002;7:53–9.
216. Ronenn R. The pathophysiology of wasting in the elderly. J Nutr. 1999;129:256S–9.
217. Zembroń-Łacny A, Dziubek W, Rogowski Ł, Skorupka E, Dąbrowska G. Sarcopenia: monitoring, molecular mechanisms, and physical intervention. Physiol Res. 2014;63:683–91.
218. Clark BC, Manini TC. Functional consequences of sarcopenia and dynapenia in the elderly. Curr Opin Clin Nutr Metab Care. 2010;13:271–6.
219. Bautmans I, Van Puyvelde K, Mets T. Sarcopenia and functional decline: pathophysiology, prevention and therapy. Acta Clin Belg. 2009;64:303–16.
220. Thalacker-Mercer AE, Fleet JC, Craig BA, Campbell WW. The skeletal muscle transcript profile reflects accommodative responses to inadequate protein intake in younger and older males. J Nutr Biochem. 2010;21:1076–82.
221. Marzetti E, Calvani R, Bernabei R, Leeuwenburgh C. Apoptosis in skeletal myocytes: a potential target for interventions against sarcopenia and physical frailty – a mini-review. Gerontology. 2012;58:99–106.
222. Nair KS. Aging muscle. Am J Clin Nutr. 2005;81:953–63.
223. Joseph AM, Adhihetty PJ, Buford TW, Wohlgemuth SE, Lees HA, Nguyen LM, Aranda JM, Sandesara BD, Pahor M, Manini TM, Marzetti E, Leeuwenburgh C. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. Aging Cell. 2012;11:801–9.
224. Drew L. Fighting the inevitability of ageing. Nature. 2018;555(7695):S15–7.
225. Galbreath M, Campbell B, LaBounty P, Bunn J, Dove J, Harvey T, Hudson G, Gutierrez JL, Levers K, Galvan E, Jagim A, Greenwood L, Cooke MB, Greenwood M, Rasmussen C, Kreider RB. Effects of adherence to a higher protein diet on weight loss, markers of health, and functional capacity in older women participating in a resistance-based exercise program. Nutrients. 2018;10(8):pii: E1070.
226. Landi F, Calvani R, Tosato M, Martone AM, Ortolani E, Savera G, Sisto A, Marzetti E. Anorexia of aging: risk factors, consequences, and potential treatments. Nutrients. 2016;8:69.
227. Tsutsumimoto K, Doi T, Makizako H, Hotta R, Nakakubo S, Makino K, Suzuki T, Shimada H. Aging-related anorexia and its association with disability and frailty. J Cachexia Sarcopenia Muscle. 2018;9(5):834–43.. [Epub ahead of print]
228. Murphy J, Holmes J, Brooks C. Measurements of daily energy intake and Total energy expenditure in people with dementia in care homes: the use of wearable technology. J Nutr Health Aging. 2017;21:927–32.
229. Heuberger RA. The frailty syndrome: a comprehensive review. J Nutr Gerontol Geriatr. 2011;30:315–68.
230. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, Xue QL, Walston JD, Kasper JD. Frailty in older adults: a nationally representative profile in the United States. J Gerontol A Biol Sci Med Sci. 2015;70:1427–34.
231. Oakland K, Nadler R, Cresswell L, Jackson D, Coughlin PA. Systematic review and meta-analysis of the association between frailty and outcome in surgical patients. Ann R Coll Surg Engl. 2016;98:80–5.
232. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15:505–22.
233. Rusanova I, Diaz-Casado ME, Fernández-Ortiz M, Aranda-Martínez P, Guerra-Librero A, García-García FJ, Escames G, Mañas L, Acuña-Castroviejo D. Analysis of plasma MicroRNAs as predictors and biomarkers of aging and frailty in humans. Oxidative Med Cell Longev. 2018;2018:7671850.
234. Candore G, Caruso C, Colonna-Romano G. Inflammation, genetic background and longevity. Biogerontology. 2010;11:565–73.
235. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001;17:632–7.
236. Friedli N, Stanga Z, Culkin A, Crook M, Laviano A, Sobotka L, Kressig RW, Kondrup J, Mueller B, Schuetz P. Management and prevention of refeeding syndrome in medical inpatients: an evidence-based and consensus-supported algorithm. Nutrition. 2018;47:13–20.

237. Fayeulle S, Renou F, Protais E, Hedouin V, Wartel G, Yvin JL. Management of the hunger strike in prison. Presse Méd. 2010;39(10):e217–22.
238. Hearing SD. Refeeding syndrome. BMJ. 2004;328:908–9.
239. Marik E, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg. 1996;131:1043–7.
240. Ekberg KB, Landau R, Wajngot A, Chandramouli V, Efendic S, Brunengraber H, Wahren J. Contributions by kidney and liver to glucose production in the post-absorptive state and after 60 h of fasting. Diabetes. 1999;48:292–8.
241. Hill GL, Bradley JA, Bradley JA. Changes in body weight and body protein with intravenous nutrition. JPEN J Parenter Enteral Nutr. 1979;3:215–8.
242. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr. 1990;14:90–7.
243. Bloom WL. Inhibition of salt excretion by carbohydrate. Arch Intern Med. 1962;109:26–32.
244. Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. N Engl J Med. 1985;312:1035–9.
245. Drenick EJ, Joven CB, Swendseid ME. Occurrence of acute Wernicke's encephalopathy during prolonged starvation for the treatment of obesity. N Engl J Med. 1966;274:937–9.
246. Cumming AD, Farquhar JR, Bouchier IAD. Refeeding hypophosphataemia in anorexia nervosa and alcoholism. BMJ. 1987;295:490–1.
247. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, Mueller B, Schuetz P. Revisiting the refeeding syndrome: results of a systematic review. Nutrition. 2017;35:151–60.
248. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, Lobo DN. Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62:687–94.
249. Kohn MR, Golden NH, Shenker IR. Cardiac arrest and delirium: presentations of the refeeding syndrome in severely malnourished adolescents with anorexia nervosa. J Adolesc Health. 1998;22:239–43.
250. Baltasar A, Del Rio J, Escrivá C, Arlandis F, Martínez R, Serra C. Preliminary results of the duodenal switch. Obes Surg. 1997;7:500–4.
251. Mason EE. Starvation injury after gastric reduction for obesity. World J Surg. 1998;22:1002–7.
252. Rudman D, Millikan WJ, Richardson TJ, Bixler TJ 2nd, Stackhouse J, McGarrity WC. Elemental balances during intravenous hyperalimentation of underweight adult subjects. J Clin Invest. 1975;55:94–104.
253. Walike JW. Tube feeding syndrome in head and neck surgery. Arch Otolaryngol. 1969;89:533–6.
254. Holroyde CP, Myers RN, Smink RD. Metabolic response to total parenteral nutrition in cancer patients. Cancer Res. 1977;37:3109–14.
255. Meier R, Stratton RJ. Basic concepts in nutrition: epidemiology of malnutrition. Eur J Clin Nutr Metab. 2008;3:4.
256. Hise ME, Kattelmann K, Parkhurst M. Evidence-based clinical practice: dispelling the myths. Nutr Clin Pract. 2005;20:294–302.
257. Morley JE. Pathophysiology of anorexia. Clin Geriatr Med. 2002;18:661–73.
258. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, Reade MC, Harrigan PW. Refeeding syndrome trial investigators group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3:943–52.
259. Chanchal R, Gupta S, Kanta C, Singh K, Koonwar S. Hypophosphataemia in severe acute malnutrition: a prospective observational. Br J Nutr. 2018;17:1–6.

Metabolism in the Trauma Patient

6

Stacy Pelekhaty and Rosemary A. Kozar

The Metabolic Response to Trauma

Ebb and Flow

Severe injury and illness result in a complex cascade of metabolic responses that attempt to restore physiologic homeostasis in the injured organism. Sir David Cuthbertson is credited with the original recognition of the metabolic stress response in patients that suffered limb injuries. In 1942, he identified that there are two temporal physiologic categories and termed them the "ebb" and "flow" phases. The ebb phase is initiated immediately after the traumatic insult and typically persists for 24 h or less but may last as long as 72 h post injury. This phase is characterized by decreased body temperature, decreased oxygen consumption (VO_2), as well as decreased basal metabolic rate and nitrogen excretion [1]. The intended physiologic responses are aimed at reducing posttraumatic energy depletion, but this initial response is short lived.

Thereafter, the hypermetabolic, hypercatabolic "flow" phase ensues. This phase is characterized by increased oxygen consumption and energy expenditure. This results in elevations of cardiac output, body temperature, gluconeogenesis, insulin resistance, and mobilization of triglycerides from adipose stores and amino acids from skeletal muscle [2]. Skeletal muscle catabolism outpaces protein deposition, resulting in negative nitrogen balance [3]. This process peaks several days after injury, and the duration is determined by the severity of the inciting stress event. If homeostasis is not achieved, multiple organ failure can develop. This is perhaps a simplified version of the cellular sequence of events that ultimately leads to a cascade of complex reactions, each inciting further autocrine and paracrine reactions.

A more contemporary perspective proposed the following three classifications of phenotypes related to the injury response: the ischemia/reperfusion phenotype, the leukocytic phenotype, and the angiogenic phenotype [4]. The first phenotype represents the nervous system-related alteration in response to injury. Afferent nerve signals from the site of injury result in humoral and neuronal responses and edema. This phase regulates the metabolic supply to cells by diffusion. The leukocytic phenotype is characterized as an intermediate phase of the response to trauma. In this phenotype, leukocytes and bacteria infiltrate edematous, injured tissues. The anaerobic environment results in shock, and hypercatabolism and hypermetabolism lead to the hyperdynamic response including hyperthermia, increased oxygen consumption, glycogenolysis, lipolysis,

S. Pelekhaty
Department of Clinical Nutrition, University of Maryland, Baltimore, MD, USA

R. A. Kozar (✉)
Department of Surgery, University of Maryland School of Medicine, Program in Trauma, Baltimore, MD, USA
e-mail: RKozar@som.umaryland.edu

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_6

proteolysis, and futile substrate cycling. The third angiogenic phenotype is the late phase and is characterized by a return of oxidative metabolism with resultant angiogenesis, tissue repair, and regeneration.

Recently, a theory of the metabolic response to stress based on mitochondrial function was proposed. In this theory, the early phase of critical illness is characterized by mitochondrial dysfunction. Provision of full nutrition needs in early critical illness exceeds mitochondrial capacity, leading to electron leak, mitochondrial rupture, cell apoptosis, and necrosis, which perpetuate the inflammatory cascade through the production of reactive oxygen and nitrogen species. Research is in progress to identify markers of the metabolic phase as each metabolic phase presents unique nutritional challenges and requires customized interventions [5].

Catabolic Response to Trauma

Traumatic injury induces inflammatory and hormonal responses that change metabolic processes and alter nutrition requirements. The metabolic response results in hormone-mediated mobilization of endogenous substrates that leads to stress catabolism. Although initially beneficial, prolonged inflammation, hypermetabolism, and catabolism induce clinical complications, delay recovery, and increase morbidity. Unmitigated stress metabolism has been associated with severe complications related to hyperglycemia, hypoproteinemia, and immunosuppression. Proper metabolic support is essential to restore homeostasis and ensure survival [6].

During the catabolic stage, metabolic changes are best understood as a redistribution of macronutrients from labile reserves to more active tissues for host defense, visceral protein synthesis, and heat production. Hyperglycemia is due to increased hepatic glucose production and peripheral insulin resistance in skeletal muscle. Lipid metabolism increases and results in fatty acid recycling, hypertriglyceridemia, increased lipolysis, and hepatic steatosis. The fatty acids liberated provide an energy source for cardiac and skeletal muscle as well as the liver and additional tissues. Skeletal muscle catabolism releases amino acids for repair of damaged tissues and energy metabolism but results in depletion of lean body mass. Hepatic protein synthesis shifts to production of acute phase reactants [2].

Significant basal metabolic rate elevations have been demonstrated in patients following acute trauma and burn injury [6]. Inflammatory, hormonal, and stress signaling mechanisms drive this hypermetabolic response including elevations of circulating catecholamines, glucocorticoids, and glucagon. Patients with major injuries that do not receive adequate nutrition can develop cumulative caloric and protein deficits leading to malnutrition of acute illness and increased incidence of infection and organ failure. Nutritional support may prevent this cascade of events from leading to MOF and death.

As homeostasis is restored, inflammatory processes are downregulated, and many patients move from the hypermetabolic, hypercatabolic phase of metabolism into the anabolic or convalescent phase of stress metabolism. In this phase, metabolic processes return to baseline, and patients are able to regain strength or lean body mass lost during critical illness. A subset of patients, however, demonstrate sustained inflammation and stress metabolism and do not progress into the anabolic phase [7].

The Cytokine Response to Trauma

Trauma induces a rapid immune response in an attempt to repair damaged elicited from the traumatic injury. Following severe injury, this response can involve the release of pathogen-associated molecular patterns (PAMPs) from "non-self" infectious agents such as bacteria, along with "self" release of damage-associated molecular patterns (DAMPs) [8]. This ideally results in a balance between pro-inflammatory and anti-inflammatory cytokines and has been referred to as the mixed antagonistic response syndrome or MARS [9]. This marked response is

designed to clear the DAMPs and PAMPs and begin the process of tissue repair. However, if the balance of these two systems is disturbed, the inflammatory response becomes systemic and deregulated as can occur with severe injury or hemorrhage. The result is whole-body activation of the inflammatory response, with subsequent disruption of normal cellular metabolism and microcirculatory perfusion. Both of these responses, if unchecked, can result in complications, such as multiple organ failure (MOF) and secondary infections. At the site of injury, endothelial cells and leukocytes coordinate the local release of mediators of the inflammatory response, including cytokines interleukins, interferons, leukotrienes, prostaglandins, nitric oxide, reactive oxygen species, and products of the classic inflammation pathway. It is this functional biologic response that becomes unregulated with a "cytokine storm" ensuing, leading to further injury. Cytokines predictive of multiple organ failure after trauma patients include inducible protein (IP)-10, macrophage inflammatory protein (MIP)-1B, interleukin (IL)-10, IL-6, IL-1Ra, and eotaxin [10]. Tumor necrosis factor (TNF) has been considered one of the most potent proinflammatory cytokines identified in systemic inflammatory response syndrome (SIRS) and sepsis. Administration of TNF to experimental animals creates the hemodynamic and metabolic observations consistent with SIRS. Analysis of cytokine serum biomarkers has shown that patients with MOF show a biphasic elevation of IL-6 and significantly higher soluble TNF receptor (sTNF-R) concentrations [11]. What causes this imbalance in some patients and not others is not clear but may involve comorbid immunosuppressive diseases, epigenetics, or alterations in the microbiome, all of which can and do lead to MOF [12, 13].

Genetic variants, particularly single-nucleotide polymorphisms (SNPs), are critical determinants for individual differences in both inflammatory responses as well as clinical outcomes in trauma patients. Individuals who possess specific genetic polymorphisms in genes controlling the synthesis of cytokines or toll-like receptors (TLR) may be predisposed to excessive inflammatory response to sepsis which increases their risk for the development of MOF. For example, toll-like receptor 9 (TLR9) signaling plays an important role in the innate immune response. Trauma patients with SNPs of TLR9 have been found to have a greater responsiveness of their peripheral blood leukocytes as well as a higher risk of sepsis and multiple organ dysfunction. These functional polymorphisms involved in innate immunity predispose patients to severe infections and death [14].

Gut Hypothesis of MOF

The gut is considered an immunologically active organ and a main barrier in the burden of infection-induced systemic inflammation. Gut barrier dysfunction can occur after a variety of stressors including trauma, shock, infection, and malnutrition. After trauma, intestinal epithelial cells release DAMPS and cytokines in response to hypoxia and hypoperfusion. The breakdown of the barrier occurs with loss of tight junctions, leading to hyperpermeability. The production of gut-derived toxins and inflammatory products reaches the systemic circulation through the intestinal lymphatics or via directly via damage to intestinal cells, leading to MOF [15]. Gut-derived changes can induce distant organ injury, and gut-focused therapeutics have the potential to mitigate such injury [16].

Chronic Critical Illness and Persistent Inflammation, Catabolism, and Immune Suppression

Moore and colleagues demonstrated that MOF follows a bimodal distribution that may be initiated by trauma, burns, infection, or inflammation [17]. Early MOF was defined as organ failure that developed within 72 h of the initial diagnosis of sepsis and late MOF as organ failure that developed after 72 h. Since that time, a more contem-

porary pattern has been described by Shepherd et al. in injured patients to include early multiple organ dysfunction syndrome (MODS), defined as lasting less than 7 days, or prolonged MODS, defined as lasting more than 7 days [18]. MODS was defined as a Sequential Organ Failure Assessment (SOFA) score of greater than five during the first 7 days of admission post trauma. The authors found that of those patients progressing to MODS, approximately 60% occurred early. Interestingly, organ dysfunction in both groups peaked within the first 2 days of admission. In those with prolonged MODS, organ dysfunction was more severe and by definition lasted longer. This group of patients also had a higher incidence of infection and mortality.

The concept of prolonged MODS has expanded to now include both chronic critical illness (CCI) and persistent inflammation and immunosuppression (PICS) [19]. CCI is defined as ≥14 days in the ICU with ongoing multisystem organ dysfunction and may be experienced in up to half of patients with sepsis. Patients with CCI exhibit ongoing inflammation, protein catabolism, and alterations in immune function. An estimated 30–50% of these patients are unable to return to metabolic homeostasis and instead demonstrate ongoing, smoldering inflammation associated with ongoing catabolism, infectious recidivism, and indolent death characteristic of PICS. Research suggests that repeat triggers of stress metabolism are a significant risk factor for progression into CCI and PICS [20].

The metabolic changes which lead to CCI and PICS are an area of expanding research. Current understanding of the pathophysiology of CCI and PICS begins with the production of myeloid-derived suppressor cells (MDSCs) early after injury, while tissue damage results in the release of DAMPs, both of which have pro-inflammatory, immune-suppressive actions. DAMPs released by skeletal muscle damage and catabolism appear to contribute to persistent inflammation, leading to further muscle catabolism. In addition to skeletal muscle, the renal tubule epithelial cells appear to be the largest producers of DAMPs. Once initiated, these pathways appear to be self-propagating [7, 20].

Neuroendocrine Response to Trauma

Part of the initial response to injury is the stimulation of the hypothalamic–pituitary–adrenal axis. Immediately following injury, afferent neural signals are sent to the hypothalamus, which releases vasopressin, also known as antidiuretic hormone, and corticotropin-releasing hormone. Vasopressin stimulates aquaporin channel insertion into the renal tubule. These channels result in the reabsorption of water back in the systemic circulation and act to conserve hydration and blood pressure in the setting of hypotension. Pain alone can stimulate the release and effects of vasopressin [21].

The hypothalamus signals the pituitary to release adrenocorticotropic hormone (ACTH) and growth hormone (GH). Increased GH results in propagation of insulin-like growth factors. Signaling via these effectors regulates catabolism by increasing protein synthesis, reducing protein catabolism, and promoting lipolysis. GH promotes hyperglycemia by stimulating glycogenolysis and through anti-insulin effects [22].

The adrenal cortex is stimulated to release cortisol by ACTH. Cortisol is a catabolic hormone that mobilizes energy stores to prepare the body for the "fight-or-flight" response. Cortisol increases hepatic gluconeogenesis and mobilizes skeletal muscle proteins and triglycerides stored in adipocytes to provide substrate for gluconeogenesis. The normal feedback inhibitory mechanisms fail due to stress, and an unregulated, hyper-response characterized by hyperglycemia and negative nitrogen balance occurs. Hyperglycemia reduces the rate of wound healing, increases the incidence of infections, and may contribute to sepsis, ischemia, and death [21].

While hyperglycemia has been associated with poor outcomes in patients with critical illness, the ideal goal glucose level remains unclear. Hyperglycemia could reflect an adaptive response to critical illness, or it could induce complications and therefore contribute to adverse outcomes. In 2001, Van Den Berghe et al. found that maintaining a blood glucose level at or below

110 mg/dl reduced mortality of critically ill patients in the surgical intensive care unit [23, 24]. Subsequent studies revealed that this strict glucose control was associated with episodic hypoglycemia, which similarly negatively affected patient outcomes [25]. The NICE-SUGAR trial found that intensive glucose control increased mortality among adults in the intensive care unit (ICU). The Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition guidelines for nutrition care of critically ill adults currently recommend a target blood glucose of 140 or 150 to 180 mg/dL to minimize the adverse effects of both hyper- and hypoglycemia [26].

In traumatic brain-injured patients, hyperglycemia is indicative of the severity of injury. In this subset of trauma patients, the mechanism for poor outcomes is associated with the conversion to anaerobic metabolism after acute injury. This results in a buildup of brain tissue lactic acid which leads to secondary brain injury. Research has demonstrated that severe hyperglycemia following traumatic brain injury is associated with poorer outcomes, including increased mortality, irrespective of severity of injury [27, 28]. On the other hand, intensive glucose control in this population also does not improve outcomes [29].

As continuous glucose monitoring technology improves and research continues to evolve, the optimal blood glucose for critically ill adults, especially those with traumatic brain injuries, can be anticipated to change.

Nutrition Support in the Trauma Patient

Once an association between MOF and persistent hypermetabolism was realized, it was proposed that early administration of exogenous substrates to meet the increased metabolic demands would slow the development of acute protein malnutrition and improve patient outcomes. In the early 1970s, enteral nutrition (EN) was initially favored as it was inexpensive and readily available. In the 1980s, parenteral nutrition (PN) became more available, and EN was delayed until the gastrointestinal tract was clearly functioning. Early PN practices such as overfeeding and suboptimal central line care resulted in increased complications such as hyperglycemia and infectious morbidity. Over the 1990s, more data emerged supporting the relationship between nutrition support, gut function, and MOF. This resulted in a shift in practice favoring early EN and reducing use of PN. Recent research suggests that PN guided by modern principles of line management, sterile compounding, and avoidance of overfeeding has reduced complication risk compared with early PN practices [30]. Nutrition support continues to be provided preferentially as EN due to both cost and positive effects on gut function and immunity. Additionally, a number of studies in the severely injured patient have substantiated the positive effect of EN with regard to decreased infections, shorter hospital stays, and improved overall outcomes [31, 32].

Nutrition Assessment

Nutritional assessment in the ICU population should begin with a thorough history and physical exam focused on identifying clinical signs of malnutrition. Indicators of malnutrition include recent unintentional weight loss, poor oral intake, and evidence of muscle and/or fat wasting on palpation [33]. Nutrition-focused physical exam may be impaired by the presence of fluid accumulation. The use of bedside ultrasound or review of CT imaging obtained for injury assessment may provide additional methods of determining baseline nutrition status [34, 35]. Preexisting malnutrition and severity of injury combine to determine nutrition risk. Validated tools such as the Nutrition Risk in the Critically Ill (NUTRIC) score may also be used to stratify patients based on nutrition risk, as patients at higher nutrition risk derive the most benefit from early nutrition interventions, while those at low nutrition risk may not [26].

Current clinical status may influence not only nutrition risk but also nutrition interventions. Nutrition support should be provided appropriate to the patient's metabolic phase. Hypocaloric

feeding is most appropriate while the patients remain in the early hypometabolic ebb phase, while isocaloric, high protein feeding best supports patients in the hypermetabolic, hypercatabolic flow phase. While EN is the preferred method of nutrition support, the overall hemodynamic status of the patient must be taken into consideration to reduce the risk of nonocclusive ischemic bowel, a rare but potentially fatal complication of EN [36]. Nutrition support should be delayed during active resuscitation and initiated once hemodynamic stability is obtained. The NUTRIREA-2 study demonstrated increased rates of nonocclusive ischemic bowel in patients with shock who received early EN on high-dose vasoactive support with a median dose of 0.5 mcg/kg/min norepinephrine equivalents [37]. However, vasoactive support is not an absolute contraindication to EN with retrospective studies demonstrating no increase in complications in enterally fed patients receiving moderate vasoactive support [38, 39].

For patients with abdominal trauma, bowel discontinuity is an absolute contraindication to enteral nutrition. However, enteral nutrition is associated with improved outcomes when started early after gastrointestinal surgery requiring anastomosis [40]. Early postoperative oral feeding has been shown to be safe for gastrointestinal surgery patients, leading to its incorporation into Enhanced Recovery after Surgery (ERAS) protocols to reduce postoperative ileus and shorten length of stay [41, 42]. Additionally, patients with open abdomens who receive enteral nutrition appear to have similar or improved outcomes to those who are left without nutrition or receive parenteral nutrition [43].

Estimating Nutrition Needs

The catabolic response to injury increases caloric requirements in the trauma patient due to increased metabolism. The increase in energy needs above baseline is dependent upon the nature and severity of trauma, with burn patients demonstrating increases up to 80% above normal [44]. Indirect calorimetry remains the most reliable method for determining energy expenditure in critically ill adults; however, this resource is not available at all institutions. Additionally, the reliability of indirect calorimetry is negatively impacted by renal replacement therapy, FiO_2 >60%, peak end-expiratory pressure >12 mm H_2O, provision of exogenous bicarbonate, tachypnea, recent painful procedures or patient stimulation, and recent changes in nutrition or mechanical ventilation [45]. Indirect calorimetry, if available, should be completed periodically as a patient's condition changes, to ensure that nutrition support is still providing an appropriate amount of energy to support metabolic demand. In the absence of indirect calorimetry, nutrition practitioners rely on predictive equations that range from simplistic kilocalories/kg of body weight to complicated equations incorporating sex, age, weight, height, minute ventilation, and maximum temperature within the past 24 h. Predictive equations are prone to errors, and many are biased toward overestimation of energy expenditure and validated in single-center studies with limited enrollment of traumatically injured patients. The energy needs of obese patients are particularly difficult to estimate, and the best performing predictive equations estimate energy expenditure within 10% of measured energy expenditure roughly 70% of the time [46].

Similar to energy needs, protein requirements vary based on the severity of injury. The 2016 SCCM/A.S.P.E.N. guidelines recommend 1.2–2 g protein/kg/day for nonobese, critically ill adults and further state that traumatically injured adults may benefit from increased protein delivery of 1.5–2 g/kg/day. Dickerson and colleagues found that patients who received 2–2.5 g/kg/day demonstrated improved nitrogen balance results without complications such as azotemia [47]. Extracorporeal support, such as continuous renal replacement therapy or extracorporeal membrane oxygenation, also appears to increase protein needs beyond general critical illness [26, 48]. Optimal nutrition delivery for patients with a

body mass index (BMI) ≥30 kg/m^2 remains controversial; however, using ideal body weight (IBW) to dose protein may ensure adequate protein delivery while avoiding overfeeding. Guidelines recommend providing ≥2 g protein/kg IBW for patients with a BMI 30–40 kg/m^2 and ≥2.5 g protein/kg IBW for patients with a BMI >40 kg/m^2 [26].

Potential Modulators of Metabolism

Arginine and glutamine are conditionally essential nutrients in states of serious illness or injury with roles in enterocyte function, nucleotide synthesis, immune function, wound healing, and antioxidant pathways [49]. A 2002 meta-analysis examining the results of enteral glutamine supplementation in critically ill patients noted a modest treatment effect [50]. Large, multicenter randomized control trials, however, demonstrated limited benefit and higher mortality rates in medical ICU patients and those with multisystem organ failure who received glutamine supplementation [51, 52].

Fish oil contains a high concentration of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Inclusion of EPA and DHA in nutrition regimens may reduce inflammatory mediators and improve immune function, exerting a positive effect on infectious morbidity [49].Additionally, it is theorized that EPA and DHA may improve neurological recovery following traumatic brain injury [53].

Immune-enhancing enteral nutrition formulations contain therapeutic levels of arginine, and fish oils provide EPA and DHA. These formulations often contain higher levels of antioxidant micronutrients such as zinc, selenium, and vitamin C and may contain nucleotides for their role in T-lymphocyte function. Glutamine-supplemented formulas are no longer commercially available, although enteral supplementation with glutamine modulators may be considered in severe trauma or burn patients without multisystem organ failure [26]. Immune-enhancing enteral nutrition should be considered in patients with traumatic brain injury or severe multitrauma and postsurgical critical illness. Medical ICU patients should not routinely receive immune enhancing nutrition [26].

CCI and PICS present new challenges which may be amenable to nutrition-related interventions. Early enteral nutrition with fish oil and arginine-supplemented formulas may improve systemic inflammation and prevent arginine deficiency resulting from arginase-1 upregulation by immature lymphocytes [54] Nutrients such as B vitamins, carnitine, and choline may offer opportunities to support normal mitochondrial function; however, optimal timing, dosing, and anticipated patient benefits have yet to be established. Anabolic steroids have been proposed as an intervention for patients with PICS. Oxandrolone, a testosterone analogue with high anabolic effect and low risk, has been studied in burn patients and has demonstrated benefit in both the acute and subacute phases following injury [55–59]. During the acute phase in adults, oxandrolone appears to reduce lean body mass catabolism and blunt hypermetabolism, resulting in reduced weight loss with retained skeletal muscle. Oxandrolone may be beneficial in critically ill trauma patients; however, it has not been thoroughly studied. Two small, single-center studies have investigated oxandrolone during acute hospitalization for trauma or surgical critical illness. Those who received oxandrolone demonstrated reduced urinary nitrogen excretion and less negative nitrogen balance; however, these differences did not reach statistical significance, possibly related to small sample size [60, 61]. In a study of mechanically ventilated, surgical ICU patients, those who received oxandrolone had longer durations of mechanical ventilation and increased reintubation rates [61]. As oxandrolone blunts the hypermetabolic response to stress, it may increase the risk of overfeeding and its associated complications, which may explain these results. Additional research is needed to determine the optimal patient, dosage, timing, and duration of anabolic therapy.

Nutritional Challenges in the Trauma Patient

Once nutrition support has been initiated, it is important to perform routine monitoring to assess the adequacy of the nutrition support being delivered and make modifications when necessary. Evidence clearly shows that ICU patients are significantly underfed [62]. Trauma patients face multiple barriers to adequate oral and enteral nutrition delivery including operating room trips, interventional radiology procedures, travelling for imaging, and impaired tolerance from ileus, which results in significant energy and protein deficits [63]. Reduced fasting protocols and volume-based feeding strategies have demonstrated improvements in nutrition delivery without increases in complications for patients receiving enteral nutrition [64–66]. Intraoperative enteral nutrition infusion has been reported to be safe in burn patients [67]. Patients with abdominal trauma or traumatic brain injury are at highest risk for inadequate nutrition delivery [68].

Supplemental parenteral nutrition may be required for patients who are unable to tolerate >60% of their goal enteral nutrition over the first week of critical care or reach at least 80% of their goal enteral nutrition infusion rate [26]. Additionally, early supplemental or total parenteral nutrition should be considered in high nutrition risk patients, especially those with preexisting malnutrition and in whom interruptions or delays to enteral nutrition are anticipated. The TOP UP (A Randomized Trial of Supplemental Parenteral Nutrition in Under and Over Weight Critically Ill Patients) pilot study demonstrated an increased nutrition adequacy over the first week of critical illness when enteral nutrition was combined with early supplemental parenteral nutrition. These improvements in nutrition adequacy were associated with trends toward improvements in functional outcomes [69]. Parenteral nutrition should not be interrupted for operations, procedures, or travel off the unit.

Monitoring the Response to Nutritional Supplementation

Numerous diagnostic tests have been investigated for their ability to assess the impact of nutritional care. These include body weight, body composition testing (bioelectrical impedance analysis, dual X-ray absorptiometry, skin folds, CT imaging, and ultrasound) and laboratory testing (urine analysis, visceral proteins, etc.). Changes in weight during the initial period of critical illness often reflect changes in fluid status rather than changes in body weight or composition. Additionally, body composition testing, especially with bioelectrical impedance analysis or skin folds testing, is negatively impacted by changes in fluid status.

Serum proteins have been relied on historically to help assess nutritional adequacy; however, the limitations of these biomarkers often outweigh the benefit until stress metabolism is resolved. The body reprioritizes hepatic protein synthesis away from constitutive proteins such as prealbumin to acute-phase reactants such as C-reactive protein (CRP). Additionally, prealbumin levels may be increased in patients with renal failure or in patients receiving corticosteroids and decreased in pregnant patients or those with liver disease. Albumin is a reliable measure of long-term nutrition status in community-dwelling patients, including those on dialysis; however, it has a long half-life and is unreliable in patients who are dehydrated or fluid overloaded. In light of these limitations, the 2016 SCCM, A.S.P.E.N. guidelines do not recommend routine visceral protein monitoring in critically ill adults, and altered visceral protein levels are not sufficient to diagnose malnutrition [26, 33].

Nitrogen balance studies can help assess the adequacy of protein provision by comparing nitrogen from protein intake to nitrogen excretion over a 24-h period. Urine urea nitrogen combined with standard factors for insensible losses is used as a reliable proxy for protein excretion.

Nitrogen equilibrium is defined as −2 to +2 gm/day. The reliability of nitrogen balance results is negatively affected by renal failure requiring renal replacement therapy, significant changes in blood urea nitrogen, unquantifiable nitrogen losses from wound or drain output, low urine output, or malabsorptive diarrhea [70]. When assessing nitrogen balance, it is important also to be aware of the amount of energy provided in a 24-h period. Use of radioisotopically labeled phenylalanine may provide better understanding of protein uptake by tissues; however, it is not available at all institutions [71]. If adequate protein is provided in the setting of inadequate energy delivery, nitrogen balance may also be negative due to shuttling of protein into gluconeogenesis. Persistent catabolism as evidenced by ongoing elevated urine urea nitrogen despite improving clinical status may be an early marker of PICS and may help identify patients who would benefit from anabolic steroid therapy.

Critically Injured Elderly

Critically injured elderly patients and their metabolic requirements represent a unique set of problems. Malnutrition is more common among the elderly compared to younger patients and is associated with poor outcome. The reported incidence of malnutrition in the elderly ranges from 1% to 5% in the community setting but up to 20% in the hospitalized elderly [72–74]. Many elderly are presenting malnourished at the time of injury and are thus at higher risk than younger patients. Additionally, the elderly have lower muscle mass and are at risk for further loss after injury. Maintaining muscle mass is important for sustaining key metabolic processes such as glucose homeostasis and immune function. When differences between elderly and non-elderly trauma patients were examined using an international database [75], the elderly were found to have similar BMIs compared to younger patients. Interestingly, only 2% of the elderly were underweight, similar to younger patients, while 54.4% were overweight or obese. Despite similar BMIs, elderly trauma patients were prescribed fewer calories and protein than younger patients. Both groups had low nutritional adequacy.

Sarcopenia, or low muscle mass, is also associated with worse outcomes in critically ill surgical patients [76–78]. Importantly, sarcopenia increases with advanced age, as does the incidence of postoperative complications. A report by Sheetz et al. demonstrated that sarcopenia was associated with high payer costs and negative margins after major surgery [79]. A number of modalities have been used to calculate muscle mass, including X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). Although DXA may be ideal for whole-body composition analysis, the use of CT scanning is more applicable for the trauma patient as CT scans are frequently performed at the time of injury [80, 81]. Single-slice CT images of the psoas muscle in the 3rd lumbar region can predict whole body muscle and adipose tissue volume in healthy [82] and disease [83] populations.

In a study of severely injured elderly patients admitted to the ICU, 71% were sarcopenic based on admission CT scans [84]. Importantly, patients identified as sarcopenic had significantly increased mortality and decreased ventilator-free and ICU-free days. Interestingly, despite the frequency of sarcopenia in this population, 7% of the patients were underweight, while 37% were normal weight and 57% were overweight/obese by body mass index. Neither BMI nor serum albumin on admission was predictive of survival, ventilator-free days, or ICU-free days. This study suggests that at-risk patients may be overlooked using traditional indicators of nutritional status such as weight and body mass index. In a subsequent study by Leeper et al., sarcopenia was the strongest predictor of out-of-hospital mortality in a cohort of injured elderly [85]. More recently,

Wallace et al. used masseter muscle thickness to diagnose sarcopenia in injured elderly and found it to be equally valid [86]. Muscularity therefore represents a potential new marker for risk of mortality and increased length of stay but more importantly may allow the early identification of patients who may benefit from aggressive nutritional and rehabilitative interventions.

Given the impact of ICU-acquired muscle weakness on clinical outcomes, recent research has focused on noninvasive methods to measuring muscle thickness. Although CT scanning is accurate and scans are typically available for trauma patients, calculation of muscle mass using CT scans is time-consuming and not universally available. Additionally, a noninvasive tool to be able to follow critically injured and ill patients over time in the ICU could prove valuable. The use of ultrasound to measure the rectus femoris muscle thickness has been proposed [87, 88]. In normal healthy volunteers, there was excellent intra- and inter-reliability in the US measurements of the rectus femoris [89]. Further evaluation of this technique is required to evaluate the validity and clinical utility in critically ill patients. The use of muscle-specific ultrasound is being tested and may make this a valid technique in this patient population [90].

References

1. Simsek T, Simsek HU, Canturk NZ. Response to trauma and metabolic changes: posttraumatic metabolism. Ulus Cerrahi Derg. 2014;30(3):153–9. https://doi.org/10.5152/UCD.2014.2653.
2. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):21S–9S. https://doi.org/10.1177/0148607113496117.
3. Wolfe RR. The 2017 Sir David P Cuthbertson lecture. Amino acids and muscle protein catabolism in critical care. Clin Nutr. 2017;37(4):1093–100. https://doi.org/10.1016/j.clnu.2017.12.010.
4. Aller MA, Arias JI, Alonso-Poza A. A review of metabolic staging in severely injured patients. Scand J Trauma Resusc Emerg Med. 2010;18(27). https://doi.org/10.1186/1757-7241-18-27.
5. McKeever L, Bonini M, Braunschweig C. Feeding during phases of altered mitochondrial activity: a theory. JPEN J Parenter Enteral Nutr. 2018;42(5):855–63. https://doi.org/10.1102/jpen.1010.
6. Preiser JC, Ichai C, Orban JC, Groeneveld ABJ. Metabolic response to the stress of critical illness. Br J Anaesth. 2014;113(6):945–54. https://doi.org/10.1093/bja//aeu187.
7. Hawkins RB, Raymond SL, Stortz JA, et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. Front Immunol. 2018;9:1511. https://doi.org/10.3389/fimmu.2018.01511.
8. Huber-Lang M, Lambris JD, Ward PA. Innate immune responses to trauma. Natu Immunol. 2018;19(4):327–41. https://doi.org/10.1038/s41590-018-0064-8.
9. Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. Crit Care Clin. 2000;16(2):337–352, vii.
10. Jastrow KM 3rd, Gonzalez EA, McGuire MF, Suliburk JW, Kozar RA, Iyengar S, et al. Early cytokine production risk stratifies trauma patients for multiple organ failure. J Am Coll Surg. 2009;209(3):320–31. https://doi.org/10.1016/j.jamcollsurg.2009.05.002.
11. Maier B, Lefering R, Lehnert M, Lefering R, Lehnert M, Laurer HL, et al. Early versus late onset of multiple organ failure is associated with differing patterns of plasma cytokine biomarker expression and outcome after severe trauma. Shock Augusta Ga. 2007;28(6):668–74.
12. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–55.
13. Mundy LM, Doherty GM. Inflammation, infection, & antimicrobial therapy. In: Current diagnosis and treatment: surgery. 13th ed. New York: McGraw-Hill; 2010.
14. Gordy S, Schreiber MA. Common problems in acute care surgery: multiple organ failure. Heidelberg: Springer; 2013.
15. Deitch EA. Gut-origin sepsis: evolution of a concept. Surg J R Coll Surg Edinb Irel. 2012;10(6):350–6. https://doi.org/10.1016/j.surge.2012.03.003.
16. Peng Z, Ban K, LeBlanc A, Kozar RA. Intraluminal tranexamic acid inhibits intestinal sheddases and mitigate gut and lung injury and inflammation in a rodent model of hemorrhagic shock. J Trauma Acute Care Surg. 2016;81(2):358–65.
17. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lesotte DC. Postinury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40(4):501–10.
18. Shepherd JM, Cole E, Brohi K. Contemporary patterns of multiple organ dysfunction in trauma. Shock. 2017;47(4):429–35.
19. Gentile LF, Cuenca AG, Efron PA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501. https://doi.org/10.1097/TA.0b013e318256e00.

20. Mira JC, Brakenridge SC, Moldawer LL, Moore FA. Persistent inflammation, immunosuppression and catabolism syndrome (PICS). Crit Care Clin. 2017;33(2):245–58. https://doi.org/10.1016/j.ccc.2016.12.001.
21. Krepska A, Hastings J, Roodenburg O. The metabolic and endocrine response to trauma. Anaesth Intensive Care Med. 2017;18(8):414–7. https://doi.org/10.1016/j.mpaic.2017.05.007.
22. Kozar R, Schwartz DA. Nutrition in the surgical patient. In: Common problems in acute care surgery, vol. 1. New York: Springer; 2013. p. 119–29.
23. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67. https://doi.org/10.1056/NEJMoa011300.
24. Vanhorebeek I, Langouche L, Van den Berghe G. Tight blood glucose control: what is the evidence? Crit Care Med. 2007;35(9 Suppl):S496–502. https://doi.org/10.1097/01.CCM.0000278051.48643.91.
25. 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(13):1283–97. https://doi.org/10.1056/NEJMoa0810625.
26. McClave SA, Taylor BE, Martindale RG, 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. 2016;40(2):1–53. https://doi.org/10.1177/0148607115621863.
27. Liu-DeRyke X, Collingridge DS, Orme J, Roller D, Zurasky J, Rhoney DH. Clinical impact of early hyperglycemia during acute phase of traumatic brain injury. Neurocrit Care. 2009;11(2):151–7. https://doi.org/10.1007/s12028-009-9228-6.
28. Badjatia M, Vespa P. Monitoring nutrition and glucose in acute brain injury. Neurocrit Care. 2014;21:S159–67. https://doi.org/10.1007/s12028-014-0036-2.
29. Hermanides J, Plummer MP, Finnis M, Deane AM, Coles JP, Menon DK. Glycaemic control targets after traumatic brain injury: a systematic review and meta-analysis. Crit Care. 2018;22(1):11. https://doi.org/10.1186/s13054-017-1883-y.
30. McCleary EJ, Tajchman S. Parenteral nutrition and infection risk in the intensive care unit: a practical guide for the bedside clinician. Nutr Clin Pract. 2016;31(4):476–89. https://doi.org/10.1177/0884533616653808.
31. Elke G, van Zanten ARH, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care. 2016;20:117. https://doi.org/10.1186/s13054-016-1298-1.
32. Doig GS, Heighes PT, Simpson F, Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. Injury. 2011;42(1):50–6. https://doi.org/10.1016/j.injury.2010.06.008.
33. Fischer M, JeVenn A, Hiskind P. Evaluation of muscle and fat loss as diagnostic criteria for malnutrition. Nutr Clin Pract. 2015;30:239–48. https://doi.org/10.1177/0884533615573053.
34. Paris MT, Mourtzakis M, Day A, et al. Validation of bedside ultrasound of muscle layer thickness of the quadriceps in the critically ill patient (VALIDUM study): a prospective multicenter study. JPEN J Parenter Enteral Nutr. 2017;41(2):171–80. https://doi.org/10.1177/0148607116637852.
35. Earthman CP. Body composition tools for the assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. JPEN J Parenter Enteral Nutr. 2015;39(7):787–822. https://doi.org/10.1177/0148607115595227.
36. Bruns BR, Kozar RA. Feeding the postoperative patient on vasopressor support: feeding and pressor support. Nutr Clin Pract. 2015;31(1):14–7. https://doi.org/10.1177/0884533615619932.
37. Reignier J, Boisrame-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomized, controlled, multicenter, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391(10116):133–43. https://doi.org/10.1016/S0140-6736(17)32146-3.
38. Merchan C, Altshuler D, Aberle C, Papadoulos J, Schwartz D. Tolerability of enteral nutrition in mechanically ventilated patients with septic shock who require vasopressors. J Int Care Med. 2016. https://doi.org/10.1177/0885066616656799.
39. Mancle EE, Muzevich KM. Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. JPEN J Parenter Enteral Nutr. 2013;37(5):641–51. https://doi.org/10.1177/0148607112470460.
40. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. JPEN J Parenter Enteral Nutr. 2011;35:473–87.
41. Feldheiser A, Aziz O, Baldini G, et al. Enhanced recovery after surgery (ERAS) for gastrointestinal surgery, part 2: concensus statement for anaesthesia practice. Acta Anaesthesiol Scand. 2016;60(3):289–334. https://doi.org/10.1111/aas.12651.
42. Willcutts KF, Chung MC, Erenberg CL, Finn KL, Schirmer BD, Byham-Gray LD. Early oral feeding as compared with traditional timing of oral feeding after upper gastrointestinal surgery: a systematic review and meta-analysis. Ann Surg. 2016;264(1):54–63. https://doi.org/10.1097/SLA.0000000000001644.
43. Moore SM, Burlew CC. Nutrition support in the open abdomen. Nutr Clin Pract. 2016;31(1):9–13. https://doi.org/10.1177/0884533615620420.
44. Porter C, Thompkins RG, Finnerty CC, Sidossis LS, Suman OE, Herndon DN. The metabolic stress response to burn trauma: current understanding and

therapies. Lancet. 2016;388:1417–26. https://doi.org/10.1016/S0140-6736(16)31469-6.
45. Fraipont V, Preiser JC. Energy estimation and measurement in critically ill patients. JPEN J Parenter Enteral Nutr. 2013;37(6):705–13. https://doi.org/10.1177/0148607113505868.
46. Frankenfeld D, Hise M, Malone A, Russell M, Gradwell E, Compher C. Prediction of resting metabolic rate in critically ill adult patients: results of a systematic review for the evidence. J Am Diet Assoc. 2007;107(9):1552–61. https://doi.org/10.1016/j.jada.2007.06.010.
47. Dickerson RN, Pitts SL, Maish GO 3rd, et al. A reappraisal of nitrogen requirements for patients with critical illness and trauma. J Trauma Acute Care Surg. 2012;73(3):549–57. https://doi.org/10.1097/TA.0b013e318256de1b.
48. Pelekhaty S, Galvagno SM Jr, Hochberg E, et al. Nitrogen balance during venovenous extracorporeal membrane oxygenation support: preliminary results of a prospective, observational study. JPEN J Parenter Enteral Nutr. 2018. https://doi.org/10.1002/jpen.1176. [Epub ahead of print].
49. McCarthy MS, Martindale RG. Immunonutrition in critical illness: what is the role? Nutr Clin Pract. 2018;33(3):348–58. https://doi.org/10.1002/ncp.10102.
50. Novak F, Heyland DK, Avenell A, Novak F, Drover J, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med. 2002;30:2022–9. https://doi.org/10.1097/01.CCM.0000026106.58241.95.
51. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1487–95. https://doi.org/10.1059/NEJMoa1212722.
52. Hofman A, Swinkels S, van Zanten ARH. Glutamin, fish oil and antioxidants in critical illness: MetaPlus trial post hoc safety analysis. Ann Intensive Care. 2016;6:119. https://doi.org/10.1186/s13613-016-0220-y.
53. Lewis MD. Concussions, traumatic brain injury, and the innovative use of omega-3's. J Am Coll Nutr. 2016;35(5):469–75. https://doi.org/10.1080/07315724.2016.1150796.
54. Patel JJ, Miller KR, Rosenthal C, Rosenthal MD. When is it appropriate to use arginine in critical illness? Nutr Clin Pract. 2016;31(4):438–44. https://doi.org/10.1177/0884533616652576.
55. Cochran A, Thuet W, Holt B, Fraklas I, Smout RJ, Horn SD. The impact of oxandrolone on length of stay following major burn injury: a clinical practice evaluation. Burns. 2013;39:1374–9. https://doi.org/10.1016/j.burns.2013.04.002.
56. Pham TN, Klein MB, Gibran NS, et al. Impact of oxandrolone treatment on acute outcomes after severe burn injury. J Burn Care Res. 2008;29(6):902–6. https://doi.org/10.1097/BCR.0b013e31818ba14d.
57. Dobbe L, Clapp C, Larumbe-Zabala E, Griswold J. Assessment of the impact of oxandrolone on outcomes in burn injured patients. Burns. 2019. https://doi.org/10.1016/j.burns.2018.11.001.
58. Demling RH, DeSanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. Burns. 2003;29:793–7. https://doi.org/10.1016/j.burns.2003.08.003.
59. Tuvdendorj D, Chinkes DL, Zhang XJ, et al. Long-term oxandrolone treatment increases muscle protein net deposition via improving amino acid utilization in pediatric patients 6 months after burn injury. Surgery. 2011;149(5):645–53. https://doi.org/10.1016/j.surg.2010.12.006.
60. Gervasio JM, Dickerson RN, Swearingen J, et al. Oxandrolone in trauma patients. Pharmacotherapy. 2000;20(11):1328–34.
61. Bulger EM, Jurkovich GJ, Farver CL, Klotz P, Maier RV. Oxandrolone does not improve outcome of ventilator dependent surgical patients. Ann Surg. 2004;240:472–80. https://doi.org/10.1097/01.sla.0000137131.22608.e2.
62. Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. Nutrition therapy in the critical care setting: what is "best achievable" practice? An international multicenter observational study. Crit Care Med. 2010;38(2):395–401.
63. Wade CE, Kozar RA, Dyer CB, Bulger EM, Mourtzakis M, Heyland DK. Evaluation of nutrition deficits in adult and elderly trauma patients. JPEN J Parenter Enteral Nutr. 2015; 39(4):449–55.
64. Pousman RM, Pepper C, Pandharipande P, Aers GD, Mills B, Diaz J, Collier B, Miller R, Jensen G. Feasibility of implementing a reduced fasting protocol for critically ill trauma patients undergoing operative and nonoperative procedures. JPEN J Parenter Enteral Nutr. 2009;33:176–80.
65. Taylor B, Brody R, Denmark R, Southard R, Byham-Gray L. Improving enteral delivery through the adoption of the "feed early enteral diet adequately for maximum effect (FEED ME)" protocol in a surgical trauma ICU: a quality improvement review. Nutr Clin Pract. 2014;29(5):639–48. https://doi.org/10.1177/0884533614539705.
66. Lee JC, Williams GW, Kozar RA, et al. Multitargeted feeding strategies improve nutrition outcome and are associated with reduced pneumonia in a level 1 trauma intensive care unit. JPEN J Parenter Enteral Nutr. 2018. https://doi.org/10.1177/0148607117699561.
67. Jenkins ME, Gottschlich MM, Warden GD. Enteral feeding during operative procedures in thermal injuries. J Burn Care Rehabil. 1994;15:199–205.
68. Haltmeier T, Inaba K, Schnuringer B, et al. Factors affecting the caloric and protein intake over time in critically ill trauma patients. J Surg Res. 2018;226:64–71. https://doi.org/10.1016/j.jss.2018.01.022.
69. Wischmeyer PE, Husselmann M, Kummerlen C, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. Crit Care. 2017;21(1):142. https://doi.org/10.1186/s13054-017-1736-8.

70. Dickerson RN. Using nitrogen balance in clinical practice. Hosp Pharm. 2005;40(12):1081–5. https://doi.org/10.1177/001857870504001210.
71. Kuchnia AJ, Teigen L, Nagel E, et al. Protein in the hospital: gaining perspective and moving forward. JPEN J Parenter Enteral Nutr. 2018;42(2):270–8. https://doi.org/10.1002/jpen.1068.
72. Feldblum I, German L, Castel H, Harman-Boehm I, Bilenko N, Eisinger M, et al. Characteristics of undernourished older medical patients and the identification of predictors for undernutrition status. Nutr J. 2007;6:37.
73. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med. 2002;18(4):737–57.
74. Saka B, Kaya O, Ozturk GB, Erten N, Karan MA. Malnutrition in the elderly and its relationship with other geriatric syndromes. Clin Nutr. 2010;29(6):745–8.
75. Kozar RA, Dyer C, Bulger E, Mourtzakis M, Wade CE, Heyland DK. Elderly trauma patients: highest risk, fewest calories. JPEN J Parenter Enteral Nutr. 2011;35:S26.
76. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211:271–8.
77. Lee JS, He K, Harbaugh CM, Schaubel DE, Sonnenday CJ, Wang SC, et al. Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. J Vasc Surg. 2011;53:912–7.
78. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107:931–6.
79. Sheetz KH, Waits SA, Terjimanian MN, Sullivan J, Campbell DA, Wang SC, Englesbe MJ. Cost of major surgery in the sarcopenic patient. J Am Coll Surg. 2013;217(5):813–8.
80. Di Sebastiano KM, Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. Appl Physiol Nutr Metab. 2012;37(5):811–21.
81. Ahmadinia K, Smucker JB, Nash CL, Vallier HA. Radiation exposure has increased in trauma patients over time. J Trauma Acute Care Surg. 2012;72:410–5.
82. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, Heymsfield SB, Heshka S. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97:2333–8.
83. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33:997–1006.
84. Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, Bulger E, Kozar RA. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Crit Care. 2013;17(5):R206.
85. Leeper CM, Lin E, Hoffman M, Fombona A, Zhou T, Kutcher M, Rosengart M, Watson G, Billiar T, Peitzman A, Zuckerbraun B, Sperry J. J Trauma Acute Care Surg. 2016;80(5):805–11. https://doi.org/10.1097/TA.0000000000000989.
86. Wallace JD, Calvo RY, Lewis PR, Brill JB, Shackford SR, Sise MJ, Sise CB, Bansal V. Sarcopenia as a predictor of mortality in elderly blunt trauma patients: comparing the masseter to the psoas using computed tomography. J Trauma Acute Care Surg. 2017;82(1):65–72. https://doi.org/10.1097/TA.0000000000001297.
87. Campbell IT, Watt T, Withers D, England R, Sukumar S, Keegan MA, Faragher B, Martin DF. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. Am J Clin Nutr. 1995;62(3):533–9.
88. Gruther W, Zorn BTC, Paternostro-Sluga T, Paternostro-Sluga T, Quittan M, Fialka-Moser V, et al. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. J Rehabil Med. 2008;40:185–9.
89. Tilquist M, Leung R, Kutsogiannis J, Wischmeyer P, Karvellas D, Preiser JC, Bird N, Kozar R, Heyland DK. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness in the critically ill. JPEN J Parenter Enteral Nutr. 2013;258(4):527–33.
90. Hill JC, Millan IS. Validation of musculoskeletal ultrasound to assess and quantify muscle glycogen content. A novel approach. Phys Sportsmed. 2014;42(3):45–52. https://doi.org/10.3810/psm.2014.09.2075.

Burns

7

Danielle M. Toepfer, Richard L. Gamelli, and Michael J. Mosier

The Body's Response to Burn Injury

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

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

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

Thus, providing the right balance of macro- and micronutrients, antioxidants, and energy is essential to mitigate the hypermetabolic and hypercatabolic state that results. Nutritional

D. M. Toepfer
The Oregon Burn Center, Legacy Emanuel Medical Center, Portland, OR, USA

R. L. Gamelli
Loyola Burn Center, Loyola University Chicago, and Stritch School of Medicine, Maywood, IL, USA

M. J. Mosier (✉)
The Oregon Burn Center and The Oregon Clinic, Portland, OR, USA
e-mail: mmosier@orclinic.com

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_7

support has long been and continues to be an important component of the management of severe burn injury.

Historical Perspective to Nutrition and What Has Been Practiced

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

A patient with a large burn may lose as much as 30 g of nitrogen a day because of protein catabolism. Not only is urinary excretion of urea nitrogen increased, but also large amounts of nitrogen are lost from the wound itself. Therefore, total urea nitrogen levels do not accurately reflect all nitrogen losses in burn patients [4]. A patient with a small burn (<10% TBSA) may lose nitrogen at a rate of 0.02 g/kg/day. A moderate burn (11–29% TBSA) may be associated with nitrogen losses equaling 0.05 g/kg/day. A large burn (>30% TBSA) may result in the loss of as much as 0.12 g/kg/day, which may be equivalent to daily losses of 190 g of protein or about 300 g of muscle. Thus, a highly catabolic adult patient with a large burn will typically require 2–2.5 g/kg/day of protein or greater to maintain a positive nitrogen balance. For the pediatric patient, protein intake should range from 3 to 4.5 g/kg/day for those younger than 6 and 2.5 to 3 g/kg/day in children greater than 6 years of age [5].

Catabolism generally continues until wounds have healed. However, once a patient becomes anabolic, pre-burn muscle takes three times as long to regain as it took to lose [6, 7]. Therefore, a patient in whom it takes 1 month for burn wounds and donor sites to heal may need 3 or more months to regain pre-burn weight and muscle mass. These statistics underscore the importance of accurately estimating each patient's caloric needs during hospitalization. Calculating a burn patient's energy requirements can be a challenge, as there are multiple factors that affect energy expenditure. Burn size, wound healing, and surgical wound closure are specific factors in the burn population that have an effect on total energy requirements. Indirect calorimetry (IC) has been considered to be the gold standard in determining resting energy expenditure in critically ill patients. In the critically ill burn population, it is recommended that IC is used to assess energy goals on a weekly basis [8]. Two randomized controlled trials (RCT) have shown a higher mean intake of energy and protein with IC compared to controls whose energy goals were calculated with predicative equations [9, 10]. Additionally, Singer and colleagues found a significant reduction in hospital mortality in patients that received IC-guided enteral nutrition compared to patients that received enteral nutrition determined by a weight-based formula. Unfortunately, the feasibility of IC at many institutions may be limited due to availability, cost, or ability to interpret results. While predicative and weight-based equations are less accurate due to fluctuating variables such as weight, body temperature, medications, and procedures, they are the most commonly utilized approach to calculate nutrition requirements in burn centers across the globe and offer a good guideline for how much to feed a given patient [11]. Over the years, a number of equations have been developed to estimate caloric needs and account for the increased metabolic demand post-burn injury. According to a survey of 65 burn centers, the Harris Benedict, kcal/kg, and the Curreri formulas are most commonly used [12]. Assessing the accuracy of these equations, a study comparing measured resting energy expenditure with IC to nine weight-based equations found the Milner [13], Carlson [14], and Harris Benedict [15] equations to be most similar to results from IC-measured energy expenditure [16] (Table 7.1).

Table 7.1 Equations used for estimating caloric requirements in burn patients

Adult:
Harris–Benedict
Men: [66 + (13.7 × WT) + (5 × HT) − (6.8 × Age)] × IF × AF
Women: [655 + (9.6 × WT) + (1.8 × HT) − (4.7 × Age)] × IF × AF
Carlson
BMR × [0.89142 + (0.01335 × TBSA)] × BSA × 24 × AF
Milner
[BMR × (0.274 + 0.0079 × TBSA −0.004 × PBD) + BMR] × 24 × BSA × AF
BMR basal metabolic rate in healthy, non-burned population, *HT* height in cm (inches/2.54), *WT* weight in kg, *AF* activity factor (typically 1.2–1.4), *IF* injury factor (range of 1–2.1 used after burn)
BMR (in kcal/m^2/h) as determined by the Fleisch equation (healthy population, 1951):
Men: 54.337821 – (1.19961 × Age) + (0.02548 × Age2) – (0.00018 × Age3)
Women: 54.74942 – (1.54884 × Age) + (0.03580 × Age2) – (0.00026 × Age3)
TBSA, (%) × 100 (use actual initial burn size, no cut-off for larger burns); BSA, (m^2) the square root of (HT × WT)/3600
Pediatric:
Galveston
0–1 year: 2100(body surface area) + 1000(body surface area × TBSA)
1–11 year: 1800(body surface area) + 1300(body surface area × TBSA)
12–18 years: 1500(body surface area) + 1500(body surface area × TBSA)

Who Needs Nutritional Support

The innate response to significant burn injury increases metabolism to such a profound degree that severely burn-injured patients would succumb to the effects of protein calorie malnutrition without nutritional supplementation [17–21]. This postburn hypermetabolism is associated with profound proteolysis resulting in lean body mass loss and muscle wasting. Appropriate monitoring for nutritional needs and deficiencies as well as provision of adequate caloric intake, nitrogen, micronutrients, and supplements is therefore critical to the success of burn care. With this in mind, it is our common practice to place a feeding tube and provide enteral nutrition to patients who are unable to meet their caloric requirements on their own. Typically, this includes intubated patients, patients with burns >15% TBSA, and patients with concomitant trauma or malnutrition.

How Much to Feed and How Soon?

Burn patients rapidly accumulate energy deficits during the first week following injury, which correlate with infectious complications and pressure sores [22–24]. Further, substantial loss of lean body mass impairs wound healing, which is critical in burn injury [25]. The European Guidelines on Clinical Nutrition in the ICU advocate that enteral feedings should begin within 48 h in critically ill patients who have a functioning gastrointestinal tract and when oral nutritional intake is not possible [26]. The most recent guidelines from the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N) for Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient specifically highlight initiating enteral nutrition within 4–6 h of injury for patients with burn injuries [8]. Additionally, enteral nutrition helps maintain immunity associated with the gut-associated lymphoid tissue; thus, even low rates of enteral nutrition have theoretical benefits [27].

Recognizing the growing energy deficits, loss of lean body mass, and that delayed enteral nutrition results in a high rate of gastroparesis and ileus, it is our practice to place a nasogastric feeding tube and initiate enteral nutrition as soon as possible following admission and advancing to goal rate as tolerated. While reviews of other centers reveal that feeding tubes are commonly placed as late as 31 h post-admission with the

initiation of enteral nutrition as late as 48 h from admission [28], it has been demonstrated that patients with burns >20% TBSA that begin enteral nutrition within 24 h of admission have a shorter ICU length of stay and reduced wound infections [29]. This is also consistent in pediatrics, where children started on enteral nutrition within 48 h of admission have been shown to have a shorter hospitalization and lower mortality rate than those with late initiation of enteral nutrition [30], highlighting the importance of starting nutrition early.

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

As early as 1976, the benefits of enteral nutrition over parenteral nutrition had already been identified for patients with functional gastrointestinal systems [31]. The problems of prolonged ileus and Curling stress ulcers in burn patients have been largely eliminated by early feeding [32]. Multiple studies have shown that patients with major thermal injury can receive adequate calories within 72 h after injury [33].

In addition to the question of when to start feeding, there is ongoing debate about where to feed and the benefits of gastric feeding versus duodenal feeding. Although feeding distal to the pylorus should pose less aspiration risk, one study found evidence of enteral formula in pulmonary secretions of 7% of patients receiving gastric feeds compared with 13% of patients receiving transpyloric feeding [34]. Hence, for burn patients with high caloric needs, the benefit of decreased aspiration with transpyloric feeds may only be theoretical and may be offset by the delay in feeding for confirmation of tube placement, though one center has published on the success of their nurse practitioner-driven protocol that has led to timely and economical placement of transpyloric feeding tubes [35].

Continuation of tube feedings during surgery in intubated patients who require multiple operations is a safe way to maximize caloric intake and decrease wound infections. There is no need to stop feedings for anesthesia induction and endotracheal intubation in the patient with a secure airway, and communication with anesthesia providers may help facilitate perioperative feedings [36]; however, intraoperative positioning, especially if the patient will be prone during surgery, may necessitate stopping feedings preoperatively. Arguing that nutrition should be provided intraoperatively, Mayes and colleagues have presented data that support continuation of tube feedings in critically ill burn patients undergoing decompressive laparotomy [37].

While we much prefer enteral nutrition to parenteral nutrition for burn patients, there are times when patients are unable to tolerate or meet their needs with enteral nutrition. Encouragingly, parenteral nutrition has fewer complications than it once did, and a relatively recent pediatric trial found parenteral nutrition to be safe and effective in pediatric burn patients unable to achieve goal enteral nutrition during times such as hemodynamic instability or severe sepsis [38].

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

Providing adequate amounts of carbohydrate is important for preserving lean body mass in the burn population as it spares protein from being used as an energy source [2]. However, it is important (especially with parenteral nutrition) not to exceed the maximum rate at which glucose can be assimilated in the body (7 g/kg/day), providing glucose in excess of the rate at which it can be oxidized [39]. While different compositions of formulas have been provided, systematic review has shown that providing severely burned patients with a high-carbohydrate, high-protein, low-fat enteral diet can lower the incidence of catabolism and pneumonia, compared to a high-fat, high-protein, low-carbohydrate product [40].

Perhaps this should not be surprising, as there is a significant change in how fat is metabolized following burn injury, and providing excess

sources of fat can result in stress on the liver [2]. An increased breakdown of peripheral fat stores immediately after injury coupled with increased beta-oxidation of fat to be used as fuel during the hypermetabolic phase leads to a potential for large accumulations of fat in the liver [41]. However, providing fat as part of the enteral diet is required to prevent essential fatty acid deficiencies, such that a minimum of 2–4% of total calories provided needs to be from essential fatty acid [2].

Protein losses following significant burn injury are severe as protein stores are depleted for energy usage and muscle tissue is broken down at rates as high as 150–190 g/day [42]. This leads to detrimental muscle loss and, in children, a significant decline in growth trajectory for a year or longer postburn, as well as decreased immune function and delayed wound healing [2]. Accordingly, long-established practices and studies have found that providing protein at 1.5–2.5 g/kg/day is typically sufficient for mitigating the hypermetabolic response in adults, and 2.5–4.5 g/kg/day is typical for children.

Specialized nutritional formulas with purported effects on metabolic rate and immunologic status have garnered a great deal of interest as adjuncts in the management of critically ill and injured patients [43]. Unfortunately, much of the information on nutritional requirements for critically ill patients was derived from an animal burn model [44], and studies on the efficacy of specialized nutritional supplements in humans have generated contradictory data. As an example, a randomized trial of nutritional formulas that were intended to enhance immune status and included essential amino acids and omega-3 fatty acids showed no clinical advantage in burn patients [45]. However, the addition of glutamine supplementation to an enteral nutrition regimen has been shown to decrease hospital and ICU length of stay as well as mortality in adult burn patients [46]. A practical advantage of utilizing specialized nutrition formulas over standard formulas is the greater provision of vitamins and trace minerals needed to support wound healing and higher protein content, therefore reducing the necessity to provide additional supplementation.

Other nutritional or metabolically active supplements that have demonstrated promise in promoting anabolism in burn patients include insulin, recombinant human growth factor, the anabolic steroid oxandrolone, and propranolol [47]. Oxandrolone in particular has produced marked improvements in weight gain, return to function, and length of hospital stay [48]; however, its use should be cautioned in non-burn patients as surgical patients have not shown the same benefit [49]. Early administration of antioxidant supplementation with α-tocopherol and ascorbic acid has been shown to reduce the incidence of organ failure and shorten intensive care unit (ICU) length of stay in critically ill surgical patients [50]. Whether this is true for burn patients remains to be demonstrated, but the relatively low cost and the low risk of complications make this an attractive intervention for burn patients at risk for acute respiratory distress syndrome (ARDS).

While providing adequate calories and protein is the foundation of nutritional support, we believe it is also important to provide vitamins and minerals, also known as micronutrients. Depressed levels of vitamin A [51], vitamin C [51], vitamin D [52], selenium [53, 54], vitamin E [51, 55], zinc, and copper [53, 56–59] have been reported in burn patients, and these losses occur mainly through the skin and urine [60] but also from increased utilization [61]. A fairly recent meta-analysis evaluating trace element supplementation after a burn injury concluded that there is evidence to support a significant decrease in infectious episodes with combined supplementation of zinc, selenium, and copper [16]. Vitamin D deficiency, while it does not have a direct role in wound healing, is of concern for critically ill burn patients over the acute hospitalization [62] as well as post hospitalization during rehabilitation [63]. With regard to the critically ill population, several meta-analysis studies have concluded that vitamin D deficiency is associated with significantly increased susceptibility to infections and sepsis, with an increased mortality

[64–66]. Affecting rehabilitation following discharge, burn patients with vitamin D deficiency have been shown to have decreased quadriceps muscle strength [63] and an increased incidence of long bone fractures among children with major burns [67]. Unfortunately, supplementation studies are scarce and have not provided guidance for appropriate micronutrient provision, and there are no clear guidelines on how to assess micronutrient status. Benefits to providing micronutrients include mitigation of the negative effects of oxidative stress, which can contribute to the systemic inflammatory response syndrome (SIRS), inflammation, and organ failure, as well as contribute to wound healing, tissue repair, and immune system support.

Support for providing micronutrients can be found in a recent survey of 65 burn centers demonstrating 100% of participants provide a multivitamin following burn injury and more than half provide vitamin C and Zinc supplementation [12], as well as the recent guidelines from the Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition published in 2016, which recommended that antioxidant vitamins C and E and trace minerals (selenium, zinc, and copper) be provided to burn patients [8]. Special considerations for micronutrient supplementation should be made for burn patients that are at risk of deficiency such as alcoholics (where one should consider thiamine, folate, and vitamin B12), those with preexisting malnutrition, growing children, and patients with malabsorptive conditions such as bariatric surgery.

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

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

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

Early Excision and Grafting

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

While early excision and grafting had been described and performed earlier, it was not until the Cocoanut Grove fire in 1942 that Cope and colleagues observed patients treated with early excision and grafting had better outcomes [68]. Other early efforts were discouraging, but Janzekovic's good results rekindled enthusiasm, and as clinical experience with early excision and grafting grew, the benefits became clear [69]. Manafo and Burke introduced and expanded Janzekovic's concept of tangential excision of the burn wound to the USA, and as experience grew, the advantages of more rapid healing, decreased blood loss, decreased hospital length of stay, and decreased hypertrophic scarring were realized [70–72]. Significantly, early total excision of full-thickness burns with immediate grafting led to a notable decrease in mortality of 24% in 1974 to 7% over 1979–1984, and what started as

limited early excision of eschar rapidly progressed to staged, total excision of the burn wound [73].

Since that time, there have been many successive studies which have repeatedly verified favorable outcomes with early excision and grafting [74–79]. Improved understanding of the systemic inflammatory response syndrome (SIRS) has suggested that immediate removal of dead and severely damaged tissue can interrupt and attenuate SIRS and normalize immune function [80–82].

Temperature Regulation

Because the burn patient has lost the barrier function of the skin, temperature regulation is an important goal of successful management. Keeping a patient warm and dry is a major goal during resuscitation, especially during the preburn center transport of patients. This includes maintaining a warm ambient temperature. Large evaporative losses combined with administration of large volumes of intravenous fluids that are at room temperature or colder may accentuate the hypovolemia, which will complicate the patient's overall course and may lead to disseminated intravascular coagulopathy [83]. Mild hyperthermia may occur in the first 24 h as a result of pyrogen release or increased metabolic rate and may cause tachycardia that misleadingly suggests hypovolemia [84]. Because infection is unlikely early on, especially within the first 72 h after injury, elevated temperatures should be treated with antipyrogens to control the energy expenditure associated with increased catabolism [85]. About 72 h after injury, patients with thermal injuries commonly develop a hyperdynamic state, the systemic inflammatory response syndrome (SIRS), which is characterized by tachycardia, hypotension, and hyperthermia, classic signs of sepsis that in this case do not have an infectious source.

Although patients with burns are likely to have elevated temperatures and may even have elevated white blood cell counts, fevers in burn patients are not reliable indicators of infections [86, 87]. At least one study has demonstrated that in pediatric burn patients, physical examination is the most reliable tool for evaluating the source of fever [86].

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

Beta-Blockade

As catecholamines are the main drivers of the hypermetabolic response to burn injury [88], with levels increasing tenfold following injury [88, 89], efforts to dampen this response hold a certain attraction. As catecholamines increase cardiac work, drive lipolysis, enhance glycogenolysis, and impair glucose clearance by altering insulin response [90], blocking the catecholamine surge could improve multiple aspects of postburn hypermetabolism. Efforts to prove this hypothesis by treating patients with propranolol have demonstrated suppression of lipolysis, decreased resting energy expenditure, preservation of lean body mass, and decreased hospital length of stay [91–96].

Propranolol significantly decreases fatty infiltration of the liver, inhibits the release of free fatty acids from adipose tissue, and decreases the rates of fatty acid oxidation and triacylglycerol secretion while increasing the efficiency of the liver to excrete fatty acids, thereby decreasing hepatic steatosis [97–100]. Propranolol has also been shown to increase lean body mass, through decreased skeletal muscle wasting, and doses titrated to target a 20% heart rate reduction from admission heart rate have been shown to increase the efficiency of muscle protein synthesis [94].

Oxandrolone

Oxandrolone is a synthetic analog of testosterone with minimal virilizing activity and hepatotoxicity compared to testosterone [101]. In skeletal muscle, oxandrolone binds to the androgen

receptor and migrates to the cell nucleus, stimulating protein synthesis and anabolism. Additionally, oxandrolone exerts anabolic effects by counteracting the catabolic effects of cortisol through competitive inhibition of glucocorticoid receptors [102].

The hypermetabolic state following burn injury leads to protein–calorie malnutrition, muscle wasting, deconditioning, and delayed wound healing. These complications are accompanied by prolonged hospital length of stay, increased hospital costs, and need for extensive and long-lasting rehabilitation. Modulation of the postburn hypermetabolism with oxandrolone can potentially improve these consequences [6, 96, 103–107]. Patients with severe burn injury treated with oxandrolone have been found to have a shorter hospital and ICU length of stay accounting for severity of illness, TBSA burn, and age [108].

Oxandrolone has been given in many varied ways to burn patients. It has been given within the first few days of admission, a week after admission, during burn rehabilitation following the acute hospitalization, or for as long as a year after injury. While each of these groups has been evaluated, no group has been as extensively studied as that of the massively burned child. Physiologic evaluation and long-term follow-up of children with >30% TBSA burns treated with oxandrolone for 1 year revealed that oxandrolone substantially decreased resting energy expenditure (REE) and increased insulin-like growth factor-1 secretion during the first year after burn injury and, when combined with exercise, considerably increased lean body mass and muscle strength [109]. When given early, within the first week of admission, the American Burn Association Multicenter Trials Group found that patients treated with oxandrolone had a shorter length of stay [106], and our work with the Glue Grant demonstrated an improved mortality [110]. Just how oxandrolone improves outcomes such as mortality and length of stay remains to be better understood, but we are encouraged by results showing an improved length of stay and lean body mass when given a week after injury [96], as well as during acute rehabilitation, where body weight and lean mass lost from injury can be restored more effectively than with nutrition alone [48, 111]. Based on these results, it is our practice to treat severe burns with oxandrolone over their acute hospitalization, with initiation following burn resuscitation.

Insulin

Both hyperglycemia and hypoglycemia are associated with increased mortality and morbidity in critically ill patients. While hyperglycemia has been believed to be an adaptive stress response, it has been associated with worse outcomes, and glucose variability has been found to be a predictor of mortality following burn injury [112–114]. The association of poor glucose control with bacteremia, reduced graft take, and higher mortality in pediatric burn patients has further supported this practice [114]. Improved survival in surgical ICU patients maintained with tight blood glucose control of 80–110 mg/dL led to the widely practiced policy of tight glycemic control [115].

Since Van den Berghe's landmark study in 2001 [115], there have been many randomized controlled trials and meta-analyses that have reported conflicting results or found that only surgical ICU patients, and not medical ICU patients, benefited from strict glucose control [112, 116]. More recently, the large multicenter Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial demonstrated that an intermediate glucose target (140–180 mg/dL) was ideal for most patients and resulted in lower mortality than stricter control (80–110 mg/dL) [117]. Based on the current literature, it is our policy to maintain blood glucose levels as close to normal as possible, without evoking unacceptable glucose fluctuations, hypoglycemia, or hypokalemia, and therefore aim for a range of 100–180 mg/dL.

Glutamine

Glutamine plays an important role in many metabolic processes and has a high turnover of approximately 1 g of glutamine per kilogram per

day [118]. As this is nearly ten times the normal dietary intake, the body relies upon endogenous sources. In a critically ill patient, the demand for glutamine increases (secondary to immune system activation and damage repair efforts), while production is decreased (secondary to immobility and insulin resistance), making glutamine conditionally essential and leading to a functional deficiency. It is not surprising, therefore, that a low plasma glutamine level has been independently associated with worse outcomes in critical illness [119], and some single center studies have shown improved outcomes related to dose and duration [120, 121]. Unfortunately, a randomized trial of nutritional formulas that were intended to enhance immune status and included essential amino acids and omega-3 fatty acids showed no clinical advantage in burn patients [45], though the addition of glutamine supplementation to an enteral nutrition regimen has been shown to decrease hospital and ICU length of stay as well as mortality in adult burn patients.

These findings could potentially be explained by glutamine's role in reducing oxidative stress through its function as a precursor to glutathione, as well as serving as a fuel for macrophages, fibroblasts, and lymphocytes, and aiding in preventing bacterial translocation through preservation of gut integrity by serving as a source for enterocytes [46]. Confirmatory support for the immune-enhancing effects of glutamine can be found in a recent meta-analysis of four randomized controlled trials, involving 155 patients, which found glutamine supplementation to be associated with a decrease in the number of patients with Gram-negative bacteremia as well as hospital mortality [122].

On the contrary, the REDOX trial, a large international RCT with a 2-by-2 factorial design involving 1223 critically ill adults, evaluated supplementation of glutamine, antioxidants, both, or placebo on 28-day mortality. The initial results concluded that there was an increased 28-day mortality associated with glutamine administration as compared with those that did not receive it. In addition, 6-month mortality was also greater in the patients that received glutamine in this study compared to those that did not. The most concerning adverse effect from glutamine was seen in patients that received a higher dose of glutamine (>0.5 kg/d) with multisystem organ failure and a majority of them in shock. Antioxidants had no effect on mortality within 28 days or at any other secondary end point in this study [123, 124]. Notably, the post hoc analysis of the REDOX trial revealed both glutamine and antioxidants were associated with increased mortality in the presence of baseline renal dysfunction and that neither intervention was associated with harm or benefit in patients without baseline renal dysfunction [125]. Regarding the REDOX trial, there are a few important characteristics to point out before the practitioner decides not to supplement glutamine on a patient with a burn injury. First, majority of the patients included in this study were critically ill medical patients. There were a small amount of critically ill trauma and surgery patients included in this study, but no burn patients. Second, patients that received glutamine received far greater doses than the maximal dose used in other studies (>30 g per day). Lastly, patients that received glutamine in the REDOX trial received both enteral and IV glutamine. This is not a common practice in the USA, nor is IV glutamine available for routine use in the USA.

Glutamine has many valuable functions that may be beneficial to burn patients, and studies have reported advantages to glutamine, perhaps explained by its trophic influence on intestinal epithelium and on the maintenance of gut integrity [46]. Studies in adult burn patients have shown enteral glutamine supplementation to preserve gut integrity [123, 126] while decreasing infectious complications [46, 123], mortality [46], and length of stay [123, 126]. Unfortunately, these studies have had small sample sizes and different dosing methods, and glutamine supplementation has not been well studied in children, leaving unanswered questions about the potential benefits of glutamine supplementation. Currently underway is a large multicenter RCT, Randomized Trial of Enteral Glutamine to Minimize Thermal Injury (RE-ENERGIZE), evaluating the effects of enteral glutamine in burn patients on in-hospital mortality, incidence of hospital-acquired

blood stream infection, and physical function of burn survivors. Hopefully, the results of this study will provide us with more burn-specific data on the benefit or harm of glutamine supplementation in critically ill burn patients. Future studies will need to take into account the nutritional status of patients, the degree of glutamine deficiency, and the duration of use rather than using a single standard dose for a short duration and being surprised by a lack of effect. Similarly, less ill patients with less of a glutamine deficiency may not benefit from additional supplementation.

Erythropoietin

While patients with large burns will often have a long hospitalization, a longer period of critical illness than many other ICU patients, and many operative interventions that can all lead to blood loss and anemia, there is no definitive study on the use of erythropoietin in the burn population. One interesting and positive study encouraging the use of erythropoietin in the ICU was performed by the EPO Critical Care Trials Group and reported in JAMA in 2002. This prospective, randomized, double-blind, placebo-controlled, multicenter trial was performed over 2.5 years and involved 1302 mixed medical and surgical ICU patients randomized to receive recombinant human erythropoietin (EPO) or placebo on ICU day 3 and then weekly for 3 doses. Interestingly, they found patients receiving EPO to be less likely to undergo transfusion, experiencing a 19% reduction in total units of red blood cells (RBCs) transfused, reduction in RBC units transfused per day alive, and increase in hemoglobin from baseline to study end, with no difference in mortality or adverse clinical events [127].

While we await definitive studies investigating the use of erythropoietin in burned humans, a recent study in burned rats demonstrated preservation of microcirculatory perfusion within endangered areas in a dose-dependent manner, leading to quicker healing with less contracture formation, as well as an increase in hematocrit [128]. Recognizing that there are differences between the human and rat response to burn injury, and that human studies are needed, remembering that erythropoietin is not just a renal hormone responsible for maintaining erythrocytes but also involved in the acute and subacute response to tissue damage, attenuating injury, and facilitating healing and restoration of function [129], may prove an opportunity to further improve future burn care.

Iron

While iron is known to play a role in wound healing, iron deficiency has not been associated with poor wound healing outcomes, and iron has not been thoroughly studied in burn patients [130]. Similar to vitamin C, iron contributes to collagen synthesis as a cofactor for hydroxylation of proline and lysine as well as plays a role in oxygen transport to tissues [130, 131]. While iron levels are known to decrease after burn injury, they typically increase back to normal levels without supplementation [132, 133], and the combination of necessary blood transfusions and iron supplementation may lead to excessive levels.

Probiotics

The World Health Organization and the Food and Agricultural Organization of the United Nations defines probiotics as "viable microorganisms that when ingested in adequate amounts, can be beneficial for health" [134]. In critical illness, there are multiple factors that influence rapid and persistent changes in the commensal microbiota such as metabolic insult, various medications (vasopressors, antibiotics, H2 antagonists), gut ischemia/reperfusion, and changes in gut motility [135, 136]. Many centers have historically feared the use of probiotics, fearing an increase in infectious complications with multidrug-resistant organisms; however, the exogenous use of probiotics in critical illness and burn patients has been shown to decrease the frequency of diarrhea [137, 138]; decrease the incidence of *Clostridium difficile* infection with antibiotic use [139];

reduce the of incidence of infections and, in some studies, reduce ventilator-associated pneumonia [138, 140, 141]; decrease the length of hospitalization [138, 142]; and decrease in need for grafting [138]. Recent studies on probiotic supplementation in the burn population have demonstrated the safety of probiotics [138, 142, 143]. However, given the lack of any large RCTs on the use of probiotics in specific critically ill populations such as burn patients, it is recommended to use caution with supplementation [8]. In our clinical practice, adult and pediatric patients prescribed with antibiotics are supplemented 1 h before or after antibiotic administration twice a day with kefir, a fermented milk product, or for patients that cannot have dairy products, *Lactobacillus rhamnosus* (LGG) capsule. Probiotic supplementation is then continued for a minimum of 2 weeks after discontinuation of the antibiotic.

Measuring Effectiveness of Nutritional Support

As postburn hypermetabolism is associated with profound proteolysis resulting in lean body mass loss and muscle wasting, appropriate monitoring for nutritional needs and deficiencies as well as provision of adequate caloric intake, nitrogen, micronutrients, and supplements is critical. Yet, providing carbohydrate, protein, and fat in excessive amounts can result in complications as well. Excess carbohydrate can lead to fat deposition in the liver and increased fat synthesis, as well as difficulties in weaning from mechanical ventilation secondary to elevated respiratory quotients and increased carbon dioxide production. Assessing and monitoring the nutritional status of a burn patient can be quite difficult. Daily weights in the critically ill patient can be inaccurate based on fluid balance or dressings. As mentioned earlier, IC can be a helpful tool to capture changes in energy requirements. Assessing nitrogen balance on a weekly basis through a 24 h urine urea nitrogen measurement can be utilized as a guide in adjustment of protein goals as wound burden changes. Determination of nitrogen balance requires dietary assessment of nitrogen intake (1 g of nitrogen = 6.25 g protein), estimation of wound nitrogen losses and non-urea nitrogen losses (such as feces), as well as an accurate 24 h urine collection [144, 145] (Table 7.2). A positive nitrogen balance of +3 to +5 is favorable [146]. While available tools for monitoring nutritional status following a burn injury are not consistently utilized among the burn community, and there is no agreed upon standard for assessing effectiveness of nutritional support, trending visceral protein measurements combined with acute phase reactants are a common practice in burn units.

Table 7.2 Calculating nitrogen balance

Step 1. Determine nitrogen (N) intake by converting grams of protein to grams of N. 1 g N = 6.25 g protein		
Step 2. Calculate total nitrogen losses (TNL) from wound output and non-urea losses		
Wound loss factor		*Non-urea losses*
<10% TBSA burn	0.02gN/kg body weight (BW)/day	2–4 g N/day
10–30% TBSA burn	0.05 g/kg BW/day	
>30% TBSA burn	0.12 g/kg BW/day	
N from urine + N wound losses + non-urea N losses = TNL		
Step 3. Calculate balance		
N intake – TNL = N balance		

Caution should be used when evaluating serum prealbumin (PAB) (also known as transthyretin) for purposes of nutrition assessment in hospitalized and critically ill burn patients. PAB is a negative acute-phase protein that decreases with inflammation. It can also be increased with severe renal failure, corticosteroid use, and oral contraceptive use [147]. A study done by Yang et al. involving 204 critically ill burn patients with burns ≥20% TBSA investigated the relationship between serum PAB levels, adequacy of nutritional intake, CRP levels, lactic acid levels, and TBSA. They concluded that serum PAB did not have a significant difference between patients that met >70% of their energy goals for 7 days. Additionally, this study concluded that serum PAB can be a useful biomarker of severity of

illness and change in patient condition [124]. To add, low serum PAB levels during the early post-burn period were independently associated with mortality in massively burned patients [148]. Normal serum PAB levels have also shown to be a predictor of good graft take for non-critically ill patients with burns <15% TBSA [149].

In addition to shorter half-life low visceral protein levels, burn patients characteristically have hypoalbuminemia that persists until wounds are healed and the rehabilitation phase of recovery has begun. In fact, one study found that patients with large burns have serum albumin levels that average 1.7 g/dL and never exceed 2.5 g/dL [150]. Suggesting that low albumin levels may be similar to low prealbumin levels, a recent collaborative study between centers in Spain and the USA found that serum albumin level 3–7 days after burn injury is reflective of the severity of injury rather than nutritional status and was predictive of hospital length of stay [151].

However, while the albumin level may be reflective of the severity of illness, similar to anemia, there has been question about what to do about the often significant hypoalbuminemia. Thus, management of hypoalbuminemia is controversial, but there is general agreement that once burn resuscitation is complete, infusion of exogenous albumin to serum levels above 1.5 g/dL does not affect burn patient length of stay, complication rate, or mortality [152, 153].

Perhaps just as important as whether or not to trend visceral proteins is critically following differences between what nutritional supplementation is ordered and what is received or absorbed. Delayed initiation of enteral nutrition, slow advancement of infusion rate, and underprescription, as well as holding tube feeds for operations, tests such as CT scans, mechanical problems such as inadvertently pulled or clogged feeding tubes, or high residuals, all contribute to a receipt of inadequate nutrition. Correspondingly, an international observational study of nutrition support in mechanically ventilated burn patients identified that patients received about 70% of their prescribed energy and protein goals [11]. Thus, when patients fall behind in what they have received for nutritional support, it may be necessary to increase the rate of enteral nutrition and critically assess obstacles to achieving desired support in an effort to catch up on missing calories until the deficit is replaced. Use of enteral feeding protocols increases the overall percentage of goal calories provided and can minimize some of these obstacles [8].

Special Considerations (Children, Elderly, Morbidly Obese)

Children

Much of what is currently practiced for nutritional support of the severely burned patient comes from lessons learned from the severely burned child. With a greater ability to survive otherwise devastating injuries and often better follow-up over time, children have provided a resource for long-term follow-up. In addition to the research on propranolol and oxandrolone, which started in children, there continues to be research on the long-term effects of what nutritional support is provided during acute hospitalization and chronic deficiencies or effects. One such lesson comes from a study of nearly 1000 children with >40% TBSA burns who were randomized to either a low-fat/high-carbohydrate diet or a high-fat diet. While demographics and caloric intake were similar, those fed the low-fat/high-carbohydrate diet had shorter ICU stays and a lower incidence of sepsis and lived significantly longer until death than those in the high-fat diet. While there was no difference in overall mortality between groups, there was less hepatic steatosis and less kidney and spleen enlargement [154]. Thus, it is important to not only look at the caloric needs of patients but the composition of the nutritional support as well.

In addition to the content of nutritional support, providing appropriate support early seems to be a universal theme across all patient populations (adult [29], pediatric [30], and obese [155]) as well. A recent randomized, prospective pediatric study demonstrated that burned children who

received enteral nutrition within 3–6 h following the burn had a shorter hospitalization and lower mortality than children who had enteral nutrition initiated 48 h after burn injury [30].

Elderly

Nutrition status prior to burn injury should be considered for elderly patients. These patients often have common social and physical causes of malnutrition such as chronic disease, poor oral health, loss of taste and smell, polypharmacy, social isolation, dementia, obesity, sarcopenia, and loss of functional capacity (inability to procure, prepare, and consume food) [156]. These factors prior to their burn injury further compromise their health status and overall recovery and impede wound healing with resultant poor outcomes if not properly addressed [157]. Often in the acute care setting, elderly patients with dementia, end-stage, or terminal illnesses may require enteral nutrition or parenteral nutrition. By having specific goal-oriented nutrition support parameters in place, it may prevent ethical dilemmas after discharge while allowing adequate nutrition for wound healing. Additionally, the elderly are more likely to live in a nursing home or be discharged to a nursing home following burn injury. This has another impact on nutritional status, as a recent systematic review of nutritional status of residents in nursing homes revealed a wide range of prevalence of low body mass index, poor appetite, malnutrition, and eating disability in nursing home residents [158]. The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient do not specifically address the geriatric population [8], so we believe assessments of nutritional deficiencies and need for support should be assessed by a dietitian upon admission to the hospital, and with understanding of the above obstacles to adequate nutritional status in the elderly, it is our practice to follow adult guidelines as described above.

Morbidly Obese

Obesity has become increasingly prevalent in the USA and resultantly in the critical care population as well, with recent demographic trends suggesting that the prevalence of obesity will only continue to grow. Unfortunately, little is known about the nutritional needs of obese burn patients. A multidisciplinary survey sent to US burn centers found that obesity was commonly defined as a BMI >30, and the Harris–Benedict equation was the most frequently used equation to calculate the caloric needs of obese burn patients at 32%, most commonly altering the calculations by using adjusted body weight. Hypocaloric formulas were not commonly used (21%), and enteral nutrition was initiated within 24 h in most centers [155].

Recognizing there may be important differences between the obese burn population and other obese ICU populations, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommends that while the basic principles of critical care nutrition apply to the obese ICU patient, a high-protein, hypocaloric regimen should be provided to reduce fat mass, improve insulin sensitivity, and preserve lean body mass [159]. They conclude that the ideal enteral formula should have a low nonprotein calorie-to-nitrogen ratio and have a variety of pharmaconutrient agents added to modulate immune responses and reduce inflammation [159].

While additional research is necessary, specifically in the obese burn population, there are many recognized obstacles to adequate nutritional support in the obese population. One such obstacle is misperceptions about obesity. For example, while greater fat mass in the obese patient may represent an energy reservoir, sarcopenic obesity, problems with futile cycling, insulin resistance, and poor fuel utilization may actually predispose the patient to greater losses of lean body mass, and delays in feeding reduce the value and impact of enteral nutrition for the critically ill obese patient [160, 161]. Additionally, the obese patient has a greater incidence of associated comorbidities and greater likelihood of

metabolic derangements that affect fuel utilization, such as insulin resistance, impaired glucose tolerance, increased fatty acid mobilization, and hyperlipidemia [161]. Finally, bariatric surgery may lead to development of nutrition complications and micronutrient deficiencies such as calcium, iron, folate, B12, copper, thiamine, and vitamin D which can uniquely complicate management of critical illness [162, 163].

Conclusions

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

References

1. Bessey PQ, Lentz CW, Edelman LS, Faraklas I, Finocchiarro MA, Kemalyna KA, et al. National Burn Repository 2013 Report. Chicago: American Burn Association; National Burn Repository; 2013 [cited 2013 Sep 30]. Available at http://ameriburn.org/2013NBRAnnualReport.pdf. Accessed 3 Mar 2014.
2. Rodriguez NA, Jeschke MG, Williams FN, Kamolz LP, Herndon DN. Nutrition in burns: Galveston contributions. JPEN J Parenter Enteral Nutr. 2011;35:704–14.
3. Curreri PW, Luterman A. Nutritional support of the burned patient. Surg Clin North Am. 1978;58:1151.
4. Waxman K, Rebello T, Pinderski L, O'Neal K, Khan N, Tourangeau S, Himes E, Cordill K. Protein loss across burn wounds. J Trauma. 1987;27:136–40.
5. Prelack K, Cunningham JJ, Sheridan RL, Tompkins RG. Energy and protein provisions revisited: an outcomes-based approach for determining requirements. J Burn Care Rehabil. 1997;18:177–81.
6. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. J Crit Care. 2000;15:12–7.
7. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, Ferrando AA, Wolfe RR, Herndon DN. Persistence of muscle catabolism after severe burn. Surgery. 2000;128:312–9.
8. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C. 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 Nurition. JPEN. 2016;40(2):159–211.
9. Saffle JR, Larson CM, Sullivan J. A randomized trial of indirect calorimetry-based feedings in thermal injury. J Trauma. 1990;30(7):776–82.
10. Singer P, Anbar R, Cohen J, 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.
11. Czapran A, Headdon W, Deane AM, Lange K, Chapman MJ, Heyland DK. International observational study of nutrition support in mechanically ventilated patients following burn injury. Burns. 2015;41(3):510–8.
12. Graves C, Saffle J, Cochran A. Actual burn nutrition care practices: an update. J Burn Care Res. 2009;30(1):77–82.
13. Milner EA, Cioffi WG, Mason AD, McManus WF, Pruitt BA Jr. A longitudinal study of resting energy expenditure in thermally injured patients. J Trauma. 1994;37:167–70.
14. Carlson DE, Cioffi WG Jr, Mason AD Jr, McManus WF, Pruitt BA Jr. Resting energy expenditure in patients with thermal injuries. Surg Gynecol Obstet. 1992;174:270–6.
15. Harris JA, Benedict FG. Biometric studies of basal metabolism in man. Washington, DC: Carnegie Institute of Washington; 1919.
16. Kurmis R, Greenwood J, Aromataris E. Trace element supplementation following severe burn injury: a systematic review and meta-analysis. J Burn Care Res. 2016;37:143–59.

17. Jeschke MG, Norbury WB, Finnerty CC, Branski LK, Herndon DN. Propranolol does not increase inflammation, sepsis, or infectious episodes in severely burned children. J Trauma. 2007;62:676–81.
18. Keleman JJ 3rd, Cioffi WG Jr, Mason AD Jr, Mozingo DW, McManus WF, Pruitt BA Jr. Effect of ambient temperature on metabolic rate after thermal injury. Ann Surg. 1996;223:406–12.
19. Matsuda T, Clark N, Hariyani GD, Bryant RS, Hanumadass ML, Kagan RJ. The effect of burn wound size on resting energy expenditure. J Trauma. 1987;27:115–8.
20. Mlcak RP, Jeschke MG, Barrow RE, Herndon DN. The influence of age and gender on resting energy expenditure in severely burned children. Ann Surg. 2006;244:121–30.
21. Hart DW, Wolf SE, Chinkes DL, Gore DC, Micak RP, Beauford RB, et al. Determinants of skeletal muscle catabolism after severe burn. Ann Surg. 2000;232:455–65.
22. Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr. 2006;25:37–44.
23. Faisy C, Candela Llerena M, Savalle M, Savalle M, Mainardi JL, Fagon JY. Early ICU energy deficit is a risk factor for Staphylococcus aureus ventilator-associated pneumonia. Chest. 2011;140:1254–60.
24. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeax RNMC, Delarue J, Berger MM. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24:502–9.
25. Moran L, Custer P, Murphy G. Nutritional assessment of lean body mass. JPEN J Parenter Enteral Nutr. 1980;4:595.
26. Singer P, Reintam Blaser A, Berger MM, Alhazzani W, Calder PC, Casaer MP. ESPEN guidelines on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48–79.
27. Alverdy J, Chi HS, Sheldon GF. The effect of parenteral nutrition on gastrointestinal immunity. The importance of enteral stimulation. Ann Surg. 1985;202:681.
28. Holt B, Graves C, Faraklas I, Cochran A. Compliance with nutrition support guidelines in acutely burned patients. Burns. 2012;38(5):645–9.
29. Mosier MJ, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL, Tompkins RG, Herndon DN. Early enteral nutrition in burns: compliance with guidelines and associated outcomes in a multicenter study. J Burn Care Res. 2011;32:104–9.
30. Khorasani EN, Mansouri F. Effect of early enteral nutrition on morbidity and mortality in children with burns. Burns. 2010;36:1067–71.
31. Blackburn GL, Bistrian BR. Nutritional care of the injured and/or septic patient. Surg Clin North Am. 1976;56:1195.
32. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. Burns. 1997;23:313.
33. Raff T, Hartmann B, Germann G. Early intragastric feeding of seriously burned and long-term ventilated patients: a review of 55 patients. Burns. 1997;23:19.
34. Esparza J, Boivin MA, Hartshorne MF, Boivin MA, Hartshorne MF, Levy H. Equal aspiration rates in gastrically and transpylorically fed critically ill patients. Intensive Care Med. 2001;27:660–4.
35. Hauschild TB, Fu KY, Hipwell RC, Baraghoshi G, Mone MC, Nirula MC, Nirula R, Kimball EJ, Barton RG. Safe, timely, convenient, and cost-effective: a single-center experience with bedside placement of enteral feeding tubes by midlevel providers using fluoroscopic guidance. Am J Surg. 2012;204(6):958–62.
36. Jenkins ME, Gottschlich MM, Warden GD. Enteral feeding during operative procedures in thermal injuries. J Burn Care Rehabil. 1994;15:199.
37. Mayes T, Gottschlich MM, Warden GD. Nutrition intervention in pediatric patients with thermal injuries who require laparotomy. J Burn Care Rehabil. 2000;21:451.
38. Dylewksi ML, Baker M, Prelack K, Weber JM, Hursey D, Lydon M, Fagan SP, Sheridan RL. The safety and efficacy of parenteral nutrition among pediatric patients with burn injuries. Pediatr Crit Care Med. 2013;14(3):e120–5.
39. Wolfe RR, Allsop JR, Burke JF. Glucose metabolism in man: responses to intravenous glucose infusion. Metabolism. 1979;28:210–20.
40. Masters B, Aarabi S, Sidhwa F, Wood F. High-carbohydrate, high-protein, low-fat versus low-carbohydrate, high-protein, high-fat enteral feeds for burns. Cochrane Database Syst Rev. 2012;1. https://doi.org/10.1002/14651858.CD006122.pub3.
41. Consensus recommendations from the U.S. summit on immune-enhancing enteral therapy. JPEN J Parenter Enteral Nutr. 2001;25:S61–2.
42. Patterson E, Wall R, Fitzgerald GF, Ross RP, Stanton C. Health implications of high dietary omega-6 polyunsaturated fatty acids. J Nutr Metab. 2012. https://doi.org/10.1155/2012/539426.
43. Gottschlich MM, Jenkins M, Warden GD, Baumer T, Havens P, Snook JT, Alexander JW. Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. JPEN J Parenter Enteral Nutr. 1990;14:225–36.
44. Saito H, Trocki O, Alexander JW, Kopcha R, Heyd T, Joffe SN. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion, and gut mucosal integrity after burn injury. JPEN J Parenter Enteral Nutr. 1987;11:1–7.
45. Saffle J, Wiebke G, Jennings K, Morris SE, Barton RG. Randomized trial of immune-enhancing enteral nutrition in burn patients. J Trauma. 1997;42:793–800.
46. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, D'Elia M, Bernier J. Decreased

mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit Care Med. 2003;31:2444–9.
47. Herndon DN. Nutritional and pharmacological support of the metabolic response to injury. Minerva Anestesiol. 2003;69:264.
48. Demling RH, DeSanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. Burns. 2003;29:793–7.
49. Bulger EM, Jurkovich GJ, Farver CL, Klotz P, Maier RV. Oxandrolone does not improve outcome of ventilator dependent surgical patients. Ann Surg. 2004;240:472–80.
50. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg. 2002;236:814–22.
51. Rock CL, Dechert RE, Khilnani R, Parker RS, Rodriguez JL. Carotenoids and antioxidant vitamins in patients after burn injury. J Burn Care Rehabil. 1997;18:269–78.
52. Gottschlich MM, Mayes T, Choury J, Warden GD. Hypovitaminosis D in acutely injured pediatric burn patients. J Am Diet Assoc. 2004;104:931–41.
53. Berger MM, Cavadini C, Bart A, Mansourian R, Guinchard S, Bartholdi I, et al. Cutaneous copper and zinc losses in burns. Burns. 1992;18:373–80.
54. Dylewski ML, Bender JC, Smith AM, Prelack K, Lydon M, Weber JM, Sheridan RL. The selenium status of pediatric patients with burn injuries. J Trauma. 2010;69:584–8.
55. Traber MG, Leonard SW, Traber DL, Traber LD, Gallagher J, Bobe G, et al. Alpha tocopherol adipose tissue stores are depleted after burn injury in pediatric patients. Am J Clin Nutr. 2010;92:1378–84.
56. Cunningham J, Leffell M, Harmatz P. Burn severity, copper dose, and plasma ceruloplasmin in burned children during total parenteral nutrition. Nutrition. 1993;9:329–32.
57. Gosling P, Rothe HM, Sheehan TM, Hubbard LD. Serum copper and zinc concentrations in patients with burns in relation to burn surface area. J Burn Care Rehabil. 1995;16:481–6.
58. Khorasani G, Hosseinimehr SJ, Kaghazi Z. The alteration of plasma's zinc and copper levels in patients with burn injuries and the relationship to the time after burn injuries. Singap Med J. 2008;49:627–30.
59. Voruganti VS, Klein GL, Lu HX, et al. Impaired zinc and copper status in children with burn injuries: need to reassess nutritional requirements. Burns. 2005;31:711–6.
60. Berger MM. Antioxidant micronutrients in major trauma and burns: evidence and practice. Nutr Clin Pract. 2006;21:438–49.
61. Nordlund M, Pham T, Gibran N. Micronutrients after burn injury: a review. J Burn Care Res. 2014;35:121–33.
62. Rousseau AF, Damas P, Ledoux D, Lukas P, Carlisi A, Le Goff C, et al. Vitamin D status after a high dose of cholecalciferol in healthy and burn subjects. Burns. 2015;41(5):1028–34.
63. Rousseau AF, Foidart-Desalle M, Ledoux D, Remy C, Croisier JL, Damas P, et al. Effects of cholecalciferol supplementation and optimized calcium intakes on vitamin D status, muscle strength, and bone health: a one year pilot randomized controlled trial in adults with severe burns. Burns. 2015;41(2):317–25.
64. Zhang YP, Wan YD, Sun TW, Kan QC, Wang LX. Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies. Crit Care. 2014;18(6):684.
65. de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis, and mortality in the critically ill: systematic review and meta-analysis. Crit Care. 2014;18(6):660.
66. Upala S, Sanguankeo A, Permalung N. Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis. BMC Anesthesiol. 2015;15:84.
67. Mayes T, Gottschlich MM, Khoury J, Kagan RJ. Investigation of bone health subsequent to vitamin D supplementation on children following burn injury. Nutr Clin Pract. 2015;30(6):830–7.
68. Cope O, Langohr J, Moore F, Webster RC. Expeditious care of full-thickness burn wounds by surgical excision and grafting. Ann Surg. 1947;125:1–22.
69. Janzekovic Z. A new concept in the early excision and immediate grafting of burns. J Trauma. 1970;10:1103–8.
70. Manafo W, Auelenbacher C, Papplardo C. Early tangential excision of the eschars of major burns. Arch Surg. 1972;104:503–7.
71. Burke J, Bondoc C, Quinby W. Primary burn excision and immediate grafting: a method for shortening illness. J Trauma. 1974;14:389–95.
72. Burke J, Quinby W, Bondoc C. Primary excision and prompt grafting as routine therapy for the treatment of thermal burns in children. Surg Clin North Am. 1976;56:447–94.
73. Thompkins RG, Burke J, Schoenfeld DA, Bondoc CC, Quinby WC Jr, Behringer GC, Ackroyd FW. Prompt eschar excision: a treatment system contributing to reduced burn mortality. Ann Surg. 1986;204:272–81.
74. Thompkins RG, Remensnyder JP, Burke JF, Tompkins DM, Hilton JF, Schoenfeld DA, et al. Significant reductions in mortality for children with burn injuries through the use of prompt eschar excision. Ann Surg. 1988;208:577–85.
75. Deitch E, Clothier J. Burns in the elderly: an early surgical approach. J Trauma. 1983;23:891–4.
76. Demling R. Effect of early burn excision and grafting on pulmonary function. J Trauma. 1984;24:830–4.

77. Gray D, Pine R, Harner T, Marvin JA, Engrav LH, Heimbach DM. Early surgical excision versus conventional therapy in patients with 20 to 40 percent burns: a comparative study. Am J Surg. 1982;144:76–80.
78. Chicarilli ZN, Cuono CB, Heinrich JJ, Fichandler BC, Barese S. Selective aggressive burn excision for high mortality subgroups. J Trauma. 1986;26:18–25.
79. Herndon D, Parks D. Comparison of serial debridement and autografting and early massive excision with cadaver skin overlay in the treatment of large burns in children. J Trauma. 1986;26:149–52.
80. Yamamoto H, Silthram S, deSerres S, Hultman CS, Meyer AA. Immediate burn wound excision restores antibody synthesis to bacterial antigen. J Surg Res. 1996;63:157–62.
81. Demling R, Lalonde C. Early burn excision attenuates the postburn lung and systemic response to endotoxin. Surgery. 1990;108:28–35.
82. Drost A, Burleson D, Cioffi W, Jordan BS, Mason AD Jr, Pruitt BA Jr. Plasma cytokines following thermal injury and their relationship with patient mortality, burn size, and time postburn. J Trauma. 1993;35:335–9.
83. Salisbury R, Carnes R, Enterline D. Biological dressings and evaporative water loss from burn wounds. Ann Plast Surg. 1980;5:270.
84. Childs C, Little RA. Acute changes in oxygen consumption and body temperature after burn injury. Arch Dis Child. 1994;71:31.
85. Gore DC, Chinkes D, Sanford A, Hart DW, Wolf SE, Herndon DN. Influence of fever on the hypermetabolic response in burn-injured children. Arch Surg. 2003;138:169.
86. Parish RA, Novack AH, Heimbach DM, Engrav LR. Fever as a predictor of infection in burned children. J Trauma. 1987;27:69.
87. Greenhalgh DG, Saffle JR, Holmes JH 4th, Gamelli RL, Palmieri TL, Horton JW, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. 2007;28(6):776–90.
88. Wilmore DW, Long JM, Mason AD Jr, Skreen RW, Pruitt BA Jr. Catecholamines: mediator of the 270 hypermetabolic response to thermal injury. Ann Surg. 1974;180:653–69.
89. Goodall M, Stone C, Haynes BW Jr. Urinary output of adrenaline and noradrenaline in severe 272 thermal burns. Ann Surg. 1957;145:479–87.
90. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. AACN Clin Issues. 2004;15:45–62.
91. Wolfe RR, Herndon DN, Peters EJ, Peters EJ, Jahoor F, Desai MH, Holland OB. Regulation of lipolysis in severely burned children. Ann Surg. 1987;206:214–21.
92. Arbabi S, Ahrns KS, Wahl WL, Hemmila MR, Wang SC, Brandt MM, Taheri PA. Beta-blocker use is associated with improved outcomes in adult burn patients. J Trauma. 2004;56:265–9.
93. Herndon DN, Barrow RE, Rutan TC, Minifee P, Jahoor F, Wolfe RR. Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. Ann Surg. 1988;208:484–92.
94. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. N Engl J Med. 2001;345(17):1223–9.
95. Herndon DN, Nguyen TT, Wolfe RR, Maggi SP, Biolo G, Muller M, Barrow RE. Lipolysis in burned patients is stimulated by the beta 2-receptor for catecholamines. Arch Surg. 1994;129:1301–4.
96. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, Herndon DN. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. Ann Surg. 2007;246:351–60.
97. Aarsland A, Chinkes D, Wolfe RR, Barrow RE, Nelson SO, Pierre E, Herndon DN. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone: rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. Ann Surg. 1996;223(6):777–89.
98. Barret JP, Jeschke MG, Herndon DN. Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. J Trauma. 2001;51(4):736–9.
99. Gore DC, Honeycutt D, Jahoor F, et al. Propranolol diminishing extremity blood flow in burned patients. Ann Surg. 1991;213(6):568–74.
100. Morio B, Irtun O, Herndon DN, Wolfe RR. Propranolol decreases splanchnic triacylglycerol storage in burn patients receiving a high-carbohydrate diet. Ann Surg. 2002;236(2):218–25.
101. Karim A, Ranney RE, Zagarella J, Maibach HI. Oxandrolone disposition and metabolism in man. Clin Pharmacol Ther. 1973;14:862–9.
102. Orr R, Fiatarone SM. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. Drugs. 2004;64:725–50.
103. Barrow RE, Dasu MR, Ferrando AA, Spies M, Thomas SJ, Perez-Polo JR, Herndon DN. Gene expression patterns in skeletal muscle of thermally injured children treated with oxandrolone. Ann Surg. 2003;237:422–8.
104. Demling RH. Comparison of the anabolic effects and complications of human growth hormone and the testosterone analog, oxandrolone, after severe burn injury. Burns. 1999;25:215–21.
105. Hart DW, Wolf SE, Ramzy PI, Chinkes DL, Beauford RB, Ferrando AA, et al. Anabolic effects of oxandrolone after severe burn. Ann Surg. 2001;233:556–64.
106. Wolf SE, Edelman LS, Kemalyan N, Donison L, Cross J, Underwood M, et al. Effects of oxandrolone on outcome measures in the severely burned:

a multicenter prospective randomized double-blind trial. J Burn Care Res. 2006;27:131–9.
107. Wolf SE, Thomas SJ, Dasu MR, Ferrando AA, Chinkes DL, Wolfe R, Herndon DN. Improved net protein balance, lean mass, and gene expression changes with oxandrolone treatment in the severely burned. Ann Surg. 2003;237:801–10.
108. Cochran A, Thuet W, Holt B, Faraklas I, Smout RJ, Horn SD. The impact of oxandrolone on length of stay following major burn injury: a clinical practice evaluation. Burns. 2013;39(7):1374–9.
109. Porro LJ, Herndon DN, Rodriguez NA, Jennings K, Klein GL, Mlcak RP, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg. 2012;214:489–504.
110. Pham TN, Klein MB, Gibran NS, Arnoldo BN, Gamelli RL, Silver GM. Impact of oxandrolone treatment on acute outcomes after severe burn injury. J Burn Care Res. 2008;29:902–6.
111. Demling RH, DeSanti L. The rate of restoration of body weight after burn injury, using the anabolic agent oxandrolone, is not age dependent. Burns. 2001;17:46–51.
112. Van den Berghe G, Schetz M, Vlasselaers D, Hermans G, Wilmer A, Bouillon R, Mesotten D. Clinical review: intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? J Clin Endocrinol Metab. 2009;94:3163.
113. Pidcoke HF, Wanek SM, Rohleder LS. Glucose variability is associated with high mortality after severe burn. J Trauma. 2009;67:990.
114. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M. Association of hyperglycemia with increased mortality after severe burn injury. J Trauma. 2001;51:540.
115. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359.
116. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180:821.
117. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283.
118. Biolo G, Zorat F, Antonione R, Ciocchio B. Muscle glutamine depletion in the intensive care unit. Int J Biochem Cell Biol. 2005;37:2169–79.
119. Oudemans-van Straaten HM, Bosman RJ, Treskas M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive Care Med. 2001;27:84–90.
120. Griffiths RD, Jones C, Palmer TEA. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition. 1997;4:296–302.
121. Griffiths RD, Allen KD, Andrews FJ, Jones C. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. Nutrition. 2002;18:546–52.
122. Lin JJ, Chung XJ, Yang CY, Lau HL. A meta-analysis of trials using the intention to treat principle for glutamine supplementation in critically ill patients with burn. Burns. 2013;39:565–70.
123. Zhou YP, Jiang ZM, Sun YH, Wang XR, Ma EL, Wilmore D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. JPEN J Parenter Enteral Nutr. 2003;27:241–5.
124. Heyland D, Muscedere J, Wischmeyer PE, et al. Randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368:1489–97.
125. Heyland D, Gunnar E, Cook D, et al. Glutamine and antioxidants in the critically ill patient: a post hoc analysis of a large-scale randomized trial. JPEN J Parenter Enteral Nutr. 2015;39:401–9.
126. Peng X, Yan H, You Z, Wang S. Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. Burns. 2004;30:135–9.
127. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, et al. Efficacy of recombinant human erythropoietin in critically ill patients a randomized controlled trial. JAMA. 2002;288:2827–35.
128. Tobalem M, Harder Y, Rezaeian F, Wettstein R. Secondary burn progression decreased by erythropoietin. Crit Care Med. 2013;41:963–71.
129. Kamolz LP, Smolle-Juettner F, Parvizi D. The use of erythropoietin in burns: sometimes good, sometimes not? Crit Care Med. 2013;41:1138–9.
130. Sherman AR, Barkley M. Nutrition and wound healing. J Wound Care. 2011;20(357–8):360, 362–7.
131. Stechmiller JK. Understanding the role of nutrition and wound healing. Nutr Clin Pract. 2010;25:61–8.
132. Sanchez-Agreda M, Cimorra GA, Mariona M. Garcia-Jolón. Trace elements in burned patients: studies of zinc, copper and iron contents in serum. Burns. 1977;4:28–31.
133. Belmonte JA, Ibanez L, Ras MR, Aulesa C, Vinzo J, Iglesias J, Carol J. Iron metabolism in burned children. Eur J Pediatr. 1999;158:556–9.
134. Food and Agriculture Organization and World Health Organization Expert Consultation. Evaluation of health and nutritional properties of powder milk and live lactic acid bacteria. Córdoba: Food and Agriculture Organization of the United Nations and World Health Organization; 2001.
135. 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.
136. Arvans DL, Vavricka SR, Ren H, et al. Luminal bacterial flora determines physiological expression

of intestinal epithelial cytoprotective heat shock proteins 25 and 72. Am J Physiol Gastrointest Liver Physiol. 2005;288(4):G696–704.
137. Schlotterer M, Bernasconi P, Lebreton F, et al. Value of Saccharomyces boulardii in the digestive acceptability of continuous-flow enteral nutrition in burnt patients. Nutr Clin Metab. 1987;1:31–4.
138. El-Ghazely MH, Mahmoud WH, Atia MA, Eldip EM. Effect of probiotic administration in the therapy of pediatric thermal burn. Ann Burns Fire Disasters. 2016;29(4):268–72.
139. McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease. Am J Gastroenterol. 2006;101:812–22.
140. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med. 2010;182(8):1058–64.
141. Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, et al. Benefits of a synbiotic formula (Synbiotic 2000 Forte) in critically ill trauma patients: early results of a randomized controlled trial. World J Surg. 2006;30:1848–55.
142. Mayes T, Gottschlich MM, James LE, et al. Clinical safety and efficacy of probiotic administration following burn injury. J Burn Care Res. 2015;36(1):92–9.
143. Koren L, Gurfinkel R, Glezinger R, et al. The effect of Lactobacillus bacteria supplement on sepsis and its complications in patients with acute burns. Burns. 2007;33:594–8.
144. Long CL, Schaffel N, Geiger JW, et al. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. JPEN J Parenter Enteral Nutr. 1979;3:452–7.
145. Milner EA, Cioffi WG Jr, Mason AD Jr, et al. Accuracy of urinary urea nitro-gen for predicting total urinary nitrogen in thermally injured patients. JPEN J Parenter Enteral Nutr. 1993;17:414–26.
146. Masters B, Wood F. Nutrition support in burns-Is there consistency in practice? J Burn Care Res. 2008;29:561–71.
147. Davis C, Sowa D, Keim K, Kinnare K, Peterson S. The use of prealbumin and C-reactive protein for monitoring nutrition support in adult patients receiving enteral nutrition in an urban medical center. J Parenter Enter Nutr. 2012;36:197–204.
148. Yang HT, Yim H, Cho YS, et al. Prediction of clinical outcomes for massively-burned patients via serum transthyretin levels in the early postburn period. J Trauma Acute Care Surg. 2012;72:999–1005.
149. Moghazy AM, Adly OA, Abbas AH, Moati TA, Ali OS, Mohamed BA. Assessment of the relation between prealbumin serum level and healing of skin-grafted burn wounds. Burns. 2010;36:495–500.
150. Sheridan RL, Prelack K, Cunningham JJ. Physiologic hypoalbuminemia is well tolerated by severely burned children. J Trauma. 1997;43:448.
151. Perez-Guisado J, de Haro-Padilla JM, Rioja LF, Derosier LC, de la Torre JI. Serum albumin levels in burn people are associated to the total body surface burned and the length of hospital stay but not to the initiation of the oral/enteral nutrition. Int J Burn Trauma. 2013;3(3):159–63.
152. Greenhalgh DG, Housinger TA, Kagan RJ, Rieman M, James L, Novak S, et al. Maintenance of serum albumin levels in pediatric burn patients: a prospective, randomized trial. J Trauma. 1995;39:67.
153. Cartotto R, Callum J. A review of the use of human albumin in burn patients. J Burn Care Res. 2012;33(6):702–17.
154. Lee JO, Gauglitz GC, Herndon DN, Hawkins HK, Halder SC, Jeschke MG. Association between dietary fat content and outcomes in pediatric burn patients. J Surg Res. 2011;166(1):e83–90.
155. Coen JR, Carpenter AM, Shupp JW, Matt SE, Shaw JD, Flanagan KE, et al. The results of a national survey regarding nutritional care of obese burn patients. J Burn Care Res. 2011;32:561–5.
156. A.S.P.E.N. The A.S.P.E.N adult nutrition support core curriculum, vol. 36. 3rd ed; 2017. p. 723–42.
157. Demling RH. The incidence and impact of preexisting protein energy malnutrition on outcome in the elderly burn patient population. J Burn Care Rehabil. 2005;26:94.
158. Bell CL, Tamura BK, Masaki KH, Amella EJ. Prevalence and measures of nutritional compromise among nursing home patients: weight loss, low body mass index, malnutrition, and feeding dependency, a systematic review of the literature. J Am Med Dir Assoc. 2013;14(2):94–100.
159. McClave SA, Kushner R, Van Way CW, Cave M, DeLegge M, Dibaise J, et al. Nutrition therapy of the severely obese, critically ill patient: summation of conclusions and recommendations. JPEN J Parenter Enteral Nutr. 2011;35:88S–96S.
160. Joffe A, Wood K. Obesity in critical care. Curr Opin Anaesthesiol. 2007;20(2):113–8.
161. Port AM, Apovian C. Metabolic support of the obese intensive care unit patient: a current perspective. Curr Opin Clin Nutr Metab Care. 2010;13:184–91.
162. Schweiger C, Weiss R, Berry E, Kaidar A. Nutritional deficiencies in bariatric surgery candidates. Obes Surg. 2010;20(2):193–7.
163. Kazemi A, Frazier T, Crave M. Micronutrient-related neurologic complications following bariatric surgery. Curr Gastroenterol Rep. 2010;12(4):288–95.

Obesity

8

Roland N. Dickerson

The obesity epidemic in the United States is staggering with recent data from 2011 to 2014 indicating 37% of adult men and women have a body mass index (BMI) of ≥30 kg/m^2 [1]. The prevalence of obesity is also increasing worldwide [2]. Thus, it is no surprise that 25–40% of patients in the intensive care unit (ICU) are obese [2, 3, 28]. Despite this universal healthcare issue, the amount of literature is very limited regarding the best means for optimizing nutrition therapy for hospitalized patients with obesity. Despite the paucity of data, the author intends to provide an evidence-based approach to the metabolic management of these complex patients.

Impact of Obesity Upon Clinical Outcomes

The diagnosis of obesity is usually based on body mass index (BMI) and is organized into classes of obesity (Table 8.1). However, it has been questioned whether BMI alone is sufficient for assessing obesity and its associated risk in clinical outcomes. Clinical outcomes for patients with obesity may be influenced by the presence of comorbid conditions including diabetes, hyperglycemia, hypoventilation syndrome, other associated metabolic perturbations, and any modifications made to their clinical care because of their obesity including nutrition therapy.

Table 8.1 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

However, studies comparing clinical outcomes for obese versus nonobese patients are conflicting [6–12, 99–102, 106]. Some studies indicate that patients with obesity have worse outcomes, others show no difference, whereas some even suggest improved outcomes. Many of these studies have limitations and are often fraught by retrospective study design and an inadequate number of patients [4]. A limitation with the large datasets is that multivariate analysis has been employed to "control" for variables such as diabetes, hyperglycemia, cardiovascular disease, and other comorbidities associated with obesity. By negating these factors, the data may be biased to omit those obese patients with an unfavorable

R. N. Dickerson (✉)
Department of Clinical Pharmacy and Translational Science, College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA
e-mail: rdickerson@uthsc.edu

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_8

metabolic profile [3]. For example, in a study evaluating 1334 trauma patients with Class III (BMI ≥40 kg/m^2) obesity, overall mortality was 7.8% compared to 4.6% for those with less severe (Classes I and II) obesity [5]. Hyperglycemia was discovered to be an independent predictor of outcome. The investigators concluded that when controlling the dataset for hyperglycemia, there was no effect of obesity upon survival. However, the etiology for hyperglycemia during critical illness is often multifactorial, and obese patients are at higher risk for hyperglycemia due to a greater incidence of insulin resistance, diabetes, and a preexisting inflammatory state due to obesity itself. By controlling for the detrimental effect of hyperglycemia upon outcome, the investigators may have negated the impact and role of obesity upon hyperglycemia which may have contributed to their overall poorer outcome.

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

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

Another factor, often not addressed in studies regarding clinical outcomes for hospitalized patients with obesity, is the presence of sarcopenia. Sarcopenic obesity is the presence of excessive body fat and reduced muscle mass with impaired physical function and strength [19]. Sarcopenia in obese patients is often difficult to detect with traditional physical assessment techniques. The presence of advanced age or impaired mobility prior to hospitalization may contribute to a high index of suspicion with regard to the presence of sarcopenia [103]. Patients, particularly ICU patients, with this body composition abnormality may have worse clinical outcomes [104, 105]. A final consideration, often not addressed in many these large studies, is the nutrition therapy given to the patients. Early initiation of nutrition therapy decreases infectious morbidity for critically ill surgical and trauma patients [20]. In a large retrospective cohort of over a million critically ill ICU patients, a survival advantage was found for those who were overweight or obese [106]. However, when examining the differences in hospital mortality between those who were obese and not obese groups of patients who

were prescribed early enteral nutrition therapy, these outcome differences were minimized [106] indicating the significant beneficial impact early nutrition therapy may provide in ICU patients. Provision of higher amounts of protein has been associated with improved survival during critical illness [21, 22]. Preliminary evidence indicates excessive caloric intake worsens morbidity for critically ill obese patients [23]. Thus, early or delayed nutrition therapy, as well as the composition and amount of nutrition therapy, may have influenced clinical outcomes.

The Obesity Paradox

Recent data have challenged the prevailing theme that increased mortality is associated with an increased BMI above normal but an inverse J-shaped curve may be present when relating BMI to survival [1, 7, 17, 24, 101, 106]. Malnourished patients with a low BMI have the worst survival rate followed by those with severe Class III obesity (BMI ≥40). Surprisingly, overweight and mild-to-moderate obese patients have similar or even improved survival rates compared to those with a normal BMI [1, 7, 17, 24, 101, 106]. Since these data appear incongruent of what would be expected, the term "obesity paradox" has been used to describe this phenomenon.

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

It has been argued that the obesity paradox is not a real phenomenon but rather reflective of selection bias in study design without adequately adjusting for confounding factors that may have influenced clinical outcomes. It has also been suggested that reverse causation may explain the apparent benefits of being overweight or having mild obesity for critically ill patients [28]. Reverse causation could potentially explain the apparent benefits of overweight and mild-to-moderate obesity if the nonobese group suffered from diseases causing weight loss (to the extent of achieving a normal or low BMI) prior to ICU admission [28]. One significant omission by the studies examining the obesity paradox is lack of consideration regarding the impact of parenteral or enteral nutrition therapy. The large retrospective cohort study by Harris and colleagues may provide insight regarding the confounding influence of early enteral nutrition upon the presence of the obesity paradox [106]. Based on the current state of evidence, critically ill patients who are malnourished (BMI <18.5 kg/m^2) or have Class III obesity (BMI ≥40 kg/m^2) are at greater risk for increased morbidity and mortality. However, further studies assessing the impact of obesity upon clinical outcomes, the presence or absence of sarcopenia, and the impact of nutrition therapy for critically ill patients are needed to conclusively determine whether the obesity paradox is real or not.

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

In developing a nutritional regimen for the critically ill obese patient, it is often necessary to modify the regimen based on obesity-associated comorbidities (Table 8.2). The greatest concern is to not overfeed the obese patient as complications from overfeeding extend beyond just a simple amplification in preexisting abundant caloric reserves. The nutritional regimen may need to be modified for hyperglycemia, hyperlipidemia, hypercapnia, congestive heart failure, or nonalcoholic fatty liver disease.

Table 8.2 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

Modification of the nutritional regimen is often complicated since many critically ill patients with obesity may experience multiple concurrent comorbidities.

Patients with even mild degrees of obesity may be insulin-resistant, but it becomes more common in the morbidly obese patient [29]. Critically ill patients with sepsis or traumatic injuries experience a post-receptor insulin resistance with increased counter-regulatory hormone production resulting in substantial hyperglycemia [30]. Thus, when obesity, critical illness, and nutrition therapy are compounded together, hyperglycemia is a prevalent complication that requires vigilant management. Given the recent data over the past decade that trauma [31–33], cardiothoracic surgery [34], thermally injured [35], and potentially other surgical patients benefit from tighter glycemic control (e.g., blood glucose concentrations less than 140–150 mg/dL) than that required of other populations (e.g., medical ICU patients) [36], glycemic control can be challenging for the critically ill, surgical patient with obesity. We found that our critically ill trauma patients with obesity-related diabetes mellitus who required a continuous intravenous insulin infusion experienced a greater hyperglycemic index and greater blood glucose concentration variability and spent less average time in the target blood glucose concentration (e.g., 70–149 mg/dL) than nondiabetics [37].

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

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

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

Table 8.3 Predictive methods for estimating resting energy expenditure (REE) for hospitalized patients with obesity

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

Provision of nutrition therapy may be problematic due to their requirement for fluid restriction.

The critically ill surgical patient with morbid obesity is also at risk for nonalcoholic fatty liver disease (NAFLD) and hepatic steatosis. The prevalence of NAFLD ranges from 57% of overweight subjects to 98% of nondiabetic obese patients [43]. About one third of patients with obesity exhibit hepatic steatosis. Older patients with obesity tend to be at greater risk for NFALD likely due to their prolonged duration of hypertension, obesity, hyperlipidemia, and diabetes [43]. Overfeeding has long been established as a common complication of parenteral nutrition therapy resulting in fatty infiltration of the liver and hepatic steatosis. Evidence of fatty infiltration of the liver and hepatic dysfunction has been demonstrated as early as 10–14 days of caloric overfeeding with parenteral nutrition [44]. Therefore, it is essential that the critically ill patient with obesity not be overfed with excessive calories.

Defining Calorie and Protein Requirements for Surgical Patients with Obesity

Defining caloric requirements for the hospitalized obese surgical or trauma patient with obesity is problematic due to the wide variability in resting energy expenditure and the lack of precision in predicting their resting energy expenditure [45]. Historically, many methods have attempted to predict energy expenditure for critically ill obese patients, but most have been found to be unsuccessful. This inaccuracy in predicting resting energy expenditure is due to the wide variability in muscle mass among obese patients as well as the myriad of diseases and conditions that can variably increase or decrease energy expenditure. Within the past decade, better methods of predicting resting energy expenditure for critically ill obese patients have been developed. Frankenfield and coworkers have developed two equations (one for older patients ≥60 years of age and the other for adults <60 years of age) which have been validated for critically ill, ventilator-dependent obese patients (Table 8.3) [46, 47, 50]. These equations tend to accurately estimate resting energy expenditure (+10%) of critically ill, ventilator patients 70% of the time, but the remaining patients will be significantly under or overestimated [47, 50]. For less sick, nonmechanically ventilated, hospitalized patients with obesity, some clinicians have favored the use of the Mifflin equations to estimate resting energy expenditure (Table 8.3). Unfortunately, the Mifflin equations were developed in "unstressed, healthy obese subjects," and its use has not been validated in the hospitalized, non-ventilator-dependent obese population. Because of the high risk for overfeeding complications in hospitalized patients with obesity and the uncertainty of accurately estimating resting energy expenditure, we have adopted the use of a hypocaloric, high-protein nutritional regimens for these patients. To understand the rationale for this type of therapy, it is necessary to review the impact of calories and protein upon nitrogen balance as well as its overall effect on changes in body composition.

Interpreting Nitrogen Balance

Despite its limitations, the most common clinical tool to assess the adequacy of a nutritional regimen in terms of net protein anabolism is nitrogen balance. Nitrogen balance is simply the difference between the amount of nitrogen given to the patient and the amount of nitrogen lost. If more nitrogen is given to the patient than lost, the patient is considered to be anabolic or "in positive nitrogen balance." If more nitrogen is lost than given, the patient is considered to be catabolic or "in negative nitrogen balance." A nitrogen balance within −4 g/day to +4 g/day is usually considered as "nitrogen equilibrium." To determine nitrogen balance, a 24 h urine collection for urea nitrogen excretion is conducted, and protein intake from the parenteral or enteral nutrition from that same 24 h period is ascertained. An appropriate nitrogen balance (NB) equation for critically ill surgical and trauma patients [51] is as follows[1]:

$$\mathrm{NB}(\mathrm{g/day}) = \text{protein intake}(\mathrm{g/day})/6.25 - \text{urine urea nitrogen}(\mathrm{g/day})/0.85 - 2$$

This NB formula is more accurate for critically ill surgical and trauma patients than the classic NB formula (NB = protein intake/6.25 – urine urea nitrogen – 4). The "fudge factor" of 4 g assumes 2 g for non-urea nitrogen in the urine and 2 g for estimation of stool and insensible losses. Catabolic, critically ill patients often experience high urinary urea nitrogen excretion rates, and the amount of urinary non-urea nitrogen excretion is often greater than the assumed 2 g and sometimes as much as 4–6 g/day [51]. We found that an estimation of ~15% of total urinary nitrogen better predicted actual urinary non-urea nitrogen excretion in our critically ill trauma patients [51]. Ideally, the goal should be to achieve positive nitrogen balance. Unfortunately, a positive nitrogen balance may not be possible during the acute phase post-injury or during sepsis as total body protein catabolism will exceed total body protein anabolism despite the provision of parenteral or enteral nutrition [52, 53]. We have generally accepted a nitrogen balance of about –4 or −5 g/day or better as successful therapy for critically ill patients. Unfortunately, some patients, despite heroic efforts to increase protein intake to 2.5–3 g/kg ideal body weight or actual weight/d for obese and nonobese patients respectively, remain in significantly negative nitrogen balance until the stress abates [54]. Given the increased risk for metabolic complications from overfeeding for obese patients, it is necessary to be conservative with caloric intake to avoid these complications yet provide an effective regimen whereby patients can achieve net protein anabolism, provide an effective immune response, heal wounds, and exhibit positive clinical outcomes. As a result, clinician researchers have pursued techniques to provide a calorie-reduced, high-protein regimen in an effort to meet these desired outcomes. To understand the rationale for hypocaloric, high-protein regimens for hospitalized and critically ill patients with obesity, it is necessary to describe the relationship between calories and protein and their effect on net protein anabolism and body composition.

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

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

The relationship between calorie and protein intake upon nitrogen balance for unstressed nutritionally depleted patients is depicted in Fig. 8.1 [55, 56]. At a fixed protein intake, nitrogen balance increases rapidly as calories are increased until a caloric intake of about 60–70% of total energy expenditure is achieved. When the caloric intake exceeds 60–70% of total energy expenditure, nitrogen balance continues to improve but at a slower accretion rate. Thus, the same nitrogen balance (slightly positive or nitrogen equilib-

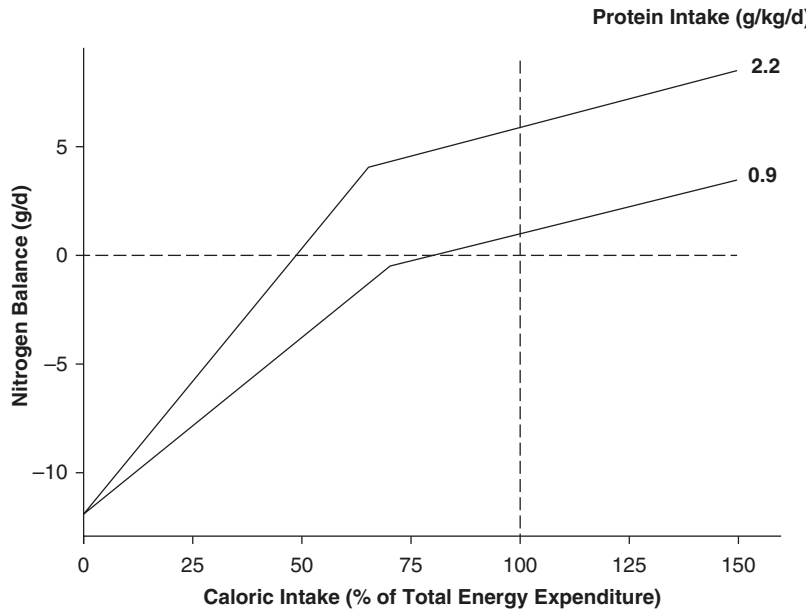

Fig. 8.1 Potential relationship between calorie and protein intake upon rates of nitrogen accretion at two different protein intakes [55]

rium) can be achieved by different macronutrient prescriptions (a low-calorie/high-protein regimen or a moderate-protein and moderate-calorie regimen). However, despite a similar nitrogen balance, each of these regimens will result in different body composition changes. The low-calorie, high-protein regimen (60% of total energy expenditure and 2.2 g/kg/d of protein) given to the unstressed protein-depleted patient will likely result in lean body mass gain and body fat loss, whereas the moderate-calorie and protein regimen (100% of total energy expenditure and 0.9 g/kg/d of protein) will likely result in lean body and body fat maintenance (possibly some minor gain in both compartments). These inferred changes in body composition are derived from the series of studies from Hill and associates that examined varying caloric and protein intakes and their influence upon changes in body protein, fat, and water compartments for surgical and gastroenterological patients requiring parenteral nutrition [57–59].

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

3-methylhistidine excretion (a marker of muscle proteolysis) among the different caloric intake groups was also noted. Increasing caloric delivery to critically ill, thermally injured patients resulted in a significant increase in total body fat especially when caloric intake exceeded 1.2 times the measured resting energy expenditure [62]. Additionally, increasing caloric intake had no significant effect on lean body mass as it remained essentially unchanged [62]. Taken together, these data suggest that protein has a more profound effect than calorie intake on net protein catabolism, nitrogen balance, and loss of body protein mass during critical illness. Increases in caloric intake may be potentially detrimental for the obese patient who is already calorically abundant and who is susceptible to overfeeding complications.

These data serve as the premise for providing hypocaloric, high-protein nutrition therapy for hospitalized patients with obesity. By providing a conservative caloric intake, the risk of complications associated with overfeeding such as worsening hyperglycemia, hypercapnia, and hepatic fat accumulation would likely be reduced. A conservative caloric intake may also result in increased lipolysis and net fat oxidation with weight loss [63] which would be a welcome secondary benefit. However, in order to compensate for the conservative caloric intake, an increase in protein supplementation is essential in an effort to achieve net protein anabolism as illustrated in Fig. 8.1.

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

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

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

Finally, and probably most importantly, protein intake was usually inadequate for the critically ill patient [54, 67–69] in many of the permissive underfeeding studies. The impact of inadequate protein intake is evident from a large, observational cohort study of international nutrition practices that indicated patients with Class II obesity (BMI 35–39.9 kg/m^2) who received a hypocaloric diet combined with a low protein intake (average intake of 1000 kcal/day or 9 kcal/

kg/day and 46 g of protein/day or 0.4 g/kg/day, respectively) experienced a worsened 60-day mortality rate [70]. In summary, we recommend that intentional permissive underfeeding with inadequate protein intake be avoided for the seriously ill surgical or trauma patient with obesity.

Table 8.4 summarizes the current literature on hypocaloric, high-protein nutrition therapy for surgical and trauma patients with obesity. Greenberg and Jeejeebhoy [108] contributed to the infancy of hypocaloric, high-protein nutrition therapy under the premise of "protein-sparing" nutrition therapy. Two different doses of amino acids (0.8 vs. 1.8 g/kg/d) without a nonprotein caloric source were evaluated in 12 patients whom were described as having "sufficient body fat stores" and moderately ill with gastrointestinal disease but not postoperative nor post-acute injury. The higher protein intake group achieved a positive nitrogen balance. The first case series documenting the use of hypocaloric, high-protein nutrition therapy for mild to moderately stressed, obese surgical patients evaluated 13 adult patients with obesity (208 ± 114% ideal body weight) and postoperative complications of sepsis with anastomotic leaks, abscesses, fistulae, or wound dehiscence were administered hypocaloric, high-protein parenteral nutrition [63]. Patients received 52% of measured resting energy expenditure as nonprotein calories (or ~70% of measured resting energy expenditure as total calories) and 2.1 ± 0.6 g/kg ideal body weight/day of protein for 48 ± 31 days. Positive nitrogen balance or nitrogen equilibrium and an increased serum protein response were achieved. Fifty to sixty-eight percent of nonprotein energy expenditure was derived from endogenous net fat oxidation, and a 2.3 ± 2.7 kg/week average weight loss occurred. All patients demonstrated complete healing, as evidenced by closed fistulae, resolution of abscess cavities, and wound closure [63].

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

In 2002, Dickerson and colleagues retrospectively examined the impact of hypocaloric vs. eucaloric enteral feeding in critically ill trauma patients with obesity. This study was different from the previously published work in that patients were enterally fed as opposed to parenterally fed. Additionally, all patients were critically ill, ICU patients [23]. Twenty-eight patients (average BMI, 41 kg/m^2) received hypocaloric feeding (<25 kcal/kg ideal body weight/day), and 12 (average BMI, 36 kg/m^2) received eucaloric feeding (25–30 kcal/kg ideal body weight/day). Protein goals were 2 g/kg ideal body weight/day for both groups. Mean nitrogen balance was not different between groups (−1.4 ± 5.8 g/day vs. −2.7 ± 5.9 g/day, respectively). In contrast to the previous studies, a modest mean negative

Table 8.4 Summary of clinical studies with hypocaloric, high-protein therapy in hospitalized obese patients

Author, year	Population characteristics No. of patients	Protein intake (g/kg/day)	Caloric intake (kcal/kg/day)	Nutritional outcome	Clinical outcome
Greenberg, 1979 [108]	Not postoperative nor post-acute injury				Blood ketones lower with higher protein intake
	n = 6 *n* = 6	0.8 IBW 1.8 IBW	3 IBW 7 IBW	NB: −3.7 g/day NB: +1.5 g/day	
Dickerson, 1986 [63]	Surgical, PN				Healed wounds, closed fistulae
	n = 13	2.1 IBW	25 IBW	NB: +2.4 g/day; increased serum albumin and TIBC	
Burge, 1994 [71]	Surgical, PN				
	n = 9	2.0 IBW	22 IBW	NB: +1.3 g/day	
	n = 7	2.2 IBW	42 IBW	NB: +2.8 g/day	
Choban, 1997 [72]	Surgical, SICU, PN				Less insulin therapy, no difference in mortality
	n = 16	2.0 IBW	22 IBW	NB: +4.0 g/day	
	n = 14	2.0 IBW	36 IBW	NB: +3.6 g/day	
Liu, 2000 [80]	Surgical, PN				No difference in morbidity or mortality
	<60 yo, *n* = 18	1.8 IBW	18 CBW	NB: +3.4 g/day	
	≥60 yo, *n* = 12	1.9 IBW	18 CBW	NB: +0.2 g/day	
Dickerson, 2002 [23]	Trauma ICU, EN				Decreased ICU stay, decreased antibiotic days, trending decrease in ventilator days
	n = 28	1.5 IBW	22 IBW	NB: −1.4 g/day, improved PA	
	n = 12	1.9 IBW	30 IBW	NB: −2.7 g/day, improved PA	
Choban and Dickerson, 2005 [29]	Surgical, SICU, trauma ICU, PN, EN BMI 30–39.9 *n* = 48 BMI ≥40 *n* = 22	Regression analysis for determination of protein requirements to achieve nitrogen equilibrium from two sites		ICU patients: BMI 30–39.9: 2 g/kg IBW/day BMI >40: 2.5 g/kg IBW/day Non ICU patients: BMI 30–39.9: 1.7 g/kg IBW/day BMI >40: 1.8 g/kg IBW/day	
Hamilton, 2011 [87]	Post-bariatric surgery with fistula/anastomotic leak, PN *n* = 23	1.2 CBW	14 CBW	7% decrease in BMI in 1.5 months Increase in serum albumin	21 out of 23 transitioned to EN or oral diet; 1 lost to follow-up
Dickerson, 2013 [67]	Trauma ICU, EN, PN				No difference in ICU LOS, ventilator days, hospital LOS
	<60 yo, *n* = 41	1.9 IBW	18 IBW	NB: −4.9 g/day at 2.3 g/kg IBW	
	≥60 yo, *n* = 33	2.1 IBW	21 IBW	NB:−3.2 g/day at 2.3 g/kg IBW Similar changes in PA; higher SUN for older patients	

BMI body mass index (kg/m^2), *CBW* current body weight, *EN* enteral nutrition, *IBW* ideal body weight, *ICU* intensive care, *LOS* length of stay, *n* number of patients, *NB* nitrogen balance, *PA* serum prealbumin concentration, *PN* parenteral nutrition, *SICU* surgery intensive care unit, *TIBC* total iron binding capacity, *yo* years old

nitrogen balance was observed due to the hypercatabolic state of the critically ill patients [54]. Serum prealbumin concentrations significantly increased for both groups. Unlike the previous studies that indicated no difference in clinical outcomes between hypocaloric and eucaloric feeding groups, enteral hypocaloric feeding (with an isonitrogenous protein intake to eucaloric feeding) was associated with improved clinical outcomes. The hypocaloric feeding group had a statistically significant shorter duration of ICU stay (19 ± 10 days vs. 29 ± 16 days), decreased antibiotic days (17 ± 12 days vs. 27 ± 17 days), and a trending decrease in days of mechanical ventilation (16 ± 11 days vs. 24 ± 17 days) [23]. Since this small, retrospective study is the only study to date to indicate improved clinical outcomes with hypocaloric, high-protein feeding for obese critically ill patients, confirmation of these data by a large prospective, randomized controlled trial is warranted.

Despite the paucity of published studies, the use of hypocaloric, high-protein nutrition therapy for the critically ill obese patient has been gaining momentum. Expert opinions from the 2013 American Society for Parenteral and Enteral Nutrition clinical guidelines on nutrition support of hospitalized patients with obesity [4], 2016 American Society for Parenteral and Enteral Nutrition and Society for Critical Care Medicine guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient [109], and 2011 summit report on nutrition therapy of the severely obese, critically ill patient [73] recommend this mode of therapy for hospitalized patients with obesity.

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

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

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

Patients with significant renal or hepatic disease may not be optimal candidates for hypocaloric, high-protein nutrition therapy as they may not be able to tolerate a large protein load due to impending uremia or worsening of encephalopathy. One empiric approach for these populations is to liberalize caloric intake by providing more calories and reduce protein intake while closely monitoring for azotemia, uremia, or worsening encephalopathy. The Penn State equations [46, 47, 50] (Table 8.3) are used to estimate resting energy expenditure, and a caloric intake designed to match (or slightly less than) the predicted resting energy expenditure is empirically given. Patients are closely monitored for evidence of overfeeding complications such as hyperglycemia and hypercapnia, and the calories are decreased (even in the face of reduced protein

intake) if necessary. For patients who are not in the ICU, we empirically use the Mifflin-St. Jeor equation (Table 8.3) in the same manner as the Penn State equation to estimate resting energy expenditure. Protein intake is adjusted based on patient response (e.g., change in serum urea nitrogen concentration) and the frequency and type of dialysis (e.g., hemodialysis, continuous renal replacement therapy) for both critically ill and non-critically ill patients with obesity.

It has been questioned whether older or elderly hospitalized patients with obesity should receive hypocaloric, high-protein nutrition therapy. Decreased sensitivity of muscle to anabolic stimuli, including amino acids, occurs during aging and has been associated with muscle mass loss [74, 75]. During critical illness with traumatic injuries, older patients tend to not experience significant nitrogen accretion until a protein intake of about 1.5 g/kg/d is achieved [80]. Additionally, the relationship between nitrogen accretion and protein intake can be expressed in a concave relationship as opposed to younger patients who exhibit a convex relationship with increased nitrogen accretion occurring as nitrogen intake is increased with a reduction in rate of accretion when protein intake exceeds about 2.2 g/kg/d [80]. As a result, older patients often need more protein to achieve the same nitrogen balance as younger patients, particularly at lower protein intakes. A concern of providing high-protein intakes, as required for hypocaloric, high-protein nutrition therapy, to older patients is the insidious decline in renal function that cannot be detected by serum creatinine concentration alone. This is because the older patients have less muscle mass (the source of creatinine appearance in the serum). Thus, a serum creatinine concentration in the "normal range" for an elderly person may be equivalent to a greater serum creatinine concentration for a young person [76]. Although the decrease in glomerular filtration rate that occurs with aging is much less than necessary to elicit symptoms of renal failure [77], concern is often expressed by clinicians about prescribing aggressive protein intakes to older patients due to anticipation of a decreased renal functional reserve [78] resulting in an increase in serum urea nitrogen (SUN) concentration.

To evaluate hypocaloric, high-protein nutrition therapy in older vs. younger patients with obesity, Liu retrospectively compared the anabolic response to parenteral nutrition in 18 patients younger than 60 years of age to 12 patients 60 years of age or older [79]. Patients were given 1.5–2 g/kg adjusted body weight/day of protein and 60–75% of their estimated caloric requirements (based on the Harris-Benedict equations [42] using an adjusted body weight). Despite similar protein and calorie intakes between age groups, nitrogen balance was lower for the older patient group (0.2 ± 5.0 vs. 3.4 ± 3.9 g/day, respectively) [79]. However, it is possible that inadequate protein intake was given to the patients as recent studies in healthy older subjects and critically ill older patients indicated that provision of greater amounts of protein can overcome this "anabolic resistance" [67, 80, 81]. Dickerson and colleagues examined nitrogen balance and clinical outcomes to hypocaloric, high-protein nutrition therapy in 33 older (>59 years of age) vs. 41 younger (<60 years of age) critically ill trauma patients with obesity [67]. When given an isonitrogenous regimen (2.3 g/kg ideal body weight/day), nitrogen balance was similar between older and younger age groups (-3.2 ± 5.7 g/day vs. -4.9 ± 9.0 g/day). Clinical outcomes of survival, duration of ICU stay, hospital length of stay, and duration of mechanical ventilation were also similar between age groups. It was concluded that older patients exhibited an equivalent net protein response as younger patients during hypocaloric, high-protein nutrition therapy when given adequate protein intake. However, older patients experienced a greater mean serum urea nitrogen concentration than the younger patients (30 ± 14 mg/dL vs. 20 ± 9 mg/dL) during hypocaloric high-protein nutrition therapy and are at greater risk for developing azotemia. Close monitoring for worsening azotemia when using hypocaloric, high-protein diets in older patients with obesity is warranted.

Because hyperglycemia is so prevalent in critically ill obese patients, clinicians often opt for use of a mixed fuel-based parenteral nutrition prescription whereby lipids are partially substituted for carbohydrate intake. However,

some patients with obesity experience hyperlipidemia with hypertriglyceridemia that does not improve when the hyperglycemia is resolved. During hypercaloric, fat-free, continuous parenteral nutrition, biochemical evidence for the development of essential fatty acid deficiency occurs in 30%, 66%, 83%, and 100% of patients after 1, 2, 3, and 4 weeks, respectively [82]. The explanation for their results was that due to the hypercaloric amount of dextrose calories provided to the patients, lipolysis was suppressed which prevented the availability of endogenous essential fatty acids. During hypocaloric feeding, even with a glucose-based parenteral nutrition solution, lipolysis would be expected to occur for energy and also provide a source for essential fatty acids. The respiratory quotient data from the case series of Dickerson et al. [63] indicated that 68 ± 19% of nonprotein energy originated from net fat oxidation. Since the parenteral nutrition solutions did not contain lipid emulsion, endogenous fat oxidation occurred [63]. Parnes and coworkers examined fatty acid profiles in 15 overweight cancer patients who were hypocalorically fed continuous, fat-free, parenteral nutrition for 2–5 weeks [83]. None of the patients experienced biochemical or clinical evidence for essential fatty acid deficiency. Despite these data, availability of endogenous fat post-injury in obese patients is not without debate. Jeevanadam and colleagues studied seven obese patients and ten nonobese, ventilator-dependent patients with multiple traumatic injuries 2–4 days after injury but before the provision of nutrition therapy [84]. Glycerol turnover (a marker of lipolysis) and net fat oxidation (from indirect calorimetry measurements) were reduced in the obese group compared to the nonobese control patients. The investigators concluded that the critically ill obese patient could not effectively use their most abundant fat fuel sources [84]. Taking the results of Parnes [83], Dickerson [63], and Jeevanandam [84] studies together, these data imply that obese patients exhibit a transient impairment in fat metabolism that occurs early after the stress event but resolves quickly during the patients' hospital course.

Metabolic Considerations Following Bariatric Surgery

It is recognized that bariatric surgery is the only treatment for morbid obesity that consistently achieves and maintains substantial weight loss, decreases obesity-related comorbidities, and improves quality of life and survival [85]. Two case series demonstrate the effectiveness of hypocaloric, high-protein parenteral nutrition therapy in achieving net protein anabolism and weight loss while facilitating wound healing for patients who experience postoperative surgical complications from obesity surgery [63, 86].

The clinical impact of surgical procedures that shorten small bowel absorptive capacity resulting in malabsorption of both macronutrients and micronutrients is evident [4, 87–91]. The most common vitamin and mineral deficiencies include iron, folate, vitamin B12, calcium, thiamine, and vitamins A, D, and K. In addition to a physical exam and patient interview for signs and symptoms of various nutrition deficiencies, laboratory evaluation is also necessary as part of the patient's long-term care. For patients with a microcytic anemia, determination of serum ferritin concentration is necessary for evaluation of potential iron deficiency. Although less common, some post-bariatric surgery patients develop microcytic anemia as a result of copper deficiency rather than iron deficiency [88]. Patients with a macrocytic anemia should be evaluated for folate or vitamin B12 deficiency using serum methylmalonic acid and homocysteine concentrations rather than folate or vitamin B12 concentrations as the former are more sensitive markers for folate or vitamin B12 depletion [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 as neurologic sequelae from vitamin B12 deficiency may not necessarily be completely reversible. Metabolic bone disease and secondary hyperparathyroidism, attributed to calcium and vitamin D deficiency, may also occur post-bariatric surgery [93].

In 2008, Aasheim recently summarized 104 reported cases of Wernicke encephalopathy from

thiamine depletion following bariatric surgery [89]. Admissions to the hospital occurred within 6 months after surgery in 94% of the cases. Intravenous glucose administration without thiamine supplementation was a risk factor in 18% of the patients. Unfortunately, an incomplete clinical recovery was observed in about half of the patients who developed Wernicke's encephalopathy. Thiamine-depleted patients can also develop beriberi (presenting either as a lactic acidosis or congestive cardiomyopathy) which also may not be completely reversible. Therefore, analogous to the patient with alcoholism, it is recommended that patients who have previously undergone bariatric surgery who are admitted to the hospital receive parenteral thiamine supplementation prior to administration of intravenous dextrose solutions [88].

The American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery guidelines recommend that post-bariatric surgery patients with compromised intestinal absorption receive two multivitamins plus minerals capsules daily, calcium citrate 1200–1500 mg/day, ≥3000 units of vitamin D daily (titrate to serum vitamin D concentration of >30 ng/mL), and vitamin B12 (sufficient to maintain normal concentrations) [87]. Additional vitamin A, thiamine, copper, zinc, and selenium may be necessary for some patients. It is recommended that routine vitamin and mineral laboratory monitoring be performed every 3–6 months and a bone density evaluation be performed at 2 years following bariatric surgery [87].

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

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

Providing a hypocaloric, high-protein enteral regimen is technically more difficult than when given via parenteral nutrition. The primary limitation with enteral nutrition is, unlike parenteral nutrition solutions whereby macronutrients are available in individual components, enteral formulas are only commercially available in fixed macronutrient concentrations (e.g., 1 kcal/mL, 62 g protein/L, etc.). Recently, a very high protein, lower caloric intake enteral formula (e.g., 1 kcal/mL, 92 g protein/L) has become commercially available in the United States that is often effective for use in developing a hypocaloric, high-protein regimen. Use of protein supplements, along with a reduction in enteral formula feeding rate, may be necessary to achieve the intended goals for some patients depending on the products available at an individual institution. It is not recommended that protein powder be added to the enteral formulation at the patient bedside as there is an increased chance for microbial contamination and inadequate mixing of the powder resulting in clumping and potential tube clogging. If this administration technique is chosen, it is preferred that the protein powder be admixed with the feeding under aseptic or clean conditions in the pharmacy and blenderized to reduce clumping. Given the wide use of ready to hang enteral products, a better alternative would be protein boluses via the feeding tube in addition to the continuous enteral feeding. Use of liquid protein solutions, as opposed to reconstitution of protein powder, may be less likely to cause tube

clogging when patients are fed via a small bore feeding tube. Use of a liquid protein solution may also reduce nursing workload. However, we have found that due to the viscosity of the liquid protein solution, administration via a small bore feeding tube requires that a 50:50 dilution with water is necessary for ease in administration [94]. Since the hypocaloric high-protein technique often requires a low enteral formula feeding rate (particularly when the 1 kcal/mL, 92 g protein/L formula is not available because of the calories being provided by the protein supplementation), daily liquid multivitamin supplementation may also be necessary to meet the daily Dietary Reference Intakes for vitamins. Dosing of the very high protein, lower calorie enteral formula based on a goal protein intake of about 2 g/kg ideal body weight/day will usually result in a regimen that is also within the intended calorie target range (e.g., 20–25 kcal/kg ideal body weight/day). For critically ill patients with a BMI ≥40 kg/m^2 [29], or those whose nitrogen balance is still markedly negative despite a protein intake of ~2 g/kg ideal body weight/day, a protein intake within 2.5–3 g/kg ideal body weight/day may be required. Intermittent administration of protein supplements along with the specialized very high protein formula may be required when attempting to achieve a high-protein intake of ≥2.5 g/kg ideal body weight/day while limiting total caloric intake to about 25 kcal/kg ideal body weight/day.

Metabolic Monitoring of the Critically Ill Surgical Patient with Obesity

Monitoring is designed to ensure efficacy of the prescribed regimen as well as prevention of complications associated with overfeeding or aggressive feeding [95]. In the ICU, despite its limitations, the best marker in routine clinical practice for objectively assessing the efficacy of the nutrition regimen is nitrogen balance. During the acute phase of illness post-trauma or surgery, if nitrogen equilibrium (e.g., about −4 to –5 g/day to +4 or greater g/day) can be achieved, we consider the regimen successful. If the nitrogen balance is markedly negative at goal protein intake, we will escalate the protein dosage. We have empirically set our maximum protein dose at 3 g/kg ideal body weight/day [54, 67]. If the patient is still in substantial negative nitrogen balance near our ceiling protein dose, we continue our current therapy and wait for the catabolic stress to diminish. Nitrogen balance determinations are performed weekly while the patient is in the ICU at our institution. Serum prealbumin concentration for assessing protein recovery is also monitored weekly. However, changes in serum prealbumin concentrations are limited in that its concentration is decreased by the presence of stress, infection, or inflammation. Resultantly, we also obtain concurrent C-reactive protein concentrations with weekly serum prealbumin concentrations to serve as a point of reference toward interpreting changes in serum prealbumin concentrations.

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

Our primary short-term goals for metabolic support of the hospitalized patient with obesity are achievement of net protein anabolism and avoidance of complications associated with nutritional overfeeding (Table 8.5). Use of a hypocaloric, high-protein regimen is primarily directed at avoiding hyperglycemia, hypercapnia, and worsening of nonalcoholic fatty liver disease. The critically ill surgical, thermally injured, and trauma patient appears to benefit from tighter glycemic control than that of other populations [31–35]; however, the impact of obesity upon insulin sensitivity and a higher incidence of

Table 8.5 Recommended nutrient intakes for the hospitalized patient with obesity

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

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

diabetes mellitus makes glycemic control more complex. Despite hypocaloric feeding with low carbohydrate intakes, use of our graduated continuous intravenous regular human insulin infusion algorithm or our tightened sliding scale coverage is often warranted to maintain blood glucose concentrations within a desirable target range (e.g., 70–149 mg/dL while the patient is in the ICU) [37, 96, 107]. Arterial blood gases are closely monitored for rises in pCO_2 concentrations not attributable to other causes [41]. Daily fluid volume intake and output, along with physical examination of the patient (with radiological evidence or hemodynamic measurements when available), are monitored for evidence of fluid overload. The presence of nonalcoholic fatty liver disease is often associated with increased serum concentrations of liver function tests, particularly the aminotransferases. Because a slow rate of weight loss may improve hepatomegaly and decrease serum ALT concentration associated with nonalcoholic fatty liver disease [97], it would be important to avoid overfeeding hospitalized obese patients. Unfortunately, it is unclear whether routine monitoring of liver function tests would be of any significant value as the presence of sepsis or inflammation confounds interpretation of these tests [98].

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

Conclusions

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

References

1. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS Data Brief. 2015:1–8.
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 CW 3rd. The outcomes of obese patients in critical care. JPEN J Parenter Enteral Nutr. 2011;35:29S–35.

4. Choban P, Dickerson R, Malone A, Worthington P, Compher C, American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. Clinical guidelines: nutrition support of hospitalized adult patients with obesity. JPEN J Parenter Enteral Nutr. 2013;37(6):714–44.
5. Diaz JJ Jr, Norris PR, Collier BR, Berkes MB, Ozdas A, May AK, et al. Morbid obesity is not a risk factor for mortality in critically ill trauma patients. J Trauma. 2009;66:226–31.
6. Hoffmann M, Lefering R, Gruber-Rathmann M, Rueger JM, Lehmann W, Trauma Registry of the German Society for Trauma Surgery. The impact of BMI on polytrauma outcome. Injury. 2012;43:184–8.
7. Hutagalung R, Marques J, Kobylka K, Zeidan M, Kabisch B, Brunkhorst F, et al. The obesity paradox in surgical intensive care unit patients. Intensive Care Med. 2011;37:1793–9.
8. Newell MA, Bard MR, Goettler CE, Toschlog EA, Schenarts PJ, Sagraves SG, et al. Body mass index and outcomes in critically injured blunt trauma patients: weighing the impact. J Am Coll Surg. 2007;204:1056–62.
9. Nasraway SA Jr, Albert M, Donnelly AM, Ruthazer R, Shikora SA, Saltzman E. Morbid obesity is an independent determinant of death among surgical critically ill patients. Crit Care Med. 2006;34:964–71.
10. Bochicchio GV, Joshi M, Bochicchio K, Nehman S, Tracy JK, Scalea TM. Impact of obesity in the critically ill trauma patient: a prospective study. J Am Coll Surg. 2006;203:533–8.
11. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. Obesity increases risk of organ failure after severe trauma. J Am Coll Surg. 2006;203:539–45.
12. Brown CV, Neville AL, Rhee P, Salim A, Velmahos GC, Demetriades D. The impact of obesity on the outcomes of 1,153 critically injured blunt trauma patients. J Trauma. 2005;59:1048–51.
13. Ray DE, Matchett SC, Baker K, Wasser T, Young MJ. The effect of body mass index on patient outcomes in a medical ICU. Chest. 2005;127:2125–31.
14. Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. Crit Care Med. 2008;36:151–8.
15. Sakr Y, Madl C, Filipescu D, Moreno R, Groeneveld J, Artigas A, et al. Obesity is associated with increased morbidity but not mortality in critically ill patients. Intensive Care Med. 2008;34:1999–2009.
16. Martino JL, Stapleton RD, Wang M, Day AG, Cahill NE, Dixon AE, et al. Extreme obesity and outcomes in critically ill patients. Chest. 2011;140:1198–206.
17. Hogue CW Jr, Stearns JD, Colantuoni E, Robinson KA, Stierer T, Mitter N, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. Intensive Care Med. 2009;35:1152–70.
18. Kumar G, Majumdar T, Jacobs ER, Danesh V, Dagar G, Deshmukh A, et al. Outcomes of morbidly obese patients receiving invasive mechanical ventilation: a nationwide analysis. Chest. 2013;144:48–54.
19. Gallagher D, DeLegge M. Body composition (sarcopenia) in obese patients: implications for care in the intensive care unit. JPEN J Parenter Enteral Nutr. 2011;35:21S–8.
20. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264–70.
21. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr. 2012;31:462–8.
22. Weijs PJ, Stapel SN, de Groot SD, Driessen RH, de Jong E, Girbes AR, et al. Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr. 2012;36:60–8.
23. Dickerson RN, Boschert KJ, Kudsk KA, Brown RO. Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition. 2002;18:241–6.
24. Pickkers P, de Keizer N, Dusseljee J, Weerheijm D, van der Hoeven JG, Peek N. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. Crit Care Med. 2013;41:1878–83.
25. Druml W. ICU patients: fatter is better? Intensive Care Med. 2008;34:1961–3.
26. Bornstein SR, Licinio J, Tauchnitz R, Engelmann L, Negrão AB, Gold P, Chrousos GP. Plasma leptin levels are increased in survivors of acute sepsis: associated loss of diurnal rhythm, in cortisol and leptin secretion. J Clin Endocrinol Metab. 1998;83:280–3.
27. Wendel M, Paul R, Heller AR. Lipoproteins in inflammation and sepsis. II. Clinical aspects. Intensive Care Med. 2007;33:25–35.
28. Oliveros H, Villamor E. Obesity and mortality in critically ill adults: a systematic review and meta-analysis. Obesity. 2008;16:515–21.
29. Choban PS, Dickerson RN. Morbid obesity and nutrition support: is bigger different? Nutr Clin Pract. 2005;20:480–7.
30. Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW. Mechanisms of insulin resistance following injury. Ann Surg. 1982;196:420–35.
31. Collier B, Diaz J Jr, Forbes R, Morris J Jr, May A, Guy J, et al. The impact of a normoglycemic management protocol on clinical outcomes in the trauma intensive care unit. JPEN J Parenter Enteral Nutr. 2005;29:353–9.
32. Scalea TM, Bochicchio GV, Bochicchio KM, Johnson SB, Joshi M, Pyle A. Tight glycemic control in critically injured trauma patients. Ann Surg. 2007;246:605–12.
33. Bochicchio GV, Joshi M, Bochicchio KM, Pyle A, Johnson SB, Meyer W, et al. Early hyperglycemic control is important in critically injured trauma patients. J Trauma. 2007;63:1353–9.
34. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin

therapy in the critically ill patients. N Engl J Med. 2001;345:1359–67.
35. Jeschke MG. Clinical review: glucose control in severely burned patients – current best practice. Crit Care. 2013;17:232.
36. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
37. Dickerson RN, Swiggart CE, Morgan LM, Maish GO III, Croce MA, Minard G, Brown RO. Safety and efficacy of a graduated intravenous insulin infusion protocol in critically ill trauma patients receiving specialized nutritional support. Nutrition. 2008;24:536–45.
38. Goldberg IJ. Clinical review 124: diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab. 2001;86:965–71.
39. Brown CV, Velmahos GC. The consequences of obesity on trauma, emergency surgery, and surgical critical care. World J Emerg Surg. 2006;1:27.
40. Askanazi J, Carpentier YA, Elwyn DH, Nordenström J, Jeevanandam M, Rosenbaum SH, et al. Influence of total parenteral nutrition on fuel utilization in injury and sepsis. Ann Surg. 1980;191:40–6.
41. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. Excess total calories vs. high proportion of carbohydrate calories. Chest. 1992;102:551–5.
42. Harris JA, Benedict FG. Biometric studies of basal metabolism in man. Washington, DC: Carnegie Institute of Washington; 1919. Publication no. 297.
43. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–85.
44. Sheldon GF, Peterson SR, Sanders R. Hepatic dysfunction during hyperalimentation. Arch Surg. 1978;113:504–8.
45. Feurer ID, Crosby LO, Buzby GP, Rosato EF, Mullen JL. Resting energy expenditure in morbid obesity. Ann Surg. 1983;197:17–21.
46. Frankenfield DC, Ashcraft CM, Galvan DA. Prediction of resting metabolic rate in critically ill patients at the extremes of body mass index. JPEN J Parenter Enteral Nutr. 2013;37:361–7.
47. Frankenfield DC, Coleman A, Alam S, Cooney RN. Analysis of estimation methods for resting metabolic rate in critically ill adults. JPEN J Parenter Enteral Nutr. 2009;33:27–36.
48. Frankenfield DC, Rowe WA, Smith JS, Cooney RN. Validation of several established equations for resting metabolic rate in obese and nonobese people. J Am Diet Assoc. 2003;103:1152–9.
49. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51:241–7.
50. Frankenfield D. Validation of an equation for resting metabolic rate in older obese, critically ill patients. JPEN J Parenter Enteral Nutr. 2011;35:264–9.
51. Dickerson RN, Tidwell AC, Minard G, Croce MA, Brown RO. Predicting total urinary nitrogen excretion from urinary urea nitrogen excretion in multiple-trauma patients receiving specialized nutritional support. Nutrition. 2005;21:332–8.
52. Shaw JH, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. The response to glucose infusion and total parenteral nutrition. Ann Surg. 1987;205:288–94.
53. Shaw JH, Wolfe RR. An integrated analysis of glucose, fat, and protein metabolism in severely traumatized patients. Studies in the basal state and the response to total parenteral nutrition. Ann Surg. 1989;209:63–72.
54. Dickerson RN, Pitts SL, Maish GO 3rd, Schroeppel TJ, Magnotti LJ, Croce MA, Minard G, Brown RO. A reappraisal of nitrogen requirements for patients with critical illness and trauma. J Trauma Acute Care Surg. 2012;73:549–57.
55. Elwyn DH. Nutritional requirements of adult surgical patients. Crit Care Med. 1980;8:9–20.
56. Elwyn DH, Gump FE, Munro HN, Iles M, Kinney JM. Changes in nitrogen balance of depleted patients with increasing infusions of glucose. Am J Clin Nutr. 1979;32:1597–611.
57. Hill GL, Church J. Energy and protein requirements of general surgical patients requiring intravenous nutrition. Br J Surg. 1984;71:1–9.
58. 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.
59. Smith RC, Burkinshaw L, Hill GL. Optimal energy and nitrogen intake for gastroenterological patients requiring intravenous nutrition. Gastroenterology. 1982;82:445–52.
60. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma. 1987;27:262–6.
61. Frankenfield DC, Smith JS, Cooney RN. Accelerated nitrogen loss after traumatic injury is not attenuated by achievement of energy balance. JPEN J Parenter Enteral Nutr. 1997;21:324–9.
62. Hart DW, Wolf SE, Herndon DN, Chinkes DL, Lal SO, Obeng MK, Beauford RB, Mlcak RTRP. Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. Ann Surg. 2002;235:152–61.
63. Dickerson RN, Rosato EF, Mullen JL. Net protein anabolism with hypocaloric parenteral nutrition in obese stressed patients. Am J Clin Nutr. 1986;44:747–55.
64. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest. 2003;124:297–305.

65. Ibrahim EH, Mehringer L, Prentice D, Sherman G, Shaiff R, Fraser V, Kollef MH. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. JPEN J Parenter Enteral Nutr. 2002;26:174–81.
66. Dickerson RN. Optimal caloric intake for critically ill patients: first, do no harm. Nutr Clin Pract. 2011;26:48–54.
67. Dickerson RN, Medling TL, Smith AC, Maish GO III, Croce MA, Minard G, Brown RO. Hypocaloric, high-protein nutrition therapy in older vs. younger critically ill patients with obesity. JPEN J Parenter Enteral Nutr. 2013;37:342–51.
68. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr. 2012;96:591–600.
69. Hoffer LJ, Bistrian BR. Why critically ill patients are protein deprived. JPEN J Parenter Enteral Nutr. 2013;37:300–9.
70. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009;35:1728–37.
71. Burge JC, Goon A, Choban PS, Flancbaum L. Efficacy of hypocaloric total parenteral nutrition in hospitalized obese patients: a prospective, double-blind randomized trial. JPEN J Parenter Enteral Nutr. 1994;18:203–7.
72. Choban PS, Burge JC, Scales D, Flancbaum L. Hypoenergetic nutrition support in hospitalized obese patients: a simplified method for clinical application. Am J Clin Nutr. 1997;66:546–50.
73. McClave SA, Kushner R, Van Way CW 3rd, Cave M, DeLegge M, Dibaise J, et al. Nutrition therapy of the severely obese, critically ill patient: summation of conclusions and recommendations. JPEN J Parenter Enteral Nutr. 2011;35:88S–96S.
74. Guillet C, Prod'homme M, Balage M, Gachon P, Giraudet C, Morin L, Grizard J, Biorie Y. Impaired anabolic response of muscle protein synthesis is associated with S6K1 dysregulation in elderly humans. FASEB J. 2004;18:1586–7.
75. 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.
76. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
77. Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. Clin Nutr. 2008;27:675–84.
78. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. J Am Soc Nephrol. 1993;3:1371–7.
79. Liu KJ, Cho MJ, Atten MJ, Panizales E, Walter R, Hawkins D, Donahue PA. Hypocaloric parenteral nutrition support in elderly obese patients. Am Surg. 2000;66:394–400.
80. Dickerson RN, Maish GO 3rd, Croce MA, Minard G, Brown RO. Influence of aging on nitrogen accretion during critical illness. JPEN J Parenter Enteral Nutr. 2015;39:282–90.
81. Guillet C, Zangarelli A, Gachon P, Morio B, Giraudet C, Rousset P, Biorie Y. Whole body protein breakdown is less inhibited by insulin, but still responsive to amino acid, in nondiabetic elderly subjects. J Clin Endocrinol Metab. 2004;89:6017–24.
82. 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.
83. Parnes HL, Mascioli EA, LaCivita CL, Gutierrez PL, Friedman J, Lopes SM, Bistrian BR. Parenteral nutrition in overweight patients: are intravenous lipids necessary to prevent essential fatty acid deficiency? J Nutr Biochem. 1994;5:243–7.
84. Jeevanandam M, Young DH, Schiller WR. Obesity and the metabolic response to severe multiple trauma in man. J Clin Invest. 1991;87:262–9.
85. 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.
86. 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.
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: co-sponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity. 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, Olberts T, Bøhmer T. Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch. Am J Clin Nutr. 2009;90:15–22.
91. Malone M. Recommended nutritional supplements for bariatric surgery patients. Ann Pharm. 2008;42:1851–8.
92. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Int Med. 1999;159:1289–98.
93. Slater GH, Ren CJ, Siegel N, Williams T, Barr D, Wolfe B, Dolan K, Fielding GA. Serum fat-soluble

vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. J Gastrointest Surg. 2004;8:48–55; discussion 54–5.
94. 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.
95. Dickerson RN, Drover JW. Monitoring nutrition therapy in the critically ill patient with obesity. JPEN J Parenter Enteral Nutr. 2011;35:44S–51.
96. Dickerson RN, Wilson VC, Maish GO 3rd, 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.
97. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:1221–31.
98. Sikuler E, Guetta V, Keynan A, Neumann L, Schlaeffer F. Abnormalities in bilirubin and liver enzyme levels in adult patients with bacteremia. A prospective study. Arch Int Med. 1989;149:2246–8.
99. De Jong A, Verzilli D, Sebbane M, Monnin M, Belafia F, Cisse M, Conseil M, Carr J, Jung B, Chanques G, Molinari N, Jaber S. Medical versus surgical ICU obese patient outcome: a propensity-matched analysis to resolve clinical trial controversies. Crit Care Med. 2018;46:e294–301.
100. Deliberato RO, Serpa Neto A, Komorowski M, Stone DJ, Ko SQ, Bulgarelli L, Rodrigues Ponzoni C, de Freitas Chaves RC, Celi LA, Johnson AEW. An evaluation of the influence of body mass index on severity scoring. Crit Care Med. 2019;47:247–53.
101. Sakr Y, Alhussami I, Nanchal R, Wunderink RG, Pellis T, Wittebole X, Martin-Loeches I, Francois B, Leone M, Vincent JL. Being overweight is associated with greater survival in ICU patients: results from the intensive care over nations audit. Crit Care Med. 2015;43:2623–32.
102. Tojek K, Wustrau B, Czerniak B, Korzycka-Wilinska W, Winiarski P, Banaszkiewicz Z, Budzynski J. Body mass index as a biomarker for the evaluation of the "obesity paradox" among inpatients. Clin Nutr. 2019;38:412–21.
103. Dickerson RN. Metabolic support challenges with obesity during critical illness. Nutrition. 2019;57:24–31.
104. Tieland M, van Dronkelaar C, Boirie Y. Sarcopenic obesity in the ICU. Curr Opin Clin Nutr Metab Care. 2019;22:162–6.
105. Peterson SJ, Braunschweig CA. Prevalence of sarcopenia and associated outcomes in the clinical setting. Nutr Clin Pract. 2016;31:40–8.
106. Harris K, Zhou J, Liu X, Hassan E, Badawi O. The obesity paradox is not observed in critically ill patients on early enteral nutrition. Crit Care Med. 2017;45:828–34.
107. Cogle SV, Smith SE, GOr M, Minard G, Croce MA, Dickerson RN. Sliding scale regular human insulin for identifying critically ill trauma patients who require intensive insulin therapy and for glycemic control in those with mild to moderate hyperglycemia. J Pharm Nutr Sci. 2017;7:106–15.
108. Greenberg GR, Jeejeebhoy KN. Intravenous protein-sparing therapy in patients with gastrointestinal disease. JPEN J Parenter Enteral Nutr. 1979;3:427–32.
109. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C. 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. 2016;40:159–211.

Malignancy

9

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

The Consequences of Nutrition in Cancer

Cancer is a major public health problem in the United States and worldwide. There will be an estimated 1.74 million cases of potentially life-threatening cancer in the United States in 2019, and approximately 610,000 people are projected to die from cancer in 2019 [1]. Cancer is a disease that also has an enormous impact worldwide [2]. In addition to a human toll, cancer exacts a significant toll on healthcare expenditures. In the United States, the total of all healthcare expenditures for cancer in 2015 amounted to $80.2 billion [3]. Nutrition and diet play a major role in cancer. Dietary factors are a significant component of the identifiable attributable risks of cancer. Cancer-related malnutrition and cancer cachexia are prominent elements that cause signs and symptoms of cancer and are major contributors to patient distress. Furthermore, malnutrition and weight loss often contribute to the death of cancer patients [4–7]. Conversely, the role of overnutrition in cancer pathogenesis and prognosis has also been emphasized. While progress has been made, heightened awareness and clinical research have yet to solve these pressing problems.

The term attributable risk refers to the proportion of cancers in which a factor plays an etiologic role. It was estimated in 1981 that 35% of all cancers in the United States could be prevented by changes in diet [8]. This avoidable risk estimate was subsequently updated and affirmed, with a confidence interval of approximately 20–42% [9]. This analysis was performed in 1995 and was more recently updated to 45% in 2018 [7]. In light of the obesity epidemic, and the relationship between obesity and cancer risk, an updated estimate would likely be higher [10]. Especially strong associations are observed between diet and cancer risk for colorectal cancer, breast cancer, prostate cancer, pancreas cancer, endometrial cancer, and gallbladder cancer [9]. Nonalcoholic steatohepatitis is closely associated with metabolic syndrome and obesity and is associated with an increased risk of hepatocellular carcinoma even if it does not progress to frank cirrhosis. In light of the current obesity epidemic, a hepatocellular carcinoma epidemic may be imminent [11]. Of additional concern is that more patients are surviving cancer and therefore may be at increased risk for

V. A. Gall · V. Koshenkov
Rutgers-Robert Wood Johnson Medical School and the Rutgers Cancer Institute of New Jersey, Department of Surgery, Division of Surgical Oncology, New Brunswick, NJ, USA

L. G. Melstrom
Division of Surgical Oncology, Department of Surgery, City of Hope Medical Center, Los Angeles, CA, USA

D. A. August (✉)
Rutgers Cancer Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: augustda@cinj.rutgers.edu

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_9

the development of a second cancer because of their dietary behaviors and obesity. Fortunately, these patients also represent an opportunity for health improvement [12–15].

Undernutrition

Malnutrition is a hallmark of cancer. An estimated 40% of cancer patients present with weight loss; the devastating consequences of cancer cachexia may be present in as many as 80% of those with advanced malignancies [16, 17]. The extent of weight loss at the time of diagnosis is prognostic for survival. More than 10% loss of usual body weight appears to be especially problematic as is a rate of weight loss of greater than 2.75% per month [14, 15]. Weight loss in cancer patients can also cause symptom distress, including fatigue, depression, and social withdrawal [18–20]. The impact of malnutrition on operative morbidity and mortality is well described in cancer patients [4]. This association was reported more than 75 years ago and continues to be observed [21, 22]. Despite the critical role of surgery in curing cancer, there are some patients who are not candidates for curative surgery because of the risk of life-threatening complications that their malnutrition confers.

Quality of Life

Malnutrition is also a significant factor that affects the quality of life (QoL) in cancer patients. In 2012, Lis et al. systematically reviewed the literature on the role of nutrition status in predicting QoL in cancer [23]. They identified 26 studies, with 6 investigating head and neck, 8 gastrointestinal, 1 lung, 1 gynecologic, and 10 heterogeneous cancers. Of these studies, 24 concluded that better nutrition status was associated with better QoL. There was only one study that concluded that there was no association. They concluded that correcting malnutrition may improve QoL in cancer patients, and this is likely an important outcome of interest to cancer patients, their caregivers, and families.

Overnutrition

Although cancer is often characterized as a wasting disease, overnutrition (overweight, body mass index greater than 25 kg/m^2, and obese, body mass index greater than 30 kg/m^2) is being seen more frequently in cancer patients as a result of the rising incidence of excess body weight in the United States and worldwide. In the authors' experience, it is not uncommon to perform major gastrointestinal cancer operations in people who weigh more than 125 or even 150 kg. In the United States in 2014, excess body weight was found to be an attributable risk factor in 7.8% of new cancer diagnoses. When combined with related risk factors like poor diet, alcohol intake, and physical inactivity, this number rose to 18.2% second only to cigarette smoking which accounted for 19%. Women are particularly affected with excess weight, alcohol, poor diet, and inactivity accounting for 22.4% of new cancer cases compared to 13.9% in men. This strong association between cancer and overnutrition in women is seen in uterine cancer (60%), breast cancer (11%), and ovarian cancer (4.3%). Obesity is associated with a variety of other cancers, including cancers traditionally associated with wasting, such as gallbladder cancer (35%), liver cancer (34%), renal cancer (33%), esophageal cancer (32%), gastric cancer (17.5%), pancreas cancer (16.9%), and colorectal cancer (5.2%) [24]. Obesity may also account for as many as 38% of all cases of hepatocellular carcinoma in the United States. Similarly, excess body weight has been associated with an increased risk of mortality from these cancers. The pathophysiology of the link between cancer mortality and obesity is unclear, but there are a number of plausible hypotheses [25]. In many animal models, severe caloric restriction increases longevity and prevents cancer. Obesity may interfere with cancer detection, as physical exam findings may be masked. The precision of cancer therapy, including surgery, radiation therapy, and chemotherapy, is compromised in obese patients, resulting in increased treatment-associated morbidity and decreased efficacy. Weight gain and decreased physical activity can modulate hormonal media-

Table 9.1 Causes of cancer-associated weight loss and cachexia

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

tors such as estrogens and may also affect the cytokine milieu in ways that adversely alter host inflammatory activation and homeostasis.

The Metabolic Milieu in Malignancy: Cancer Cachexia

Cancer cachexia is a syndrome that is frequently encountered in cancer patients and is associated with a poor prognosis. Clinically, it is characterized by progressive weight loss from both fat and skeletal muscle tissues, anorexia, fatigue, and anergy. The underlying etiologies include anatomic, physiologic, and metabolic derangements that result in a state of undernutrition [26] (Table 9.1). Cancer cachexia can be seen in the early stages of tumor growth but more commonly presents in advanced stages of the disease. The extent of undernutrition parallels the type of neoplasm, with more severe malnutrition observed with upper gastrointestinal and pancreatic cancers and less severe malnutrition with lymphomas, breast cancers, and sarcomas [16] (Table 9.2). Multiple factors contribute to undernutrition, and their interplay is variable among different patients.

Energetics

One of the potential etiologies of cancer cachexia is a change in the metabolic rate. Resting energy expenditure (REE) has been studied extensively in relation to cancer cachexia, but the findings of the published literature have been inconsistent. While many studies have reported an increase in REE of cancer patients [27–32], other reports have indicated that REE may be decreased or remain unchanged [33–35]. This has led some investigators to postulate that the metabolic response to cancer is highly variable and may be dependent on the type of a malignancy and the host response [29, 31]. It has been shown that patients with lung cancer and gastric cancer are usually hypermetabolic [36–39], while those with hepatobiliary tumors are predominantly hypometabolic [40]. With respect to esophageal, pancreatic, and colorectal neoplasms, the metabolic rates are more evenly distributed [39]. However, different responses of REE for patients with the same type of cancer have also been observed [41]. Some data suggest those patients who are hypermetabolic may be at greater risk for developing cancer cachexia [42].

Resting energy expenditure has also been postulated to be affected by the aggressiveness and the duration of the disease. Although reports by Ravasco et al. and Cao et al. showed that REE was significantly higher in patients with advanced cancer [31, 32], findings from other reports suggest that tumor stage does not play a role in REE [34]. Moderately or poorly differentiated histology, increased acute-phase proteins, and a prolonged duration of illness have all been associated with elevated REE [29, 31–33, 35].

Table 9.2 The incidence of weight loss or malnutrition in adult cancer patients by primary tumor site

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

In order to understand these conflicting results, a thorough understanding of factors that affect REE is required. Age, gender, height, and weight are major determinants of REE [33]. Women have a propensity to become hypometabolic with cancer. With respect to height and weight, an elevated metabolic rate is found in taller and heavier individuals [43]. Additionally, it is important to note that cancer patients losing weight tend to initially lose fat mass. The fat-free mass (FFM) contributes more to REE. Consequently, any calculation that does not account for a different body composition of a weight-losing individual will yield erroneous data. Unfortunately, the most commonly used formulas to predict REE, such as the Kleiber formula and the Harris Benedict formula, do not account for the changes in body composition that are frequently seen in cancer patients [44, 45]. As a result, earlier studies looking at metabolism in cancer patients did not measure FFM and erroneously suggested an elevated REE. Since then, attempts have been made to adjust the formulas for certain illnesses known to increase the metabolic rate, such as surgery, sepsis, and burns, by adding a stress factor to the equation [46, 47]. Despite these efforts, overestimation of REE because of a stress factor and the general nonuniformity of lean body mass have been reported, posing further difficulties to the accuracy of metabolic rate calculation in cancer patients [30, 35, 48].

It seems safe to conclude that there is great variability of REE in response to cancer. It seems that the energy requirements of cancer patients do not follow a Gaussian distribution. Moreover, cancer patients do not adjust food intake to changes in metabolic rate appropriately, leading their intake to be chronically below energy expenditure [26]. Cancer patients with an elevated REE may be at greater risk for developing cancer cachexia [42]. Consequently, the assessment of nutritional requirements is challenging and can impair clinicians' abilities to appropriately replete patients nutritionally.

Intermediary Metabolism [49–51]

The hallmark metabolic changes in patients with cancer cachexia result in an overall state of intermediary metabolic cycling. Net rates of carbohydrate, protein, and lipid turnover are increased without any apparent metabolic benefit, resulting in energy wasting. These metabolic changes are cytokine mediated, and the resulting cachexia is not reversed solely with increased nutrition intake. The mainstay of treatment should be management of the underlying malignancy.

Much of the weight loss associated with cancer cachexia is a result of the depletion of fat stores. Total body fat can be decreased by as much as 85% [52]. The primary mechanism behind this is elevated fat cell lipolysis. Fat cell lipolysis, not reduced lipogenesis, is considered the primary mechanism of fat loss in cancer cachexia [52]. Lipid-mobilizing factor (LMF) is central to the process of adipocytic lipolysis via regulation of hormone-sensitive lipase (HSL) [53]. Lipid-mobilizing factor is detectable in weight-losing cancer patients, but not weight-stable cancer patients [54]. Its role in lipolysis is to regulate hormone-sensitive lipase. There may also be a role for brown fat in the pathogenesis of cancer cachexia. In animal models, generation of brown fat cells in white adipose may occur early, before the appearance of clinical signs; this may be related to the effects of IL-6, an important cytokine associated with wasting. There is evidence this may be relevant to humans as well [55]. The alteration of lipid metabolism is frequently accompanied by a change in the serum lipid profile, creating a lipid profile similar to type IV hyperlipidemia [56]. Although increased serum levels of lipids may aid host substrate utilization, tumor cells may also derive benefit from the elevated lipid levels because of their high requirement for polyunsaturated fatty acids [57].

The dramatic diminution of fat stores that occurs in cancer cachexia is accompanied by a significant depletion of skeletal muscle mass. While the muscle protein component may be reduced by as much as 75%, the nonmuscle visceral protein compartment remains largely unchanged [49]. Muscle wasting results in weakness, fatigue, and respiratory complications that are observed in weight-losing patients with advanced cancer. Respiratory failure and pneumonia are responsible for the deaths of a significant percentage of cancer patients [53]. This severe muscle atrophy is a consequence of an

unfavorable combination of depressed protein synthesis and increased protein degradation. Proteolysis-inducing factor (PIF) is a major mediator of protein catabolism in cancer patients; it activates nuclear factor kappa B (NF-κB), which then turns on the ubiquitin-proteasome proteolytic pathway [58].

The metabolism of carbohydrates is frequently deranged in cancer cachexia. Much of the alteration stems from the fact that most cancer cells use glycolysis as their main source for energy generation. The Warburg effect refers to the observation that cancer cells derive most of their adenosine triphosphate (ATP) from the sustained conversion of glucose into lactate, while mitochondrial oxidation is suppressed [59]. As a result of tumor cells' reliance on glycolysis, an energy-inefficient process, gluconeogenesis is significantly increased to provide the necessary fuel. The Cori cycle is activated in response to the excessive production of lactic acid [60, 61]. Increased hepatic gluconeogenesis occurs for several reasons. First, an abundance of lactic acid from widespread glycolysis is resynthesized into glucose. Second, elevated concentrations of peripherally released alanine and glycerol are converted into glucose [62, 63]. Third, insulin resistance is commonly encountered in patients with cancer cachexia [64, 65]. There is evidence to suggest that insulin resistance develops because of decreased levels of leptin, an adipocyte-derived hormone that plays a role in appetite regulation [66, 67]. The end result of these changes is that normal tissues may be energy-starved from the increased rate of hepatic gluconeogenesis, as this is an energy-consuming process, and this likely has clinical significance for patients.

Cytokine Milieu

The primary driver of cancer cachexia is the alteration in cytokine milieu observed in many cancer patients (Table 9.3). Cytokines are polypeptides that provide short-range signaling between cells in multiple physiologic processes. Tumor necrosis factor-α (TNF) is believed to play a central role in the body's response to a variety of immunologic challenges [68]. Other cytokines, such as interferon (INF)-γ, interleukin-1 (IL-1), and interleukin-6 (IL-6), mediate various pro-inflammatory biologic functions. Both tumor cell production and host immune response to tumor contribute to the generation of pro-inflammatory cytokines [69].

Table 9.3 Cytokine milieu and effects in cancer cachexia

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

In the presence of injury, infection, and inflammation, TNF is important to local host defenses. Unfortunately, its systemic effects may be deleterious. The administration of TNF leads to metabolic changes that are associated with cachexia, such as lipolysis, muscle catabolism, and increased glucose turnover and utilization [68]. Tumor necrosis factor-α enhances lipolysis through activation of HSL. It also decreases lipogenesis by inhibiting production of lipoprotein lipase [70]. With respect to proteolysis, TNF and other cytokines have been found to mediate the ubiquitin-proteasome pathway and nitric oxide synthase (NOS) expression [71]. High levels of nitric oxide inhibit key enzymes of oxidative phosphorylation and can impair contractile performance of skeletal muscle [69].The end-organ effects of TNF are dependent upon the site of production/administration. When it is produced locally in the brain, anorexia ensues, while muscle inoculation causes chronic cachexia and muscle atrophy [72].

Evidence from multiple studies concerning TNF serum concentrations in cancer cachexia is conflicted. Some authors report consistently elevated levels of TNF, while others do not [67]. In some situations, antibodies used to neutralize TNF in vivo can relieve the anorexia and cachexia observed in cancer patients [69].

Interferon-γ possesses biological activities that overlap those of TNF. Its effects on fat and protein metabolism are similar in that it potentiates lipolysis, inhibits lipoprotein lipase, and decreases protein synthesis [70]. Additionally, animal models have demonstrated that implantation of tumors that produce IFN induces cancer cachexia syndrome, but passive immunization against it can eliminate this response [73]. As is the case with TNF, serum levels of IFN are not consistently elevated. Antibodies to IFN are able to suppress some of the metabolic changes that are found in cancer cachexia [70].

IL-1 and IL-6 are the cytokines shown to play important roles in cancer cachexia. Interleukin-1 seems to act centrally to induce anorexia by causing early satiety and increases proteolysis peripherally [70, 74]. However, the major contribution of IL-1 to the development of cancer cachexia may reside in its ability to enhance the production and release of IL-6 [75]. Interleukin-6 can be detected in the serum of tumor-bearing animals, where it functions to increase hepatic gluconeogenesis and proteolysis [76, 77]. In animal models, IL-6 has been shown to induce a more severe wasting than TNF [70]. Animal models have demonstrated that cachexia can be eliminated by administration of an antibody to IL-6. In contradistinction to TNF, IL-6 is readily detected in the serum of patients with cancer, and the extent of amplification correlates with tumor burden. IL-6 may mediate cancer cachexia indirectly, through mechanisms different than TNF and IL-1 [70].

Despite the above discussion, it is important to note that no single anti-cytokine agent has been shown to reverse all of the features of cancer-associated wasting; cancer cachexia is attributable to alterations in the overall host cytokine milieu involving many factors [69].

Leptin is an adipocyte-derived hormone that regulates adipose tissue mass and reduces appetite, increases REE, and regulates insulin levels [67]. It affects appetite and energy expenditure via hypothalamic neuropeptides. Loss in body fat reduces leptin levels and decreases REE; weight gain similarly increases REE. These processes are mediated by increased activity of ghrelin and neuropeptide Y and decreased production of corticotropin-releasing factor and melanocortin. Persistently increased levels of leptin can lead to unfavorable metabolic alterations that contribute to cancer cachexia [78].

Surgery in Cancer Patients

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

Nutrition-directed therapies should not be expected to benefit well-nourished patients. In fact, there are clear data that some nutrition-directed therapies such as the routine use of parenteral nutrition in well-nourished patients are actually harmful [79]. A prerequisite for the use of nutritional therapy in surgery patients must therefore be the presence of malnutrition. Based on a validated assessment of preoperative nutrition status, a practical approach can be developed to optimize outcomes.

Traditional nutrition assessment parameters such as serum albumin, total lymphocyte count, skin test reactivity (as markers of immunocompetence), anthropometric changes (triceps skinfold test), and body composition may be confounded by the severity of the underlying cancer [80]. For example, hypoalbuminemia is associated with poor healing, sepsis, and increased surgical mortality and morbidity [79]. However, acute-phase response proteins in the perioperative setting can confound the use of traditional nutrition indicators such as serum albumin and prealbumin. There is some evidence that neither serum

albumin nor weight loss alone is a specific predictor of perioperative complications; however, they may be useful in the context of multivariable models [81].

Several nutrition assessment formulas have been developed to predict morbidity and mortality in surgical patients [82]. However, cancer patients are unique in their physiology. In the past the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics have issued recommendations that all cancer patients undergo nutrition screening as a critical component of their initial evaluation [83–85]. What is uniformly stated by experts in the field is that no single parameter is a definitive, encompassing factor that comprehensively captures the nutritional state of a cancer patient. That being said, the ideal screening tool for such a task needs to offer ease of use, reliability, validity, sensitivity, and cost-effectiveness [83].

There are screening tools that meet many of the above criteria. Some examples include the Patient-Generated Subjective Global Assessment (PG-SGA, a modification of an earlier tool called the Subjective Global Assessment), the Mini Nutritional Assessment (MNA), the Malnutrition Screening Tool (MST), the Malnutrition Universal Screening Tool (MUST), and the Nutritional Risk Screening (NRS) [86–93].

Of the choices listed above, the authors and many clinicians use the PG-SGA as a screening tool (Table 9.4). The PG-SGA has a patient-completed portion (documenting weight history, oral intake, activity) and a clinician-completed portion (documenting the specific cancer type and its effects on nutrition requirements/metabolic demand and a physical assessment). The patient and clinician sections are each scored on a scale of 4–8. A total score of 9 or greater indicates that the patient is at a nutrition risk which may be characterized as mild, moderate, or severe. The result is an assessment of the presence and degree of malnutrition, which can then be used to guide the development of a nutrition care plan [94]. Longitudinal use of the PG-SGA can help determine the response to the nutrition care plan and guide modifications as appropriate [95].

Table 9.4 Patient-generated subjective global assessment (PG-SGA)

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

Effect of Surgery on Nutrition in Cancer Patients

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

Nutrition Support in Surgical Patients with Cancer

Evidence-based guidelines for the use of nutrition support (enteral and parenteral) have been developed by multiple organizations, including the American Society for Parenteral and Enteral Nutrition and the European Society for Parenteral and Enteral Nutrition (ESPEN) [96, 97]. Table 9.5 summarizes the ASPEN and ESPEN guidelines. The oral route for nutrition care is optimal because it is generally very safe and cost-effective. Preferably via education and supplementation in the form of protein powders and supplements, patients can optimize their caloric intake to be nutritionally robust. If there are anatomic or physiologic factors that prohibit oral

Table 9.5 Nutrition support guideline recommendations during adult anticancer treatment (ASPEN and ESPEN clinical guidelines) [96, 97]

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

intake, access to the GI tract may be obtained via a gastrostomy or a jejunostomy feeding tube. The enteral route for nutrition support is generally preferred over parenteral nutrition because it is more cost-effective and is associated with fewer infection-related complications [96, 97]. If enteral nutrition support is not feasible (e.g., bowel obstruction, malabsorption secondary to short gut syndrome, enterocutaneous fistulae, etc.), then the parenteral route is an option.

Preoperative nutrition support has been hypothesized to benefit patients undergoing cancer surgery by mitigating the consequences of suboptimal nutrition on postoperative morbidity and mortality. The routine (routine referring to administration regardless of the patient's nutrition status) use of preoperative parenteral nutrition is not appropriate. The most frequently cited relevant study evaluating the use of perioperative total parenteral nutrition in surgical patients is the Veterans Affairs Cooperative study published in 1991 [79]. The investigators studied 395 patients (99% male) who required a laparotomy or noncardiac thoracotomy, 66% of whom had cancer (gastrointestinal cancer (51%), lung cancer (11%), or other cancer (4%)). On entry to the study the subjects were stratified according to nutrition status (no or mild malnutrition, moderate malnutrition, or severe malnutrition). They were randomly assigned to receive either TPN for 7–15 days before surgery and 3 days afterward (the TPN group) or no perioperative TPN (the control group). The patients were subsequently monitored for complications for 90 days after surgery. At 30 days after surgery, there was a statistically significant improvement in nutrition status in the TPN group as determined by the subjective global assessment (SGA). Patients with mild malnutrition did not benefit from TPN and actually had more infectious complications. In contrast, in severely malnourished patients who received TPN, the rate of noninfectious complications and "healing" complications (e.g., wound dehiscence, anastomotic leak, fistula formation) was significantly lower. Their conclusion was that the use of preoperative TPN should be limited to patients who are severely malnourished unless there are other specific indications. These results were similar to findings by Muller et al. who demonstrated reduced morbidity and mortality when TPN was provided before gastrointestinal surgery in patients who were severely malnourished [98].

There have been additional studies comparing preoperative parenteral nutrition, enteral nutrition,

and standard oral intake. Meijerink et al. studied malnourished patients with gastric or colorectal cancer and demonstrated no differences in mortality; however there was a reduced incidence of intra-abdominal abscesses with parenteral nutrition in those who were severely malnourished [99].

Forschi et al. compared preoperative enteral nutrition versus standard oral intake in patients with percutaneous biliary drains undergoing surgery and demonstrated that there was reduced morbidity and mortality in the enteral nutrition group [100].

Perioperative Nutrition Support

As in most clinical settings, judgment for the use of perioperative nutrition is paramount. It is clear that the perioperative use of nutritional support may be useful in specific circumstances. Based in part on the data above, the 2009 ASPEN clinical guidelines for nutritional support therapy during adult anticancer treatment state that perioperative nutrition support therapy may be beneficial in moderately or severely malnourished patients if administered for 7–14 days preoperatively. However, they state that the potential benefits of nutrition support must be weighed against the potential risks of the nutrition support therapy itself delaying the operation [96]. Their review of the data indicates that the majority of parenteral versus standard oral intake studies find no differences in morbidity or mortality with the use of parenteral nutrition versus standard oral diet [4, 96]. Additionally, little difference has been found in morbidity and mortality in studies comparing enteral to parenteral nutrition [4, 96, 99, 101]. Enteral nutrition is favored because it is thought to be more cost-effective and facilitates glycemic management. Based on the review of available studies, it appears that most studies report no difference in morbidity or mortality in enteral nutrition versus standard oral intake in patients with malignancy. This has been studied both in the preoperative and postoperative setting [6, 97].

In 1997, Heslin et al. published a prospective randomized trial of early enteral feeding via an operatively placed jejunostomy tube after resection of upper gastrointestinal malignancy [102]. The purpose of this study was to determine whether early postoperative enteral feeding with an immune-enhancing formula (IEF) decreases morbidity, mortality, and length of hospital stay in these patients. The study was performed with the knowledge that feeding with an IEF improved outcomes in trauma and critical care patients. The study randomized 195 patients to IEF via jejunostomy or control. The tube feedings were supplemented with arginine, RNA, and omega-3 fatty acids and begun on postoperative day 1. Their results demonstrated no significant differences in the number of minor, major, or infectious complications between the groups. There was one patient with bowel necrosis associated with the IEF requiring operation. Hospital mortality was 2.5%, and the median length of hospital stay was 11 days, which was not different between groups. They concluded that early enteral feeding with an IEF was not beneficial and should not be used in a routine fashion after surgery for upper gastrointestinal malignancies. A subsequent study by a group in the United Kingdom reached similar conclusions [103].

Immune-Enhancing Formulae

Glutamine, arginine, nucleic acids, and fatty acids are nutrients that have the potential to modulate immune function. This may be especially important in patients with cancer, who are beset with metabolic disturbances and are immunosuppressed but who simultaneously may have exaggerated inflammatory responses mediated by IL-6 [104].

Glutamine is the most abundant amino acid in plasma. It constitutes more than half of the body's amino acid pool [105]. It is considered to be a nonessential amino acid. However, catabolism-inducing states like surgery, sepsis, and trauma can lead to a spike in glutamine consumption, outstripping the body's production. For this reason, glutamine should be viewed as a "conditionally essential" amino acid [105]. One of glutamine's major functions is to shuttle nitrogen between organs. It can also serve as fuel for rapidly proliferating cells such as enterocytes, colonocytes,

lymphocytes, and fibroblasts [105]. Glutamine is also involved with intermediary metabolism, signal transduction, and neutralization of oxidative stress associated with rapid metabolism and other causes [106, 107].

The oncogene c-myc plays a role in glutamine uptake and degradation, and glutamine affects several signaling pathways that promote tumor growth [107]. Glutamine generates ATP and provides intermediates for macromolecular synthesis in tumor cells. Skeletal muscle in cancer patients has been shown to be depleted of glutamine [108]. For this reason, it has been hypothesized that glutamine supplementation for cancer patients may improve immune function by resupplying this fuel to the noncancer tissues that are starved of it. Hypothesized glutamine enhancement of tumor growth has not been observed [109].

Enteral administration of glutamine is usually in combination with other immunonutrients and has been demonstrated to ameliorate immunosuppressive and inflammatory responses in surgical cancer patients [110]. There are few data available regarding single-agent enteral glutamine supplementation, and there is no evident beneficial effect on nutrition status or clinical outcomes [110, 111]. Parenteral administration has been associated with improved nitrogen balance and a shorter postoperative hospital stay in surgical patients. A meta-analysis of randomized controlled trials in surgical patients revealed that parenteral glutamine administered alone reduced the rate of infectious complications and lowered hospital length of stay, without having any impact on mortality [103].

Arginine is another amino acid that has been studied for its role as an immune-enhancing nutrient during cancer treatment. Like glutamine, it is a nonessential amino acid that becomes conditionally essential during catabolic states [112]. It functions as a substrate for protein, creatinine, polyamine, and nitric oxide synthesis. In cancer patients, arginine improves nitrogen balance and boosts host immune function. This is accomplished by augmenting natural killer cell activity and macrophage cytotoxicity through stimulation of protein synthesis in the host, but not the cancer cells [112]. It has been studied as an enteral immunonutrient, both in combination and as a sole agent [109]. When given alone, arginine reduced the incidence of wound complications, hospital length of stay, and improved both disease-free and overall survival in head and neck cancer patients [112, 113].

Nucleic acids are another nutrient that has been studied in cancer patients. Synthetic polyribonucleotides stimulate immune function, possibly via modulation of intracellular regulatory enzymes [114]. Nucleic acids seem to modulate both the cell-mediated and humoral immune systems through an increased production of IFN. As sole agents, nucleotides have only been studied in parenteral form, and the results have been contradictory. In the setting of breast cancer, improved disease-free survival was demonstrated in patients who received nucleic acids [114], but there was no benefit in patients with colorectal cancer [115]. The paucity of data on this nutrient as a solitary agent limits conclusions about its potential benefits.

Essential polyunsaturated fatty acids (PUFAs) are either of the omega-6 (n-6) series derived from linoleic acid or the omega-3 (n-3) series derived from linolenic acid. One of the main physiologic functions of essential fatty acids is to maintain the structure and function of cell membranes. By virtue of this involvement, PUFAs can alter the expression of membrane-bound receptors. They are also central to the synthesis of intermediate compounds, such as prostaglandins, leukotrienes, and hydroxy acids. These eicosanoids affect cellular metabolism through regulation of intracellular calcium and modulation of inflammation and host defenses [116]. Omega-3 PUFAs increase the production of eicosanoids that improve immune response, while attenuating inflammatory response. Single-agent enteral supplementation with omega-3 PUFAs has been shown to increase total energy expenditure and physical activity in pancreatic cancer patients [117]. This nutrient has been studied mostly in combination with arginine and nucleic acids (Table 9.6).

Enteral formulations containing combinations of these immunonutrients (so-called immune-enhancing formulae) have been studied in preoperative, perioperative, and postoperative settings.

Table 9.6 Factors that may improve immunity

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

A well-designed trial of early postoperative feeding after resection of upper gastrointestinal malignancy detected no benefits for an enteral formula containing immunosupplements [102]. However, this study did not exclude well-nourished patients. Multiple other studies have demonstrated improvement of intermediate endpoint immune parameters with the use of immune-enhancing formulae [104, 111]. More clinically relevant benefits were also observed in trials demonstrating a lower incidence of infections and a shorter length of stay when immune-enhancing formulae are used [118–120]. Senkal et al. demonstrated decreased infectious complications and decreased cost of complications in patients who received both pre- and postoperative enteral nutrition with an immune-enhancing formula containing omega-3 fatty acids, arginine, and RNA [101]. Similar beneficial findings have been found by other groups [119, 120]. Several meta-analyses have shown a decreased rate of infectious complications with immune-enhancing enteral formulae, with a greater impact in surgical as opposed to critically ill patients [121, 122].

Special Considerations

Esophageal Cancer

As many as 90% of esophageal cancer patients present with dysphagia and weight loss [123]. These symptoms may persist after esophagectomy. Loss of the lower esophageal sphincter, dysmotility of the remnant portion of the esophagus, gastric dysmotility following vagotomy, and bile reflux from disruption of the pylorus all contribute to a high incidence of postoperative symptomatic foregut dysmotility [124]. Patients may also suffer from dumping syndrome, which is characterized by postprandial hypotension, flushing, and diarrhea. This is caused by abnormally rapid movement of hyperosmotic, undigested food into the small bowel and subsequent hypersecretion of succus and extracellular fluid into the bowel lumen. Nutritional counseling focuses on the use of frequent, small, energy-dense meals consumed without large volumes of liquid and avoidance of concentrated carbohydrates and fats.

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

Gastric Cancer

Following gastric surgery, there may be problems with both malabsorption and absence of an adequate reservoir for oral intake in addition to a variety of dysmotility syndromes [125, 126]. Iron absorption may be compromised if the duodenum is bypassed. With major gastric resections, there may be insufficient intrinsic factor synthesis which can lead to vitamin B12 malabsorption and deficiency with resultant development of megaloblastic anemia and dementia. These patients will require 1000 mcg of monthly intramuscular vitamin B12 supplementation for the entirety of their lives. It is important to counsel patients preoperatively regarding this possibility. To address the lack of reservoir function, patients are counseled on a postgastrectomy diet that may include six smaller meals daily and the avoidance of concentrated carbohydrates and fats to prevent dumping.

Small Bowel Resection

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

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

The jejunum is the absorptive powerhouse for carbohydrates, protein, and water-soluble vitamins. Larger segmental jejunum resections may lead to malabsorptive diarrhea and thus contribute to malnutrition. The ileum functions to absorb lipids, fat-soluble vitamins, cholesterol, bile salts, and vitamin B12. Patients who have diverting or end ileostomies are at significant risk for electrolyte abnormalities and are encouraged to ingest approximately 1 liter more electrolyte-containing liquids daily than their stoma output to avoid dehydration [127].

If there is extensive loss of jejunum and/or ileum, the malabsorption that ensues may become so severe that hydration and caloric needs cannot be met enterally. The clinical severity of symptoms relates to multiple factors, including the length of bowel resected, the physiologic status of the remaining bowel, the presence or absence of colon, and the presence or absence of the gastrointestinal tract sphincters that slow transit time and prevent reflux (the gastroesophageal sphincter, the pylorus, and the ileocecal valve). These patients may require prolonged or even lifelong supplementation with parenteral nutrition if/until small bowel hypertrophy and adaptation occur [128, 129]. Mainstays of the treatment of patients with small bowel malabsorption and short bowel syndrome include use of (1) easily absorbed oral electrolyte-containing solutions to prevent electrolyte imbalances and dehydration; (2) proton pump inhibitors to suppress the hypersecretion of gastric acid and fluid that results from hypergastrinemia seen in patients with short bowel syndrome; (3) cholestyramine to bind bile acids and prevent their entry into the colon where they cause an irritative diarrhea; and (4) antimotility agents to slow small bowel and colon transit time.

The small bowel is also a major contributor to bacterial homeostasis. Specifically, if transit time is decreased and acidic small bowel contents reach the colon, carbohydrates can be fermented by bacteria into d-lactic acid. Buildup of d-lactic acid may result in lactic acidosis, yielding increased serum d-lactate, an increased anion gap, and decreased serum bicarbonate. This can occur in short bowel syndrome or after jejunoileal bypass surgery; it can present as altered mental status, slurred speech, and ataxia most frequently after ingestion of a high-carbohydrate meal. Recommendations to avoid this are to restrict large carbohydrate meals, antibiotics, and probiotics [129].

Pancreatic Cancer

Pancreatic resection for pancreas cancer, whether proximal or distal, can result in diabetes and/or malabsorption [130]. The majority of the exocrine function of the pancreas resides in the uncinate and head, whereas much of the neuroendocrine function is found in the body and tail. Patients who have undergone a pancreaticoduodenectomy are also at risk of suffering from dumping syndrome. For malabsorption symptoms following pancreatic resection (weight loss, bloating, foul smelling diarrhea, postprandial cramping), it is often more practical to proceed directly to oral pancreatic enzyme replacement than to undertake a complex and costly physiologic evaluation.

Liver and Gallbladder Cancer

Liver neoplasms are unique in that there are some specific electrolyte derangements in the immedi-

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

Colon Cancer

The function of the colon is primarily to absorb water and electrolytes. The right colon contributes most to this function; removal of the ascending colon with the ileocecal valve often leads to a period of more frequent and less formed bowel movements. During this period, patients should be counseled to avoid dehydration. This can be especially problematic in older patients. Additionally, if there is impaired intestinal peristalsis, bacterial overgrowth may ensue. It is thought that although clinically patients may have an improvement in as early as a few weeks, it can take over 2 years to undergo structural and functional adaptation to compensate nutritionally after colon resection.

Practical Notes to the Perioperative Nutritional Support of Cancer Patients

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

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

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

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

Lastly, as a general principle, the palliative use of nutrition support therapy in terminally ill cancer patients is rarely indicated [127]. If patients are to benefit from parenteral nutrition, the general guidelines are that they (1) must be physically and emotionally capable of participating in their own care; (2) should have an estimated life expectancy of >40–60 days; (3) have ample social and economic support at home with an in-home lay caretaker; and (4) failed other less costly and invasive therapies.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
3. American Cancer Society. Cancer facts & figures 2018. Atlanta: American Cancer Society; 2018.

4. August D, Huhmann M. Nutritional care of cancer patients. In: Norton J, Barie P, Bollinger R, Chang A, Lowry S, Mulvihill S, et al., editors. Surgery: basic science and clinical evidence. 2nd ed. New York: Springer; 2008. p. 2123–49.
5. Warren S. The immediate cause of death in cancer. Am J Med Sci. 1932;185:610–5.
6. Inagaki J, Rodriguez V, Proceedings BGP. Causes of death in cancer patients. Cancer. 1974;33(2):568–73. PubMed PMID: 4591273.
7. Islami F, Sauer AG, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68:31–54.
8. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981;66(6):1191–308. PubMed PMID: 7017215.
9. Willett WC. Diet, nutrition, and avoidable cancer. Environ Health Perspect. 1995;103(Suppl 8):165–70. PubMed PMID: 8741778; Pubmed Central PMCID: 1518978.
10. Polednak AP. Estimating the number of U.S. incident cancers attributable to obesity and the impact on temporal trends in incidence rates for obesity-related cancers. Cancer Detect Prev. 2008;32(3):190–9. PubMed PMID: 18790577.
11. Marengo A, Rosso C, Bugianesi E. Liver cancer: connections with obesity, fatty liver, and cirrhosis. Annu Rev Med. 2016;67:103–17.
12. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220–41. PubMed PMID: 22700443.
13. Zaorsky NG, Churilla TM, Egleston BL, et al. Causes of death among cancer patients. Ann Oncol. 2017;28:400–7.
14. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62(4):243–74. PubMed PMID: 22539238.
15. DeWys WD. Anorexia as a general effect of cancer. Cancer. 1979;43(5 Suppl):2013–9. PubMed PMID: 376105.
16. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology. Group Am J Med. 1980;69(4):491–7. PubMed PMID: 7424938.
17. Tan BH, Fearon KC. Cachexia: prevalence and impact in medicine. Curr Opin Clin Nutr Metab Care. 2008;11(4):400–7. PubMed PMID: 18541999.
18. McClement S. Cancer anorexia-cachexia syndrome: psychological effect on the patient and family. J Wound Ostomy Continence Nurs. 2005;32(4):264–8. PubMed PMID: 16030467.
19. Ottery FD. Supportive nutrition to prevent cachexia and improve quality of life. Semin Oncol. 1995;22(2 Suppl 3):98–111. PubMed PMID: 7740324.
20. Puccio M, Nathanson L. The cancer cachexia syndrome. Semin Oncol. 1997;24(3):277–87. PubMed PMID: 9208884. Epub 1997/06/01. eng.
21. Studley H. Percentage of weight loss. JAMA. 1936;106:458–60.
22. Mullen JT, Davenport DL, Hutter MM, Hosokawa PW, Henderson WG, Khuri SF, et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. Ann Surg Oncol. 2008;15(8):2164–72. PubMed PMID: 18548313.
23. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer–a systematic review of the epidemiological literature. Nutr J. 2012;11:27. PubMed PMID: 22531478; Pubmed Central PMCID: 3408376.
24. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68(1):31–54. PubMed PMID: 29160902.
25. August DA, Huhmann MB. Nutritional support of the cancer patient. In: Ross CA, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, editors. Modern nutrition in health and disease. Philadelphia, PA: Lippincott, Williams and Wilkins; 2013. p. 1194–213.
26. Kern KA, Norton JA. Cancer cachexia. JPEN J Parenter Enteral Nutr. 1988;12(3):286–98. PubMed PMID: 3292798.
27. Arbeit JM, Lees DE, Corsey R, Brennan MF. Resting energy expenditure in controls and cancer patients with localized and diffuse disease. Ann Surg. 1984;199(3):292–8. PubMed PMID: 6703790; Pubmed Central PMCID: 1353395.
28. Hyltander A, Drott C, Korner U, Sandstrom R, Lundholm K. Elevated energy expenditure in cancer patients with solid tumours. Eur J Cancer. 1991;27(1):9–15. PubMed PMID: 1826450.
29. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg. 1994;219(4):325–31. PubMed PMID: 7512810; Pubmed Central PMCID: 1243147.
30. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609–15. PubMed PMID: 16704954.
31. Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Investig. 2007;25(5):308–14. PubMed PMID: 17661205.
32. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72–7. PubMed PMID: 19647909.

33. Knox LS, Crosby LO, Feurer ID, Buzby GP, Miller CL, Mullen JL. Energy expenditure in malnourished cancer patients. Ann Surg. 1983;197(2):152–62. PubMed PMID: 6824369; Pubmed Central PMCID: 1353103.
34. Hansell DT, Davies JW, Burns HJ. The relationship between resting energy expenditure and weight loss in benign and malignant disease. Ann Surg. 1986;203(3):240–5. PubMed PMID: 3082302; Pubmed Central PMCID: 1251083.
35. Johnson G, Salle A, Lorimier G, Laccourreye L, Enon B, Blin V, et al. Cancer cachexia: measured and predicted resting energy expenditures for nutritional needs evaluation. Nutrition. 2008;24(5):443–50. PubMed PMID: 18359195.
36. Vaisman N, Lusthaus M, Niv E, Santo E, Shacham-Shmueli E, Geva R, et al. Effect of tumor load on energy expenditure in patients with pancreatic cancer. Pancreas. 2012;41(2):230–2. PubMed PMID: 21926936.
37. Jebb SA, Osborne RJ, Dixon AK, Bleehen NM, Elia M. Measurements of resting energy expenditure and body composition before and after treatment of small cell lung cancer. Ann Oncol. 1994;5(10):915–9. PubMed PMID: 7696163.
38. Simons JP, Schols AM, Buurman WA, Wouters EF. Weight loss and low body cell mass in males with lung cancer: relationship with systemic inflammation, acute-phase response, resting energy expenditure, and catabolic and anabolic hormones. Clin Sci. 1999;97(2):215–23. PubMed PMID: 10409477.
39. Dempsey DT, Feurer ID, Knox LS, Crosby LO, Buzby GP, Mullen JL. Energy expenditure in malnourished gastrointestinal cancer patients. Cancer. 1984;53(6):1265–73. PubMed PMID: 6692317.
40. Fearon KC, Hansell DT, Preston T, Plumb JA, Davies J, Shapiro D, et al. Influence of whole body protein turnover rate on resting energy expenditure in patients with cancer. Cancer Res. 1988;48(9):2590–5. PubMed PMID: 3356019.
41. Fredrix EW, Wouters EF, Soeters PB, van der Aalst AC, Kester AD, von Meyenfeldt MF, et al. Resting energy expenditure in patients with non-small cell lung cancer. Cancer. 1991;68(7):1616–21. PubMed PMID: 1654199.
42. Jouinot A, Vazeille C, Goldwasser F. Resting energy metabolism and anticancer treatments. Curr Opin Clin Nutr Metab Care. 2018;21:145–51.
43. DuBois EF. Basal metabolism in health and disease. 3rd ed. Philadelphia: Lea and Febiger; 1936.
44. Kleiber M. The fire of life: an introduction to animal energetics. Malabar, FL: Krieger; 1961.
45. Harris JA. A biometric study of basal metabolism. Washington, DC: Carnegie Institute of Washington; 1919.
46. Barak N, Wall-Alonso E, Sitrin MD. Evaluation of stress factors and body weight adjustments currently used to estimate energy expenditure in hospitalized patients. JPEN J Parenter Enteral Nutr. 2002;26(4):231–8. PubMed PMID: 12090688.
47. MacDonald A, Hildebrandt L. Comparison of formulaic equations to determine energy expenditure in the critically ill patient. Nutrition. 2003;19(3):233–9. PubMed PMID: 12620525.
48. Bosy-Westphal A, Reinecke U, Schlorke T, Illner K, Kutzner D, Heller M, et al. Effect of organ and tissue masses on resting energy expenditure in underweight. normal weight and obese adults Int J Obes Relat Metab Disord. 2004;28(1):72–9. PubMed PMID: 14647174.
49. Fearon KC. The Sir David Cuthbertson Medal Lecture 1991. The mechanisms and treatment of weight loss in cancer. Proc Nutr Soc. 1992;51(2):251–65. PubMed PMID: 1438334.
50. Agustsson T, Ryden M, Hoffstedt J, van Harmelen V, Dicker A, Laurencikiene J, et al. Mechanism of increased lipolysis in cancer cachexia. Cancer Res. 2007;67(11):5531–7. PubMed PMID: 17545636.
51. Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev. 2009;89(2):381–410. PubMed PMID: 19342610.
52. Tisdale MJ. Cancer cachexia. Curr Opin Gastroenterol. 2010;26(2):146–51.
53. Tisdale MJ. Tumor-host interactions. J Cell Biochem. 2004;93(5):871–7.
54. Todorov PT, McDevitt TM, Meyer DJ, Ueyama H, Ohkubo I, Tisdale MJ. Purification and characterization of a tumor lipid-mobilizing factor. Cancer Res. 1998;58(11):2353–8.
55. Rogers CJ, Prabhu KS, Vijay-Kumar M. The microbiome and obesity-an established risk for certain types of cancer. Cancer. 2014;20:176–80.
56. Dilman VM, Berstein LM, Ostroumova MN, Tsyrlina YV, Golubev AG. Peculiarities of hyperlipidaemia in tumour patients. Br J Cancer. 1981;43(5):637–43.
57. Hussey HJ, Tisdale MJ. Effect of polyunsaturated fatty acids on the growth of murine colon adenocarcinomas in vitro and in vivo. Br J Cancer. 1994;70(1):6–10. PubMed PMID: 8018542.
58. Miyamoto Y, Hanna DL, Zhang W, et al. Molecular pathways: Cachexia signaling – a targeted approach to cancer treatment. Clin Cancer Res. 2016;22:3999–4004.
59. Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309–14.
60. Bongaerts GP, van Halteren HK, Verhagen CA, Wagener DJ. Cancer cachexia demonstrates the energetic impact of gluconeogenesis in human metabolism. Med Hypotheses. 2006;67(5):1213–22. PubMed PMID: 16797873.
61. Lelbach A, Muzes G, Feher J. Current perspectives of catabolic mediators of cancer cachexia. Med Sci Monit. 2007;13(9):RA168–73. PubMed PMID: 17767131.
62. Lundholm K, Edstrom S, Karlberg I, Ekman L, Schersten T. Glucose turnover, gluconeogenesis from glycerol, and estimation of net glucose cycling in cancer patients. Cancer. 1982;50(6):1142–50. PubMed PMID: 7104955.
63. Waterhouse C, Jeanpretre N, Keilson J. Gluconeogenesis from alanine in patients with pro-

gressive malignant disease. Cancer Res. 1979;39(6 Pt 1):1968–72. PubMed PMID: 445395.
64. Lundholm K, Holm G, Schersten T. Insulin resistance in patients with cancer. Cancer Res. 1978;38(12):4665–70. PubMed PMID: 719645.
65. Rofe AM, Bourgeois CS, Coyle P, Taylor A, Abdi EA. Altered insulin response to glucose in weight-losing cancer patients. Anticancer Res. 1994;14(2B):647–50. PubMed PMID: 8010722.
66. Shaw JH, Wolfe RR. Fatty acid and glycerol kinetics in septic patients and in patients with gastrointestinal cancer. The response to glucose infusion and parenteral feeding. Ann Surg. 1987;205(4):368–76. PubMed PMID: 3105476.
67. Smiechowska J, Utech A, Taffet G, Hayes T, Marcelli M, Garcia JM. Adipokines in patients with cancer anorexia and cachexia. J Investig Med. 2010;58(3):554–9. PubMed PMID: 20215915.
68. Garcia-Martinez C, Costelli P, Lopez-Soriano FJ, Argiles JM. Is TNF really involved in cachexia? Cancer Investig. 1997;15(1):47–54. PubMed PMID: 9028389.
69. Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A. Cancer cachexia–pathophysiology and management. J Gastroenterol. 2013;48(5):574–94. PubMed PMID: 23512346; Pubmed Central PMCID: 3698426.
70. Toomey D, Redmond HP, Bouchier-Hayes D. Mechanisms mediating cancer cachexia. Cancer. 1995;76(12):2418–26. PubMed PMID: 8625066.
71. Lenk K, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. J Cachexia Sarcopenia Muscle. 2010;1(1):9–21. PubMed PMID: 21475693; Pubmed Central PMCID: 3060644.
72. Tracey KJ, Morgello S, Koplin B, Fahey TJ 3rd, Fox J, Aledo A, et al. Metabolic effects of cachectin/tumor necrosis factor are modified by site of production. Cachectin/tumor necrosis factor-secreting tumor in skeletal muscle induces chronic cachexia, while implantation in brain induces predominantly acute anorexia. J Clin Invest. 1990;86(6):2014–24.
73. Matthys P, Dijkmans R, Proost P, Van Damme J, Heremans H, Sobis H, et al. Severe cachexia in mice inoculated with interferon-gamma-producing tumor cells. Int J Cancer. 1991;49(1):77–82.
74. Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptides. Curr Opin Clin Nutr Metab Care. 2004;7(4):427–34.
75. Fischer E, Marano MA, Barber AE, Hudson A, Lee K, Rock CS, et al. Comparison between effects of interleukin-1 alpha administration and sublethal endotoxemia in primates. Am J Phys. 1991;261(2 Pt 2):R442–52.
76. Gelin J, Moldawer LL, deMan P, Svanborg-Eden C, Lowry SF, et al. Appearance of hybridoma growth factor/interleukin-6 in the serum of mice bearing a methylcholanthrene-induced sarcoma. Biochem Biophys Res Commun. 1988;157(2):575–9.
77. Argiles JM, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Med Res Rev. 1999;19(3):223–48.
78. Diakowska D, Krzystek-Korpacka M, Markocka-Maczka K, Diakowski W, Matusiewicz M, Grabowski K. Circulating leptin and inflammatory response in esophageal cancer, esophageal cancer-related cachexia-anorexia syndrome (CAS) and non-malignant CAS of the alimentary tract. Cytokine. 2010;51(2):132–7.
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. Huhmann MB, August DA. Perioperative nutrition support in cancer patients. Nutr Clin Pract. 2012;27(5):586–92.
81. Jensen GL. Inflammation as the key interface of the medical and nutrition universes: a provocative examination of the future of clinical nutrition and medicine. JPEN J Parenter Enteral Nutr. 2006;30(5):453–63.
82. Hirsch S, de Obaldia N, Petermann M, Covacevic S, Burmeister R, Llorens P, et al. Nutritional status of surgical patients and the relationship of nutrition to postoperative outcome. J Am Coll Nutr. 1992;11(1):21–4.
83. Directors ABo, the Clinical Guidelines Task F. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26(1 Suppl):1SA–138SA.
84. Council on Practice (COP) Quality Management Committee. Identifying patients at risk: ADA's definitions for nutrition screening and nutrition assessment. J Am Diet Assoc. 1994;94(8):838–9.
85. Mueller C, Compher C, Ellen DM, American Society for Parenteral and Enteral Nutrition Board of Directors. A.S.P.E.N. Clinical Guidelines: Nutrition screening, assessment, and intervention in adults. JPEN J Parenter Enteral Nutr. 2011;35(1):16–24.
86. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15–9.
87. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8–13. PubMed PMID: 3820522.
88. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: the mini nutritional assessment as part of the geriatric evaluation. Nutr Rev. 1996;54(1 Pt 2):S59–65. PubMed PMID: 8919685.
89. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients.

Nutrition. 1999;15(6):458–64. PubMed PMID: 10378201.
90. Ferguson ML, Bauer J, Gallagher B, Capra S, Christie DR, Mason BR. Validation of a malnutrition screening tool for patients receiving radiotherapy. Australas Radiol. 1999;43(3):325–7. PubMed PMID: 10901927.
91. Malnutrition Advisory Group. A consistent and reliable tool for malnutrition screening. Nurs Times. 2003;99(46):26–7. PubMed PMID: 14666817.
92. Bauer J, Capra S. Comparison of a malnutrition screening tool with subjective global assessment in hospitalised patients with cancer–sensitivity and specificity. Asia Pac J Clin Nutr. 2003;12(3):257–60. PubMed PMID: 14505986.
93. Kondrup J, Johansen N, Plum LM, Bak L, Larsen IH, Martinsen A, et al. Incidence of nutritional risk and causes of inadequate nutritional care in hospitals. Clin Nutr. 2002;21(6):461–8. PubMed PMID: 12468365.
94. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr. 2002;56(8):779–85. PubMed PMID: 12122555.
95. Ferguson M. Patient-generated subjective global a. Oncology. 2003;17(2 Suppl 2):13–4. Discussion 14–6. PubMed PMID: 12632872.
96. August DA, Huhmann MB, American Society for Parenteral and Enteral Nutrition Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr. 2009;33(5):472–500.
97. Arends JM, Bachmann P, Baraco V, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11–48.
98. Muller JM, Brenner U, Dientst C, et al. Lancet 1982;1:68–71.
99. Meijerink WJ, von Meyenfeldt MF, Rouflart MM, Soeters PB. Efficacy of perioperative nutritional support. Lancet. 1992;340(8812):187–8. PubMed PMID: 1352609.
100. Forschi D, Cavagna G, Callioni F, Morandi E, Rovati V. Hyperalimentation of jaundiced patients on percutaneous transhepatic biliary drainage. Br J Surg. 1986;73(9):716–9.
101. Senkal M, Zumtobel V, Bauer KH, Marpe B, Wolfram G, Frei A, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. Arch Surg. 1999;134(12):1309–16.
102. Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg. 1997;226(4):567–77. Discussion 77–80.
103. Wang Y, Jiang ZM, Nolan MT, Jiang H, Han HR, Yu K, et al. The impact of glutamine dipeptide-supplemented parenteral nutrition on outcomes of surgical patients: a meta-analysis of randomized clinical trials. JPEN J Parenter Enteral Nutr. 2010;34(5):521–9.
104. Braga M, Gianotti L, Cestari A, Vignali A, Pellegatta F, Dolci A, et al. Gut function and immune and inflammatory responses in patients perioperatively fed with supplemented enteral formulas. Arch Surg. 1996;131(12):1257–64. Discussion 64-5.
105. Coster J, McCauley R, Hall J. Glutamine: metabolism and application in nutrition support. Asia Pac J Clin Nutr. 2004;13(1):25–31.
106. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev. 2003;29(6):501–13.
107. DeBerardinis RJ, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene. 2010;29(3):313–24.
108. Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. Eur J Nutr. 2010;49(4):197–210.
109. Wu GH, Zhang YW, Wu ZH. Modulation of postoperative immune and inflammatory response by immune-enhancing enteral diet in gastrointestinal cancer patients. World J Gastroenterol. 2001;7(3):357–62.
110. Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Koller M, Konig W, et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg. 1998;227(2):302–8.
111. Coghlin Dickson TM, Wong RM, Offrin RS, Shizuru JA, Johnston LJ, Hu WW, et al. Effect of oral glutamine supplementation during bone marrow transplantation. JPEN J Parenter Enteral Nutr. 2000;24(2):61–6.
112. De Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, Aller R. High dose of arginine enhanced enteral nutrition in postsurgical head and neck cancer patients. A randomized clinical trial. Eur Rev Med Pharmacol Sci. 2009;13(4):279–83.
113. Buijs N, van Bokhorst-de van der Schueren MA, Langius JA, Leemans CR, Kuik DJ, Vermeulen MA, et al. Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. Am J Clin Nutr. 2010;92(5):1151–6.
114. Lacour J, Laplanche A, Delozier T, Berlie J, Mourali N, Julien JP, et al. Polyadenylic-polyuridylic acid plus locoregional and pelvic radiotherapy versus chemotherapy with CMF as adjuvants in operable breast cancer. A 6 1/2 year follow-up analysis of a randomized trial of the French Federation of Cancer Centers (F.F.C.C.). Breast Cancer Res Treat. 1991;19(1):15–21.
115. Lacour J, Laplanche A, Malafosse M, Gallot D, Julien M, Rotman N, et al. Polyadenylic-polyuridylic

acid as an adjuvant in resectable colorectal carcinoma: a 6 1/2 year follow-up analysis of a multicentric double blind randomized trial. Eur J Surg Oncol. 1992;18(6):599–604.
116. Heys SD, Gough DB, Khan L, Eremin O. Nutritional pharmacology and malignant disease: a therapeutic modality in patients with cancer. Br J Surg. 1996;83(5):608–19.
117. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996–1002.
118. Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. Crit Care Med. 1998;26(1):24–30.
119. Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology. 2002;122(7):1763–70.
120. Braga M, Vignali A, Zuliani W, Radaelli G, Gianotti L, Martani C, et al. Metabolic and functional results after laparoscopic colorectal surgery: a randomized, controlled trial. Dis Colon Rectum. 2002;45(8):1070–7.
121. 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.
122. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. JPEN J Parenter Enteral Nutr. 2010;34(4):378–86.
123. Posner MC, Goodman KA, Ilson DH. In: DeVita VT, Lawrence TS, Rosenberg SA, editors. Cancer: principles and practice of oncology. 11th ed. Philadelphia: Wolters Kluwer; 2019. p. 718–61.
124. Lee MK, Yost KJ, Pierson KE, Blackmon SH. Patient-reported outcome domains for the esophageal CONDUIT report card: a prospective trial to establish domains. Health Qual Life Outcomes. 2018;16:197–209.
125. Cai Z, Zhou Y, Wang C, et al. Optimal reconstruction methods after distal gastrectomy for gastric cancer. A systematic review and network meta-analysis. Medicine. 2018;97:20–8.
126. Rogers C. Postgastrectomy nutrition. Nutr Clin Prac. 2011;26:126–36.
127. Justiniano CF, Temple LK, Swanger AA, et al. Readmissions with dehydration after ileostomy creation: rethinking risk factors. Dis Colon Rectum. 2018;61:1297–305.
128. Bharadwaj S, Tandon P, Meka K, et al. Intestinal failure: adaptation, rehabilitation, and transplantation. J Clin Gastroenterol. 2016;50:366–72.
129. Pironi L. Definitions of intestinal failure and the short bowel syndrome. Best Pract Res Clin Gastroenterol. 2016;30:173–85.
130. Berry AJ. Pancreatic surgery: indications, complications, and implications for nutrition intervention. Nutr Clin Prac. 2013;28:330–57.

Sepsis and Nutrition

10

Laura J. Moore

Introduction

Sepsis continues to be a common and often highly morbid condition. The United States Centers for Disease Control and Prevention estimates that 1.7 million American adults develop sepsis on an annual basis. Mortality rates from sepsis continue to remain high with nearly 270,000 deaths due to sepsis annually. It is also estimated that one out of every three inpatient hospital deaths is secondary to sepsis. The global burden of sepsis is even more alarming with more than 19 million cases per year and 5 million deaths.

As a result of the significant impact of sepsis, tremendous research efforts have been undertaken. These efforts have included development of sepsis screening programs to assist in the early identification of sepsis and creation of evidence-based guidelines designed to aid clinicians in delivering optimal care. Providing adequate nutritional support to these critically ill patients is a key factor in improving patient outcomes. Ensuring adequate delivery of nutrition can attenuate the patient's metabolic response to the stress of sepsis, modulate the inflammatory/immune response, and decrease the risk of developing secondary, nosocomial infections. The purpose of this chapter is to review the pathophysiology of sepsis and provide a review of the current literature regarding optimal utilization of nutritional support in patients with sepsis.

Defining Sepsis

Despite the fact that the clinical entity of sepsis has existed for centuries, the term sepsis was not defined until the end of the twenty-first century. Sepsis syndrome was first defined in the literature by Roger Bone in 1989 [1]. This was followed by the American College of Chest Physicians and the Society of Critical Care Medicines Consensus Conference in 1991 that defined the systemic inflammatory response syndrome (SIRS) (see Table 10.1) and multiple organ dysfunction syndrome (MODS) [2]. This initial consensus conference defined sepsis as the presence of systemic inflammatory syndrome (SIRS) secondary to presence of infection. If sepsis was complicated by the development of organ dysfunction, then

Table 10.1 Systemic inflammatory response syndrome (SIRS) criteria (two or more of the following)

Heart rate	>90
Respiratory rate	>20
Temperature, °C	>38 or <36
White blood cell count	>12,000/mm^3 or <4000/mm^3 or >10% bandemia

L. J. Moore (✉)
Department of Surgery, Division of Acute Care Surgery, The University of Texas Health Science Center at Houston, Houston, TX, USA
e-mail: laura.j.moore@uth.tmc.edu

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_10

the term severe sepsis was used. Finally, septic shock was defined as sepsis associated with hypotension despite adequate volume resuscitation. In response to ongoing criticism from experts in the field, a second consensus conference was convened in 2001 to revise the original definitions. The updated consensus conference definitions included an expanded list of the signs and symptoms of sepsis [3].

Recently, these original sepsis definitions have been updated, due in part to a perceived lack of evidence supporting the original definitions. The end result was the proposed Sepsis-3 definition which defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [4]. With the increased focus on organ dysfunction as a defining feature of sepsis comes the need to identify the presence of organ dysfunction in a systematic, categorical fashion. According to Sepsis-3, organ dysfunction is defined as an acute change in total Sequential Organ Failure Assessment (SOFA) score [5] of ≥2 points due to the development of an infection. Due to the cumbersome nature of calculating a SOFA score, the Sepsis-3 authors created an abbreviated version of the SOFA score known as the quick SOFA (qSOFA). The qSOFA elements include a systolic blood pressure of <100 mmHg, a respiratory rate of >22 breaths per minute, and the presence of altered mental status. Patients with two or more of these criteria are considered to have a positive qSOFA score. Another change with the Sepsis-3 definition is the elimination of the term severe sepsis. The only subgroup within the new definitions is septic shock which is defined sepsis with persistent hypotension requiring vasopressors and a serum lactate of >2 mmol/L despite adequate resuscitation.

The Sepsis-3 definition has been met with controversy and has not been widely accepted. This controversy stems primarily from the fact that the new definition was not prospectively validated in a generalizable population prior to publication. In addition, the requirement that a patient develops organ dysfunction prior to qualifying for sepsis may in fact result in delayed recognition of sepsis. This is particularly concerning since many of the interventions that have been shown to improve outcomes in patients with sepsis rely upon the early recognition of sepsis [6–8].

Sepsis Pathophysiology: A Brief Review

While a complete review of the pathophysiology of sepsis is beyond the scope of this text, having a basic understanding of the complex inflammatory and immune cascades that are generated in response to infection is helpful. The progression from infection to sepsis or septic shock is an intricate process based upon the characteristics of the inciting organism and the innate immune response of the host. This complex inflammatory cascade results in the production of multiple inflammatory cytokines, procoagulants, and adhesion molecules. This results in systemic inflammation, coagulation, and disordered fibrinolysis. The end result of these events is end organ damage and in some cases death.

Under normal circumstances, a complex immune response focused on controlling bacterial invasion via activation of both circulating and fixed phagocytic cells occurs. The primary goal is recognition and binding of bacterial components with resultant destruction via phagocytosis. This binding of immune cell surface receptors also initiates the release of pro-inflammatory mediators such as tumor necrosis factor-α, interleukin-1, adhesion molecules, and nitric oxide. The purpose of these pro-inflammatory mediators is to recruit additional inflammatory cells such as leukocytes to aid in the immune response. The end result is destruction of the infectious organism and restoration of host homeostasis.

In patients that develop sepsis, the inflammatory response is overly exuberant, leading to a more systemic response to the infectious insult. If the initial inflammatory response is not well balanced, it can lead to an overwhelming SIRS response with development of early multiple organ failure and death. Patients that survive the initial pro-inflammatory state can then progress into a compensatory anti-inflammatory state often referred to as compensatory anti-inflammatory response syndrome (CARS). While

multiple phenotypes exist, this combination of pro-inflammatory and anti-inflammatory mediators can cause direct cellular injury, endothelial damage with subsequent impairment of capillary function, altered rates of programmed cell death, and generalized microcirculatory dysfunction [9–11]. Due to the systemic nature of this dysregulated immune response, every organ system can be potentially impacted.

As the largest immune organ in the body, the gastrointestinal (GI) tract plays an integral role in the immune response to infection. Shock is defined as tissue hypoperfusion. This lack of perfusion directly injures the GI tract, and the resultant reperfusion injury results in the release of additional pro-inflammatory mediators, worsening the SIRS response to infection. At the local level, the release of these inflammatory mediators results in GI dysfunction including gastroparesis, gastric alkalinization, ileus, duodenogastric reflux, impaired mucosal blood flow, epithelial apoptosis, and impaired local gut immunity. This GI dysfunction can be further amplified by early, aggressive crystalloid resuscitation by creating bowel edema which promotes ileus. This problem is compounded by many of our typical intensive care unit (ICU) interventions including the need for vasopressors (which decreases GI mucosal perfusion), stress ulcer prophylaxis (which worsens gastric alkalinization), and antibiotic administration (which promotes bacterial overgrowth). In a matter of hours, the normally sterile upper GI tract can become heavily colonized with potential pathogens. The GI tract quickly becomes a reservoir for bacteria that can escape from the GI tract via pulmonary aspiration with resultant development of nosocomial infections that further contribute to patient morbidity and mortality.

Provision of Nutritional Support in Critical Illness: Initial Assessment

In 2009, the American Society for Parenteral and Enteral Nutrition (ASPEN) in conjunction with the Society of Critical Care Medicine (SCCM) published guidelines for the provision and assessment of nutritional support in critically ill patients [12]. These guidelines were recently updated in 2016 [13]. The purpose of these guidelines is to provide clinicians with a comprehensive summary of the best available evidence for the provision of nutritional support in critically ill patients.

The guidelines recommend assessment of a patient's nutritional status upon admission to the ICU. This includes assessment of the patient's nutritional risk and calculation of both protein and energy requirements. While multiple tools are available, the Nutritional Risk Screening (NRS 2002) [14] and the NUTRIC score [15] provide a comprehensive assessment of both nutritional status and disease severity and are therefore the preferred assessment tools. The NRS 2002 assigns points based upon nutritional status (0–3) and severity of disease (0–3). An additional point is added if the patient is older than 70. If the score is ≥ 3, then the patient is considered to be at risk, and early nutritional support is recommended. The NUTRIC score calculates a score based upon the patient's age, APACHE II score, SOFA score, number of comorbid conditions, number of days from hospital to ICU admission, and IL-6 level. A NUTRIC score of ≥ 5 is associated with worse clinical outcomes and indicates the patient is most likely to benefit from aggressive nutrition therapy.

It is important to note that the traditional serum protein markers (albumin, prealbumin, and transferrin) do not accurately reflect nutritional status in critically ill patients. When predicting energy requirements during critical illness, indirect calorimetry is the best option if available. If this is not available, energy requirements can be estimated using predictive equations. Once nutritional support has been initiated, it is important to monitor the response to nutritional therapy. Since protein appears to be the most critical macronutrient for supporting immune function and maintaining lean body mass, the requirements for protein are proportionally higher than other macronutrients. As a result, standard enteral formulations are unlikely to deliver adequate protein, and protein supplementation is often needed.

Impact of Early Nutritional Therapy

Sepsis and septic shock result in a catabolic stress state with risk for development of secondary, nosocomial infections, organ failure, prolonged ICU and hospital length of stay, and increased mortality rates. Significant improvements in our understanding of the pathophysiology of critical illness had resulted in a focus on not merely providing nutritional support but rather providing nutritional therapy. By providing enteral nutrition, we can attenuate the metabolic response to stress, favorably modulate the immune response to infection, and minimize or eliminate oxidative cellular injury.

As described above, the GI tract plays an integral role in the immune response to sepsis. This also means that the GI tract is a potential target for modulating the immune response. Delivering early enteral nutrition stimulates splanchnic perfusion and supports the immune function of gut-associated lymphoid tissue (GALT) [16]. Providing enteral nutrition also helps maintain the integrity of the GI epithelium, stimulates intestinal contractility which prevents bacterial overgrowth and ileus, and promotes release of anti-inflammatory mediators from CD4 lymphocytes [17].

Perhaps more important than the benefits of early enteral nutrition are the negative consequences of withholding enteral nutrition. Depriving the intestinal epithelium of luminal nutrients results in the loss of both structural and functional integrity of the gut epithelium. Withholding enteral nutrition decreases GI contractility with resultant bacterial overgrowth. The proliferation and overgrowth of these pathogenic bacteria can lead to attachment to the GI epithelium which leads to cytokine release and programmed cell death [18]. The death of epithelial cells further compromises the integrity of the gut barrier, increasing permeability. This increased permeability of the GI epithelium results in increased exposure of the GI tract's immune system to intraluminal bacteria. This leads to diffuse activation of macrophages which further promote a systemic pro-inflammatory state, worsening the already present SIRS response.

It is recommended that early enteral nutrition be initiated within 24–48 h. Several clinical studies evaluating the impact of early vs. delayed enteral nutrition have been undertaken. In a meta-analysis by Heyland et al., early enteral nutrition demonstrated a trend toward decreased mortality in those patients that received enteral nutrition within 48 h as compared to those that did not [19]. Another meta-analysis by Marik et al. showed similar results with a significant decrease in infectious complications and hospital length of stay when enteral nutrition was started within 36 h of ICU admission [20].

The initiation of early enteral nutrition in critically ill patients is not dependent upon clinical evidence of bowel function (flatus, passage of stool). GI dysfunction is very common in critically ill patients occurring in 30–70% of patients. The etiology of this GI dysfunction is multifactorial, and contributing factors include comorbid conditions, the need for mechanical ventilation, disruption of the epithelial mucosal barrier, and altered motility. The presence or absence of bowel sounds does not reflect the status of the gut epithelial barrier or the absorptive capacity of the bowel. Given all of these factors, it is important to have an established enteral nutrition protocol that combines advancement of enteral nutrition to a goal rate. Tolerance of enteral nutrition can be determined based upon physical examination of the abdomen, passage of flatus and/or stool, and absence of patient complaints such as abdominal pain or distention. Patients with intolerance to enteral nutrition will typically demonstrate emesis, abdominal distention, high nasogastric tube output or high gastric residual volume, diarrhea, or complaints of abdominal discomfort.

The decision to deliver gastric vs. small bowel feeds remains an area of disagreement. To date, there is no research that has demonstrated a difference in ventilator days, ICU length of stay, or mortality. There is some evidence that suggests small bowel feedings are associated with a lower incidence of gastroesophageal reflux [21]. There is also some evidence that small bowel feeds are associated with a decreased rate of ventilator-associated pneumonia as compared to

gastric feeds [22]. The most common indications for small bowel enteral nutrition are severe gastroparesis, gastroesophageal reflux, intolerance to a trial of gastric feeding, and high aspiration risk. Another potential benefit of small bowel feeding is the ability to continue nutritional support up to or even during the operating room, thus eliminating the disruption in enteral nutrition that frequently occurs in surgical patients.

Enteral vs. Parenteral Nutrition

The goals of nutritional therapy are to deliver an adequate number of calories to support the metabolic needs of the patient. While both parenteral and enteral nutrition can meet this goal, there are some important differences between these two modes of nutritional support. The administration of early enteral nutrition vs. parenteral nutrition has been debated in the medical literature for nearly 40 years. There is now a substantial body of clinical evidence that clearly demonstrates a benefit to enteral nutrition over parenteral nutrition [23–25]. Parenteral nutrition is considered to be more invasive and has been associated with an increased risk of infectious complications as compared to enteral nutrition. In most critically ill patients, it is possible to deliver enteral nutrition, and this method of nutritional support should be chosen whenever feasible.

Early initiation of enteral nutrition may provide some physiologic benefit for patients with severe sepsis or septic shock. Benefits include those mentioned above including maintenance of gut integrity with prevention of gut permeability, modulation of metabolic responses with subsequent decrease in insulin resistance, and suppression of the inflammatory response (references 561 and 562 from SSC guidelines). Enteral nutrition has been consistently shown to reduce the rates of infectious morbidity and ICU length of stay as compared to parenteral nutrition. Moore et al. conducted a prospective, randomized controlled trial comparing early enteral nutrition to early parenteral nutrition and found that early enteral nutrition was associated with reduced infections, specifically pneumonia [26]. Delivery of enteral nutrition has also been associated with improved return of cognitive function [27].

Parenteral nutrition may still be of benefit in those patients that cannot have their caloric needs met via the enteral route alone. In a prospective, multicenter randomized trial, Van den Berghe et al. compared early parenteral nutrition (within 48 h of ICU admission) to late parenteral nutrition (after ICU day 8). They found that patients in the late parenteral nutrition group had a faster recovery and fewer complications compared to patients in the early group [28]. However, in patients that are deemed to be at high nutrition risk (defined as NRS2002 $\geq$ 5 or NUTRIC score $\geq$ 5) in which enteral nutrition is not feasible, the early use of parenteral nutrition is recommended. In a meta-analysis by Heyland et al., the use of parenteral nutrition in severely malnourished ICU patients was associated with significantly fewer overall complications [29].

There will also be patients in which enteral nutrition has been initiated but in whom their caloric needs cannot be met via enteral nutrition alone. In these situations, it is recommended that supplemental parenteral nutrition be initiated after 7 days if patients are unable to meet >60% of calorie and protein requirements by the enteral route alone. However, it is important to note that initiation of early parenteral nutrition (either exclusive or supplemental) should be avoided in patients with sepsis. Initiating supplemental parenteral nutrition prior to day 7 has not been shown to be of any benefit and is associated with a significant increase in cost [28]. In a prospective observational study of 415 patients with severe sepsis and septic shock, Elke et al. found a significantly higher mortality rate in patients receiving parenteral nutrition (either exclusive or mixed with enteral) as compared to patients receiving only enteral nutrition [30].

Enteral Nutrition and Vasopressors

Patients that have progressed to septic shock require continuous infusion of vasopressors (typically norepinephrine) for 24–48 h to maintain their mean arterial pressure (MAP). Understanding

the impact of vasopressor use on the GI tract is critical when determining the optimal strategy for delivering enteral nutrition. Enteral nutrition is often held in patients receiving vasopressor support for septic shock primarily due to concern for mesenteric ischemia. Nonocclusive bowel necrosis has a reported incidence of 0.3–8.5% with an associated mortality rate of 46–100% [31–33]. The recent update to the ASPEN/SCCM guidelines recommend withholding enteral nutrition in patients with a MAP less than 50 mmHg and in those patients with escalating vasopressor needs [13]. In contrast, the 2013 Canadian Critical Care practice guideline states that early enteral nutrition may be beneficial for patients receiving vasopressors [34]. This lack of consensus is due in large part to a lack of clear evidence supporting either practice.

A recent study by Pinton et al. evaluated adult ICU patients receiving norepinephrine and/or epinephrine infusions and compared them with a control population [35]. They evaluated intestinal fatty acid binding protein (I-FABP), a substance which is released by enterocytes and is a marker of small bowel ischemia. Patients receiving epinephrine and/or norepinephrine had higher levels of I-FABP, higher lactate levels, and higher 28-day mortality rates, suggesting escalating vasopressor doses contribute to intestinal injury.

The type of vasopressor that the patient is receiving may also play a role in the risk of mesenteric ischemia. In a small case series comparing patients in septic shock that were receiving epinephrine + dobutamine infusions vs. norepinephrine alone, it was found that epinephrine caused lower splanchnic flow and oxygen uptake, lower mucosal pH, and higher hepatic vein lactate levels [36]. In multiple studies, administration of vasopressin has been shown to cause splanchnic hypoperfusion. Nygren et al. demonstrated decreased jejunal mucosal perfusion after administration of low to moderate doses of vasopressin [37]. Klinzing et al. also demonstrated impaired gastric mucosal perfusion in patients receiving the standard septic shock dose of vasopressin at 0.04 IU/kg/hour [38]. While these studies did report impaired mucosal perfusion, there was no mention made of any adverse clinical outcomes associated with the splanchnic hypoperfusion.

A recent retrospective review by Patel et al. evaluated the impact of early trophic enteral nutrition in mechanically ventilated patients with septic shock [39]. In this study, trophic feeds were defined as <600 kcal/day which is roughly 20 ml/hour. The authors reported that patients receiving trophic feeds within 48 h had a shorter duration of mechanical ventilation and decreased length of stay compared to patients who did not receive any enteral nutrition and those receiving higher rates of enteral nutrition. Of note, no patients developed NOBN. In another retrospective study, Rai et al. evaluated sepsis and septic shock patients receiving enteral nutrition shock [40]. They noted that patients in septic shock receiving enteral nutrition had higher gastric residual volumes compared to those patients with sepsis. However, there was no difference in the percentage of patients that reached their caloric goals.

Unfortunately, there is no prospective, randomized data evaluating the optimal utilization of enteral nutrition in patients requiring vasopressors for septic shock. However, given the limited available data, it appears that the administration of trophic enteral nutrition is safe. Escalation of vasopressors and the patient's tolerance of enteral nutrition should all be taken into account when advancing beyond trophic feeds.

Immunonutrition and Immune-Enhancing Diets: Is There a Role?

With our increasing understanding of the role of the GI tract in the immune response to infection has come an increased interest in the concept of immunonutrition. The term immunonutrition refers to the administration of a particular nutrient in order to induce a specific metabolic response or immunologic function. The addition of specific substances to enteral nutrition formulas could potentially modulate the immune response, improve wound healing, and reduce the oxidative stress associated with sepsis. In this section, we will discuss a variety of compounds

and their role in the nutritional support of patients with sepsis.

Glutamine

Glutamine is the most abundant nonessential free amino acid in the body. It is primarily stored in skeletal muscle and plays a role in protein synthesis and acid-base homeostasis in the kidney. Glutamine is also a critical nitrogen donor for rapidly dividing cells such as those found in the GI tract and immune system. Glutamine's beneficial effects include antioxidant effects, maintaining GI tract integrity (gut barrier function) by fueling enterocytes, and serving as an energy substrate for lymphocytes and neutrophils. During catabolic stress states, including sepsis, the body's stores of glutamine become rapidly depleted. This renders glutamine a conditionally essential amino acid during sepsis. Glutamine depletion results in an impaired immune response and contributes to infectious complications. Decreased circulating levels of glutamine have been associated with increased mortality [41, 42].

There have been multiple clinical trials that have reported beneficial outcomes in patients receiving supplemental glutamine, primarily in the setting of emergent GI surgery [43–47]. The benefits observed were believed to be primarily related to improvements in gut mucosal atrophy/integrity and reduced bacterial translocation in patients receiving glutamine. Several single-center studies have shown that intravenous glutamine supplementation in patients on total parenteral nutrition can improve outcome [48, 49]. Despite these early promising data, more recent trials have called into question the benefit of glutamine supplementation. The Scandanavian Glutamine Trial failed to demonstrate a difference in 6-month mortality in patients receiving glutamine supplementation compared to placebo [50]. The REDOX trial demonstrated a trend toward increased 28-day mortality in patients receiving glutamine vs. placebo (32.4% vs. 27.2%, $p = 0.05$). Additionally, in-hospital mortality and mortality at 6 months were significantly higher among those patients who received glutamine than among those who did not. Glutamine also had no effect on rates of organ failure or infectious complications [51]. The results of the REDOX trial have called into question the benefits of glutamine supplementation in critically ill patients. Not only is there question of benefit, but there may also be potential for harm to patients that receive supplemental glutamine. As a result, the Surviving Sepsis Campaign Guidelines recommend against the use of glutamine in patients with sepsis and septic shock [52]. The ASPEN/SCCM Nutritional Support Guidelines also recommend against glutamine supplementation in the ICU [13].

Arginine

Arginine is a nonessential amino acid that is derived from oral protein intake or can be synthesized endogenously in the proximal renal tubule by converting citrulline to arginine. Citrulline is primarily derived from the intestinal conversion of arterial and luminal glutamine via the glutamate-to-ornithine pathway. Arginine is an essential component for the stimulation and release of growth hormone, prolactin, insulin, and glucagon. It is also a critical substrate for the synthesis of nitric oxide (NO) by the enzyme nitric oxide synthase (NOS). Under stressed conditions such as sepsis, arginine becomes an essential amino acid because the normal quantities produced to maintain muscle mass are insufficient secondary to increased turnover rates. Both plasma and muscle levels of arginine are markedly decreased in sepsis [53–55]. Low levels of arginine have been correlated with worse prognosis in patients with sepsis [56]. The combination of decreased arginine levels in sepsis combined with the link to worsening prognosis led to an interest in arginine as a possible supplement for immunomodulation.

Clinical trials evaluating the use of arginine supplementation in humans are limited and show conflicting results. In a prospective, randomized, multicenter trial, Galban et al. [57] evaluated the impact of an enteral formula supplemented with arginine, mRNA, and omega-3 fatty acids in

patients with sepsis. They demonstrated a significant reduction in mortality, but since the formula utilized was supplemented with multiple elements, it was difficult to attribute the benefit to arginine alone. In another multicenter trial by Bertonline et al. [58], an enteral diet containing L-arginine, omega-3 fatty acids, vitamin E, beta-carotene, zinc, and selenium was compared to administration of parenteral nutrition in patients with severe sepsis. Patients that received the immune enhanced enteral formula had higher mortality rates than patients in the parenteral nutrition group. One potential explanation for the higher mortality rate is the potential for high-dose arginine supplementation to cause unwanted vasodilation and resultant hypotension. As mentioned above, arginine is a critical substrate in the synthesis of NO. Remember that septic shock is a vasodilatory shock state. Arginine administration could result in excessive NO production which could worsen vasodilation and have deleterious effects. Given the conflicting results and the potential for harm, additional investigation into the optimal use of arginine supplementation in patients with sepsis is needed. In light of this, the current ASPEN/SCCM Guideline [13] and the Surviving Sepsis Campaign Guidelines [52] recommend against the use of arginine supplementation in patients with sepsis.

Omega-3 Fatty Acids

Omega-3 fatty acids refer to three separate fatty acids: alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Both EPA and DHA are metabolites of ALA. These omega-3 fatty acids are polyunsaturated fatty acids, also known as PUFAs, and are a major component of the cell membrane. Dietary supplementation with PUFAs has been shown to reduce platelet aggregation, slow clot formation, and limit the production of pro-inflammatory cytokines [59]. The ability of omega-3 fatty acids to modulate the production of pro-inflammatory cytokines brought into question their utility in the treatment of sepsis. However, clinical evidence related to omega-3 supplementation in sepsis has shown conflicting results. A recent meta-analysis by Tao et al. evaluated 11 trials with a total of 808 patients [60]. The administration of omega-3 fatty acids had no effect on overall mortality, but the duration of mechanical ventilation was decreased in patients receiving omega-3 supplementation. In another recent systematic review by Chen et al. [61], the use of omega-3 fatty acid supplementation was associated with a lower mortality as compared to controls. A 2017 systematic review by Lu et al. demonstrated that omega-3 fatty acid supplementation reduced ICU length of stay and duration of mechanical ventilation but had not impact on patient mortality [62]. One common limitation among these systematic reviews is the very low quality of overall evidence. This lack of quality evidence to support routine omega-3 fatty acid supplementation has led the Surviving Sepsis Campaign Guidelines to recommend against the use of omega-3 fatty acids in critically ill patients with sepsis or septic shock [52].

Antioxidant Supplementation

As mentioned above, sepsis results in the production of free radicals with increased levels of reactive oxygen species. The presence of these reactive free oxygen species results in cellular injury through a variety of mechanism. To combat the presence of these free oxygen species, the host utilizes an antioxidant defense system that relies upon superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. During stress states, these enzymes can become overwhelmed, and alternate defense mechanisms must be utilized to prevent further cellular damage. These alternate defense systems include nonenzymatic antioxidants such as selenium, zinc, vitamin C, vitamin E, and beta-carotene.

Recently, there has been a significant amount of enthusiasm regarding the potential benefits of vitamin C administration in patients with septic shock. In a retrospective before and after study, Marik et al. reported on the use of hydrocortisone, thiamine, and vitamin C in patients with septic shock. Patients in the treatment group were

given the following: vitamin C 1500 mg IV every 6 h plus hydrocortisone 50 mg IV q 6 h plus thiamine 200 mg IV q 12 h. Patients in the control group received standard therapy. The hospital mortality was 8.5% (4 of 47) in patients in the treatment group compared with 40.4% (19 of 47) in the control group ($p < 0.001$). In addition, there was a lower rate of organ dysfunction in patients receiving the treatment. While these data do show promise, this was a retrospective before and after study with a very small number of patients. The upcoming Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Trial will attempt to replicate the results of the Marik study in a prospective, randomized single-center study.

Selenium is another antioxidant that has been shown to be diminished in patients with sepsis. There have been two recent meta-analyses performed evaluating the role of selenium supplementation in sepsis that demonstrated a weak trend toward decreased mortality [63, 64]. The recommended dose of selenium supplementation is 500–750 mcg/day with a duration of 7–21 days [65].

References

1. Balk RA, Bone RC. The septic syndrome. Definition and clinical implications. Crit Care Clin. 1989;5:1–8.
2. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20:864–74.
3. Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international Sepsis definitions conference. Intensive Care Med. 2003;29:530–8.
4. Singer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
5. Vincent JL, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707–10.
6. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. Crit Care. 2005;9:R764–70.
7. Moore LJ, et al. Validation of a screening tool for the early identification of sepsis. J Trauma. 2009;66:1539–46; discussion 1546-1547.
8. Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589–96.
9. Marik PE, Flemmer M. The immune response to surgery and trauma: implications for treatment. J Trauma Acute Care Surg. 2012;73:801–8.
10. Moldawer LL. Interleukin-1, TNF alpha and their naturally occurring antagonists in sepsis. Blood Purif. 1993;11:128–33.
11. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med. 2001;29:S99–106.
12. McClave SA, 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.
13. McClave SA, 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. 2016;40:159–211.
14. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22:321–36.
15. Heyland DK, Dhaliwal R, Jiang 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:R268.
16. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. Am J Surg. 2002;183:390–8.
17. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. Nutr Clin Pract. 2009;24:305–15.
18. Krezalek MA, DeFazio J, Zaborina O, Zaborin A, Alverdy JC. The shift of an intestinal 'microbiome' to a 'Pathobiome' governs the course and outcome of sepsis following surgical injury. Shock. 2016;45:475–82.
19. Heyland DK, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27:355–73.
20. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264–70.
21. Lien HC, Chang CS, Chen GH. Can percutaneous endoscopic jejunostomy prevent gastroesophageal reflux in patients with preexisting esophagitis? Am J Gastroenterol. 2000;95:3439–43.

22. 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:S51–5; discussion S56-57.
23. Moore FA, Moore EE. The evolving rationale for early enteral nutrition based on paradigms of multiple organ failure: a personal journey. Nutr Clin Pract. 2009;24:297–304.
24. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma–a prospective, randomized study. J Trauma. 1986;26:874–81.
25. Moore FA, et al. Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. J Trauma. 1994;37:607–15.
26. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma–reduced septic morbidity. J Trauma. 1989;29:916–22; discussion 922-923.
27. 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;27:2525–31.
28. Casaer MP, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365:506–17.
29. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA. 1998;280:2013–9.
30. Elke G, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis. A secondary analysis of the VISEP trial. Med Klin Intensivmed Notfallmed. 2013;108:223–33.
31. Kowal-Vern A, McGill V, Gamelli RL. Ischemic necrotic bowel disease in thermal injury. Arch Surg. 1960. 1997;132:440–3.
32. Marvin RG, McKinley BA, McQuiggan M, Cocanour CS, Moore FA. Nonocclusive bowel necrosis occurring in critically ill trauma patients receiving enteral nutrition manifests no reliable clinical signs for early detection. Am J Surg. 2000;179:7–12.
33. Smith-Choban P, Max MH. Feeding jejunostomy: a small bowel stress test? Am J Surg. 1988;155:112–7.
34. 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.
35. Piton G, et al. Catecholamine use is associated with enterocyte damage in critically ill patients. Shock. 2015;43:437–42.
36. Meier-Hellmann A, et al. Epinephrine impairs splanchnic perfusion in septic shock. Crit Care Med. 1997;25:399–404.
37. Nygren A, Thorén A, Ricksten S-E. Vasopressin decreases intestinal mucosal perfusion: a clinical study on cardiac surgery patients in vasodilatory shock. Acta Anaesthesiol Scand. 2009;53:581–8.
38. Klinzing S, Simon M, Reinhart K, Meier-Hellmann A, Sakr Y. Moderate-dose vasopressin therapy may impair gastric mucosal perfusion in severe sepsis: a pilot study. Anesthesiology. 2011;114:1396–402.
39. Patel JJ, et al. Early trophic enteral nutrition is associated with improved outcomes in mechanically ventilated patients with septic shock: a retrospective review. J Intensive Care Med. 2016;31:471–7.
40. Rai SS, O'Connor SN, Lange K, Rivett J, Chapman MJ. Enteral nutrition for patients in septic shock: a retrospective cohort study. Crit Care Resusc J Australas Acad Crit Care Med. 2010;12:177–81.
41. Roth E, Oehler R. Hypothesis: muscular glutamine deficiency in sepsis–a necessary step for a hibernation-like state? Nutrition. 2010;26:571–4.
42. Oehler R, et al. Glutamine depletion impairs cellular stress response in human leucocytes. Br J Nutr. 2002;87(Suppl 1):S17–21.
43. Jian ZM, et al. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of 120 patients. JPEN J Parenter Enteral Nutr. 1999;23:S62–6.
44. Jacobi CA, et al. Effect of alanyl-glutamine in postoperative total parenteral nutrition on postoperative immunosuppression and morbidity. Preliminary results of a prospective randomized study. Langenbecks Arch Chir Suppl Kongressbd. 1998;115:605–11.
45. Karwowska KA, Dworacki G, Trybus M, Zeromski J, Szulc R. Influence of glutamine-enriched parenteral nutrition on nitrogen balance and immunologic status in patients undergoing elective aortic aneurysm repair. Nutrition. 2001;17:475–8.
46. Mertes N, et al. Cost containment through L-alanyl-L-glutamine supplemented total parenteral nutrition after major abdominal surgery: a prospective randomized double-blind controlled study. Clin Nutr. 2000;19:395–401.
47. Morlion BJ, et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg. 1998;227:302–8.
48. Goeters C, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med. 2002;30:2032–7.
49. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition. 1997;13:295–302.
50. Wernerman J, Kirketeig T, Andersson B, Berthelson H, Ersson A, Friberg H, Guttormsen AB, Hendrikx S, Pettilä V, Rossi P, Sjöberg F, Winsö O, Scandinavian Critical Care Trials Group. Scandinavian glutamine trial: a pragmatic multi-centre randomised clinical trial of intensive care unit patients. Acta Anaesthesiol Scand. 2011;55(7):812–8.

51. Heyland D, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368:1489–97.
52. Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486–552.
53. Luiking YC, Deutz NEP. Exogenous arginine in sepsis. Crit Care Med. 2007;35:S557–63.
54. Luiking YC, Poeze M, Dejong CH, Ramsay G, Deutz NE. Sepsis: an arginine deficiency state? Crit Care Med. 2004;32:2135–45.
55. Luiking YC, Poeze M, Ramsay G, Deutz NEP. The role of arginine in infection and sepsis. JPEN J Parenter Enteral Nutr. 2005;29:S70–4.
56. Freund H, Atamian S, Holroyde J, Fischer JE. Plasma amino acids as predictors of the severity and outcome of sepsis. Ann Surg. 1979;190:571–6.
57. Galbán C, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med. 2000;28:643–8.
58. Bertolini G, et al. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. Intensive Care Med. 2003;29:834–40.
59. Alexander JW. Immunonutrition: the role of omega-3 fatty acids. Nutrition. 1998;14:627–33.
60. Tao W, Li P-S, Shen Z, Shu Y-S, Liu S. Effects of omega-3 fatty acid nutrition on mortality in septic patients: a meta-analysis of randomized controlled trials. BMC Anesthesiol. 2016;16:39.
61. Chen H, et al. Correlation analysis of omega-3 fatty acids and mortality of sepsis and sepsis-induced ARDS in adults: data from previous randomized controlled trials. Nutr J. 2018;17:57.
62. Lu C, et al. Omega-3 supplementation in patients with sepsis: a systematic review and meta-analysis of randomized trials. Ann Intensive Care. 2017;7:58.
63. Alhazzani W, et al. The effect of selenium therapy on mortality in patients with sepsis syndrome: a systematic review and meta-analysis of randomized controlled trials. Crit Care Med. 2013;41:1555–64.
64. Valenta J, Brodska H, Drabek T, Hendl J, Kazda A. High-dose selenium substitution in sepsis: a prospective randomized clinical trial. Intensive Care Med. 2011;37:808–15.
65. Berger MM, Shenkin A. Selenium in intensive care: probably not a magic bullet but an important adjuvant therapy. Crit Care Med. 2007;35:306–7.

Management of Intestinal Failure

11

Melissa Warren, Michael Chapek,
Douglas L. Nguyen, Nathan Knapp,
Stephen A. McClave, and Robert G. Martindale

Introduction

Intestinal failure was first defined in 1981 by Fleming and Remington as "a reduction in the functioning gut mass below the minimum amount necessary for adequate digestion and absorption of food" [1]. Home parenteral nutrition support is the primary treatment for intestinal failure and has dramatically improved outcomes of patients with chronic intestinal failure [2]. In the USA, estimating the number of patients that require home PN is complicated by the vast number of prescribers and multiple healthcare payor system. Data obtained from a Home Parenteral Nutrition National Registry from 1985 to 1992 indicated 40,000 patients required PN support for intestinal failure annually [3]. Statistics for home PN prevalence have been absent since suspension of the registry until 2017 when Mundi and his colleagues reported 25,011 patients (20,833 adults) required home PN per year. This number represents a significant decline in the prevalence of PN use in the USA has declined from 157 people requiring PN per million people to 79 per million people over the last 20 years. Prevalence of HPN in Europe is noted to be much lower than the USA, ranging from 5.4 to 14.6 per million [4]. Recently, retrospective studies have published HPN duration and survival statistics. In a multicenter international study including Europe and the USA, survival probability was found to be 88% at 1 year, 74% at 3 years, and 64% at 5 years. Approximately 37% of patients in the study were weaned off home parenteral nutrition within the first year. Younger participants were more likely to survive, and death was most likely to occur within 2 years of initiating home parenteral nutrition [5]. In the largest reported data set to date from a single referral center in the UK, Dibb et al. reported HPN dependence in 545 patients to be 83% at 1 year, 63% at 5 years, 59% at 10 years, and 53% at 15 years. Overall survival in patients without malignancy was 93%, 71%, 59%, and 28% at 1, 5, 10, and 20 years, respectively [6].

M. Warren
Division of General Surgery, Department of Surgery, Oregon Health & Science University, Portland, OR, USA

M. Chapek
Department of Surgery, Oregon Health and Science University, Portland, OR, USA

D. L. Nguyen
University of California-Irvine, Orange, CA, USA

N. Knapp
Division of GI and General Surgery, Oregon Health & Science University, Portland, OR, USA

S. A. McClave
Division of Gastroenterology, Hepatology and Nutrition, University of Louisville Hospital, Louisville, KY, USA

R. G. Martindale (✉)
Division of General Surgery, Oregon Health & Science University, Portland, OR, USA
e-mail: martindr@ohsu.edu

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_11

Table 11.1 Intestinal failure classification

	IV volume (milliliters/day)			
Energy provided by PN (Kcal/kg/day)	1 = <1000 ml	2 = 1001–2000	3 = 2001–3000	4 = >3000
A = 0 kcal/kg day	A1	A2	A3	A4
B = 1–10 kcal/kg day	B1	B2	B3	B4
C = 11–20 kcal/kg day	C1	C2	C3	C4
D = >20 kcal/kg day	D1	D2	D3	D4

Historical data regarding the use of home parenteral nutrition has led to current classifications of intestinal failure. Previous population-based definitions focused on durations of time that parental nutrition (PN) was needed, while clinical definitions tend to be based on functionality and pathophysiology of the intestinal failure [7, 8]. To date the definition of intestinal failure has evolved to include descriptors of etiology, staging, and treatment of intestinal failure. Most recently, the Home Artificial Nutrition & Chronic Intestinal Failure and the Acute Intestinal Failure Special Interest Groups of the European Society for Clinical Nutrition and Metabolism reached a consensus to define and classify intestinal failure in order to improve patient management, clinical research, and communication and collaboration among professionals [9]. According to the ESPEN-endorsed definition, two criteria must be present simultaneously for a diagnosis of intestinal failure, (1) "decreased absorption of macronutrients and/or water and electrolytes due to a loss of gut function" and (2) the "need for intravenous supplementation" [9]. The symptoms of intestinal failure can include some or all of the following: diarrhea, dehydration, weight loss, macro- and micronutrient deficiency, and/or obstructive symptoms. In addition to defining the criteria for intestinal failure, there are functional, pathophysiological, and clinical classifications of intestinal failure. The functional classification is based on the onset and expected outcome of intestinal failure called Type 1, Type II, and Type III intestinal failure. The mechanism or etiology of intestinal failure is known as the pathophysiological classification, and finally the clinical classification of intestinal failure is defined by the type and volume of IV support needed [9]. Pironi et al. later conducted an international cross-sectional observational study approved by ESPEN to investigate the applicability of the chronic intestinal failure classification system. Their results from the large cohort data set resulted in a proposal to simplify the classification system of chronic intestinal failure to eight clinical categories that identifies the amount of energy from PN and volume of IV support necessary (separated into four volume categories) (Table 11.1) [10].

Functional Classification of Intestinal Failure

The functional classification of intestinal failure includes three types of intestinal failure based on the onset and duration of failure and treatment [9]. Type I failure commonly occurs following abdominal surgery or during critical illness where enteral or oral nutrition is poorly tolerated and IV hydration/parenteral nutrition may be necessary in the short term until gut function returns. Type I intestinal failure refers to gut dysfunction that is short-lived, easily managed, and fully reversible as in the case of postoperative ileus. Type II intestinal failure is defined as prolonged gut failure that persists in the context of severe illness requiring weeks to months of IV hydration/parenteral nutrition before resolution as in the postsurgical patient with numerous complications requiring multiple operations and eventually transition to long-term care for rehabilitation. Like Type I, Type II is usually reversible; however Type II may progress to chronic failure or Type III intestinal failure. Type III is considered chronic intestinal failure (CIF) in a stable patient that may require months to years of IV supplementation to maintain health. Type III intestinal failure is rare and may or may not be reversible [9, 11]. Recent observational studies indicate that it may take

more than 5 years for recovery and liberation from parenteral supplementation in patients with Type III intestinal failure. These patients typically require home parenteral nutrition and/or IV hydration indefinitely. A strong multidisciplinary team that is well versed on home parenteral nutrition management, IV access, and insurance coverage is necessary for optimal patient outcomes.

Pathophysiology of Intestinal Failure

In most cases, intestinal or gut failure is the inability to absorb adequate macronutrients (energy, protein, fat, and fluid) and micronutrients (vitamins and minerals) with oral or enteral intake alone to maintain health and growth [12].

Intestinal failure is a complex disease entity with a myriad of etiologies, surgical and/or medical. In a large international survey of chronic intestinal failure of benign disease, short bowel syndrome was found to be the most common etiology. Other mechanisms for intestinal failure include intestinal dysmotility, intestinal fistulas, mechanical obstruction, and extensive mucosal diseases. Crohn's disease was the most common underlying disease for chronic intestinal failure. Mesenteric ischemia, surgical complications, chronic intestinal pseudo-obstruction, and radiation enteritis were also among the most prevalent underlying causes for chronic intestinal failure (Table 11.2) [10].

Table 11.2 Pathophysiology and etiology of intestinal failure

Pathophysiology of intestinal failure	Etiology
Intestinal dysmotility	Postoperative ileus
	Critical illness-associated dysmotility
	Ogilvie syndrome
	Acute or chronic intestinal pseudo-obstruction
	Severe gastroparesis
Intestinal fistula	Inflammatory: Crohn's disease, diverticular disease, radiation enteritis
	Postoperative complications (anastomotic leak, wound dehiscence, intra-abdominal abscesses)
	Infectious complications
	Foreign body
	Neoplasm
	Trauma
Mechanical obstruction	Anastomotic strictures
	Abdominal adhesions related to previous surgery or peritonitis
	Hernias with strangulated bowel
	Inflammatory bowel disease or radiation enteritis (stenosis or strictures)
	Obstructing intrinsic or extrinsic neoplasms
	Peritoneal carcinomatosis
	Volvulus
	Bezoars
Short bowel syndrome	Extensive surgical resection for mesenteric infarction from either arterial or venous occlusion, Crohn's disease, intestinal volvulus, abdominal trauma, bariatric surgery complications
	Congenital causes including gastroschisis, intestinal atresia
Extensive small bowel mucosal disease	Celiac sprue, tropical sprue
	Ischemic enteropathy
	Inflammatory bowel disease
	Infectious enteritis
	Radiation enteritis
	Amyloidosis
	Common variable immune deficiency

Normal Digestion and Absorption of Nutrients

The normal human small intestine reaches full length by the approximate age of 9, and is estimated to be between 4 and 6 m, depending on the method of measurement and technique used to evaluate length, including radiologic, or measurements taken at time of surgery or autopsy [13–15]. Short bowel syndrome (SBS) is the most prevalent etiology of intestinal failure and is loosely defined as <200 cm of functional bowel remaining. SBS is characterized by diarrhea or steatorrhea, dehydration, and/or malnutrition [16]. Symptoms range dramatically in presentation and severity from patient to patient. For

example, a subset of patients with SBS with less than 150 cm may be able to sustain adequate absorption of macronutrients but will often need additional IV fluids, while other patients with >200 cm will require PN to sustain life [17]. It is imperative to understand the anatomy and function of remaining bowel in intestinal failure in order to formulate a management plan that can maintain health and nutrition. Table 11.3 provides a summary of nutrient absorption in the intestinal tract.

The majority of the digestive and absorptive processes take place in the duodenum and proximal jejunum (usually within the first 100 cm of small bowel). The protein digestion process begins in the stomach, when gastric pepsinogen is converted to pepsin by gastric acid. Pepsin then starts the protein digestion process primarily by unraveling the tertiary structure of proteins, so that completion of digestion and absorption of peptides can take place in the duodenum. The rate and volume of delivery of chyme from the stomach is closely controlled by a variety of hormonal and neural controls, allowing for efficient mixing with pancreatobiliary secretions. The gallbladder and pancreas are stimulated by the acidification and presence of nutrients in the duodenal lumen. The mucosal endocrine cells release cholecystokinin (CCK) and secretin into the portal circulation, which feeds back to secondarily stimulate more biliary and pancreatic secretion.

Table 11.3 Location and nutrient absorption in the gastrointestinal tract

Gastrointestinal location	Nutrient absorption
Stomach	Water, ethyl alcohol, copper, iodide, fluoride, molybdenum
Duodenum	Calcium, phosphorus, magnesium, iron, copper, selenium, thiamin, riboflavin, niacin, biotin, folate, vitamins A, D, E, and K
Jejunum	Lipids; monosaccharides; amino acids; small peptides; calcium; phosphorus; magnesium; iron; thiamin; riboflavin; niacin; pantothenate; biotin; folate; vitamin B_6; vitamin C; vitamins A, D, E, and K; zinc; chromium; manganese; molybdenum
Ileum	Amino acids, vitamin C, folate, vitamin B12, vitamin D, vitamin K, magnesium, bile salts
Colon	Water, sodium, chloride, potassium, vitamin D, biotin, short-chain fatty acids

The jejunum has long villi, sizeable absorptive surfaces, highly concentrated digestive enzymes, and carrier proteins. As previously mentioned, this is the primary digestive and absorptive site for most nutrients. Over 90% of macronutrients (carbohydrates, lipids, and amino acids) are absorbed in the proximal 100–150 cm of the intestines. The villi are longer, and the crypts are deeper in the proximal jejunum than in the ileum; therefore, the loss of part of the jejunum initially compromises nutrient absorption more than the loss of an ileal segment of the same length, because of the morphologic and functional differences in the segment of small bowel. The ileum, however, is eventually able to compensate for the jejunal loss by augmenting villous length and crypt depth, but the jejunum is unable to fully compensate for ileal absorption. The ileum has specialized receptors for the absorption of bile salts, and vitamin B12, which are not present or inducible in the jejunum.

Normal digestion and absorption are also highly dependent on gradual gastric emptying of partially digested nutrients and the adequate mixing of these nutrients with bile and pancreatic enzymes in the duodenum, allowing for efficient nutrient absorption in the jejunum. Lipid or fat malabsorption and maldigestion occur in absence of appropriate mixing with pancreatic enzymes and bile as this is part of complex set of steps that allows for the formation of emulsion droplets or micelles. Once at the enterocyte, the brush border breaks down the triglyceride into two fatty acids and a 2-monoacylglycerol. These metabolic products are taken up by specific receptors on the enterocytes and then re-esterified in the enterocyte endoplasmic reticulum, packaged by the Golgi apparatus into chylomicrons, and exit the cell to the lymphatics. Medium- and short-chain fatty

acids can be absorbed directly into the portal vein. In malabsorptive conditions associated with gut failure, the utilization of MCT oil can be a beneficial way to increase calories without exacerbating malabsorption.

Patients with proximal jejunostomy lose the inhibitory mechanisms that delay gastric emptying, which then results in rapid gastric emptying and intestinal transit. This results in inadequate mixing of pancreatobiliary secretions and food, yielding poor enzymatic digestion and micelle formation, which in turn results in inadequate absorption. The ileocecal valve, along with normal neuronal mechanisms, acts as a brake to slow intestinal transit and increase nutrient-enterocyte contact time, facilitating enhanced absorption. The loss of the ileocecal valve can also result in reflux of colonic bacteria into the small bowel, resulting in small bowel bacterial overgrowth. This can worsen nutrient and vitamin B12 malabsorption, and deconjugate bile salts, worsening diarrhea. The bacteria in the distal small bowel will also compete with enterocytes for nutrient assimilation (Table 11.4).

Table 11.4 Effect of small bowel bacteria overgrowth on nutrients

Macronutrient/ mechanism	Effect
Fat	Malabsorption
	Bacterial deconjugation of bile acids
	Production of lithocholic acids (toxic)
Carbohydrate	Metabolism
	Bacterial fermentation of carbohydrate
	Production of hydrogen, CO_2
	Maldigestion, osmotic load, diarrhea, pain
	D-lactate production
Protein	Metabolism
	Degradation of proteins, reduced AA absorption
	Lower enterokinase, less pancreatic proteases
Vitamins	Alterations in metabolism
	Bacterial utilization of B12
	Malabsorption of fat-soluble A, D, K, E
	Bacteria produce folate, vitamin K

If complex carbohydrates, such as soluble fibers, that are not absorbed in the proximal gut reach the colon, they are fermented by the bacterial enzymes in the colon, resulting in the production of short-chain fatty acids. The short-chain fatty acids are absorbed by specific receptors on the colonocytes. It is estimated that the intracolonic digestive process by bacteria can generate in the range of 150–500 kcal/day for the patient [18]. In many cases this process is beneficial to the patient's immune function and contributes a significant number of calories to help maintain nutritional status. However, in some patients with SBS and an intact colon, non-absorbed fermentable carbohydrates may exacerbate diarrhea and electrolyte loss. Due to a variety of mechanisms in SBS, the D-lactate-producing bacteria (*Lactobacillus fermenti*, *Lactobacillus acidophilus*, and *Streptococcus*) may become predominant in the colon decreasing the pH and contributing to a D-lactate acidosis when the D-lactate is absorbed by the colonic mucosa. A course of antibiotics and even probiotics can decrease the concentration of D-lactate-producing bacteria [16].

In addition to macronutrient malabsorption, the loss of intestinal absorptive surface area often results in significant losses of electrolytes, water, minerals, and trace elements through fecal losses. The proximal small bowel receives approximately 7–9 L of fluid and electrolytes from endogenous secretions and oral intake per day, with 6–8 L being reabsorbed in the small bowel and approximately 2 L reabsorbed in the colon. For someone with a healthy GI tract, only 100–200 mL of water is lost in the stool each day. The colon has a large absorptive capacity, where up to 6 L of solution can be absorbed. Depending on the site of intestinal resection, stool losses can be more than 6 L from a jejunostomy and more than 2.5 L from ileostomies. The presence or absence of the colon, along with multiple other factors, plays a key role in a patient's ability to attain gut autonomy (Fig. 11.1).

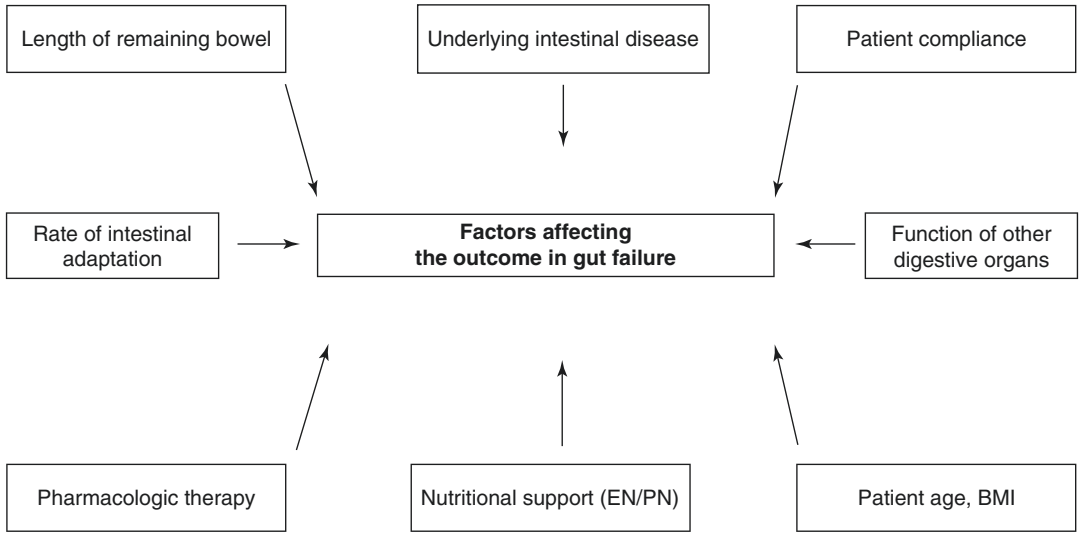

Fig. 11.1 Factors affecting the outcome of gut failure

Factors Influencing Intestinal Failure and Adaptation

The type and severity of clinical manifestations of intestinal failure are highly variable, and numerous factors will affect the clinical presentation. In some patients, caloric needs are adequately met with volitional intake, or enterally with formulae, but vitamin and mineral deficiencies may occur. Meanwhile, in other patients, fluid and electrolyte losses are the predominant clinical problems, while nutrient absorption is sufficient.

Small intestinal length is an important determinant of intestinal function. In adults, the average length of the small intestine is approximately 480 cm. Adults with residual small intestines (with less than 200 cm of absorptive surface either by resection, mucosal abnormality, or fistula) are at risk for developing gut failure. In particular, those patients with less than 60 cm of functional small intestine are unlikely to ever be independent of PN or reach gut autonomy [19, 20]. In addition to small intestinal length, several other factors contribute to intestinal function, including the presence or absence of an ileocecal valve, presence of a colon, intestinal motility, function and health of the remaining small bowel, and the gradual process of intestinal adaptation after surgical resection (Fig. 11.2).

Several factors contribute to the intestinal adaptation process including presence of colon, presence of ileocecal valve, length and segment of remaining bowel, health and function of the remaining bowel, patient's age, inflammatory state, and patient's comorbid conditions [21]. In addition, active mucosal inflammatory disease, such as Crohn's disease, radiation enteritis, carcinoma, or pseudo-obstruction involving the remaining bowel may diminish a patients' adaptation response. In patients with large segments of resected or nonfunctional bowel, PN is initially the mainstay of nutrition support. As the patient tolerates, and as nutrition parameters allow, PN should be transitioned to enteral nutrition (EN). Oral intake should also be initiated, as tolerated. The ultimate goal is to achieve gut autonomy.

Site of Intestinal Resection

Jejunum

The symptoms associated with chronic gut failure are dependent on the physiology of the

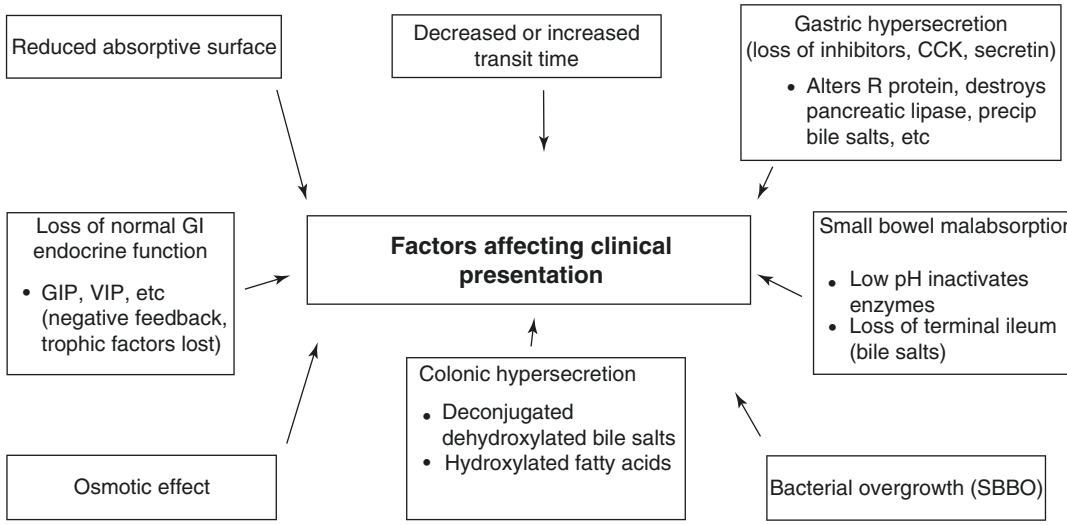

Fig. 11.2 Factors affecting clinical presentation of gut failure

remaining small intestines, because each segment of the small bowel has unique functional capacities and differing abilities to adapt as described earlier [17, 22, 23]. The duodenum and jejunum have long villi, large absorptive surfaces, highly concentrated digestive enzymes, and carrier proteins. This is the primary digestive and absorptive sites for most nutrients. After large segments of jejunum are resected, or the mucosal absorptive surface is injured by ischemia, infection, etc., there is a temporary reduction in absorption of most nutrients. The jejunum, however, exhibits modest adaptive changes by increasing functional capacity, including increasing mucosal weight, DNA, and protein [24, 25].

Ileum

The ileum has specialized functions not available in the rest of the small bowel, including specific receptors for vitamin B12 and bile acids absorption, which are present only in the distal ileum. In adults, if 20–60 cm of ileum is resected, there is a moderate chance of vitamin B12 malabsorption, but if more than 60 cm of ileum is resected, vitamin B12 malabsorption will occur [26]. If greater than 100 cm of ileum is resected, it can lead to disruption of the enterohepatic circulation, resulting in bile salt deficiency and fat malabsorption from inability to form micelles. In addition to the specialized absorptive surface, the ileal mucosa serves as the source of peptide YY, which is secreted when unabsorbed lipids are present in the ileum. Peptide YY, through this feedback, delays gastric emptying and facilitates absorption of nutrients in the small intestine. This essentially allows for longer proximal gut luminal exposure and better absorption. The loss of this "ileal brake" may contribute to worsening diarrhea, commonly observed in SBS, or high-output proximal fistula.

Presence of the Ileocecal Valve

The importance of the ileocecal valve in short bowel and intestinal failure cannot be overstated. It serves as an important barrier to reflux of colonic bacteria and fecal material into the small intestine. The valve structure is responsible for the regulation of the passage of fluid and nutrients from the ileum into the colon. The loss of the ileocecal valve reduces small intestine transit time, which results in a decrease in exposure time of small bowel content to the mucosal

absorptive surface and impairs nutrient absorption. In particular, the loss of the ileocecal valve is associated with a longer duration of the requirement for PN [27]. Infants with less than 30 cm of small bowel and lacking the ileocecal valve were less likely to be liberated from PN [28]. Furthermore, the absence of the ileocecal valve commonly promotes small bowel bacterial overgrowth; if the overgrowth is significant, it can alter vitamin B12 absorption and bile salt metabolism [29, 30].

Colon

The colon has a role in the absorption of water, electrolytes, and short-chain fatty acids (SCFAs). The colon may also slow intestinal transit, via feedback loops. In addition to its role in sodium and water absorption, the colon normally plays a small but significant role in salvaging energy via absorption of SCFAs, primarily acetate, butyrate, and propionate. An estimated 10–20% of the total daily energy requirement can be absorbed from the colonic mucosa, via specific receptors for SCFAs [31]. The undigested carbohydrates in the proximal gut are fermented by colonic bacteria-yielding SCFAs. In patients with SBS with a remaining colon, it has been shown that the colon can absorb as much as 20% of the energy requirements for patients consuming soluble fiber in their diet, yielding fermentable substrates for the colonic bacteria [18, 32]. Further, the formation of SFCAs by the gut microbiota may also hormonally compensate for deficits that are a result of short bowel. As previously discussed, a decrease in peptide YY as a result of ileal resection or inflammation ultimately results in shorter luminal exposure in the proximal gut due to lack of gastric emptying delay. It has been shown that SFCAs induce peptide YY secretion through activation of specific receptors on enteroendocrine L cells [33, 34]. Clinically, this suggests that ileal resection with associated decrease of peptide YY could potentially be mitigated by microbiota producing SCFAs to induce peptide YY secretion.

Phases of Intestinal Adaptation Following Resection

After a massive enterectomy, or loss of mucosal absorptive surface, the intestine begins to adapt within days of the loss. This adaptation can continue for over 2 years before it reaches maximal maturity. Intestinal adaptation can be categorized into three different phases—Phase 1, the acute phase; phase 2, the primary period of intestinal adaption; and phase 3, the late period after full intestinal adaptation has occurred. Each presentation will be dependent upon the specific etiology, preexisting conditions, and extent of bowel, either lost or nonfunctional.

Phase 1 can be considered as the acute phase, which may last for 1–2 weeks. This phase is characterized by significant fluid and electrolyte losses, often resulting in voluminous diarrhea [35]. During this early phase, after correction of volume deficits, the highest priority goal is the administration of PN to make up for the nutrient losses and prevent fluid and electrolyte abnormalities. An H2-receptor antagonist (H2RA), or proton pump inhibitor (PPI), should be considered, at least initially intravenously, to suppress gastric hypersecretion. PPI has been shown to be better than H2RA at decreasing both acid and volume of gastric content. By minimizing gastric hypersecretion, a decrease in pancreatic and biliary secretion is noted, secondary to removing the stimulus for excessive pancreatic exocrine secretion stimulated by acidification of the duodenum. In patients with jejunal resection, gastric emptying of liquids is more rapid, although the total intestinal transit time may remain normal. The “ileal brake” can compensate for this ileal resection-induced increased transit time [35]. Additionally, in distal intestinal resection patients and patients without a residual colon, there is a loss of inhibition on gastric emptying, because there is significant decrease in peptide YY, glucagon-like peptide 1, and neurotensin [36]. Once the patient’s volume status and electrolytes are stabilized, slow introduction of enteral feeding is indicated. This can be administered either orally or by feeding tube. A percutaneous endoscopic gastrostomy (PEG) tube can

be considered, if long-term need for tube feeding is expected (>30–60 days). The use of PEGs are controversial but should be considered if oral intake is limited. Continuous tube feedings in the postoperative period have been shown to increase net absorption of lipids, proteins, and energy, compared to intermittent oral feeding [37]. Furthermore, enteral feedings, either via oral intake or tube feeding, have been shown to stimulate long-term intestinal adaptation via feedback mechanisms from GI hormones which have trophic effects [38].

Phase 2 can take up to 2–3 years for maturation to fully complete. During this phase, the intestine adapts to ensure maximal efficiency of the absorption per unit length. Muscular and mucosa hypertrophy is noted along with mucosal and villous hyperplasia, with greater villus height and crypt density in compensatory distal small bowel after proximal small bowel resection than in compensatory proximal small bowel after distal small bowel resection [39]. Intestinal hormones and growth factors promote structural and functional changes. The result is an increase in cell number, as well as cell size [40]. The intestine hypertrophies, and the villus height increases, effectively increasing the surface area for more efficient absorption [15, 41]. Phase 3 is the late period after full adaptation has taken place. Generally, the length of remaining small bowel necessary to prevent long-term dependence of PN is approximately 100 cm, in the absence of a functional colon, or 60 cm of small intestine in the presence of a normally functioning colon [15, 41]. In animal models for SBS and now in some human trials, enteroglucagon, glucagon-like peptide II (GLP-2), epidermal growth factor, growth hormone, CCK, gastrin, insulin, and neurotensin appear to contribute to the intestinal adaptation response [42].

Diagnostic Method and Clinical Assessment

Clinical laboratory assessment of nutritional status in gut failure is similar to the clinical assessment for any acute or chronic disease. No specific lab testing, other than that for serum citrulline levels, has shown benefit over routine nutrition parameters. Citrulline is a nonprotein amino acid with the majority of citrulline being produced by the enterocyte from dietary arginine. Citrulline has been proposed as a "surrogate biomarker" for short bowel. It is not exactly clear whether serum citrulline levels reflect enterocyte mass or relative enterocyte function or possibly both. Several clinicians routinely dealing with gut failure have suggested that measuring serum citrulline may constitute an objective, quantitative, relatively simple, and reproducible parameter to give an estimate of the quantity of functional enterocyte mass. Serum citrulline appears to be relatively independent of current nutritional status, the presence of gut local inflammation, location of intestinal resection, and the exact etiology of the loss of mucosal mass. Serum citrulline is also independent of age and the various etiologies of intestinal failure, such as villous atrophy, radiation enteritis, chemotherapy-induced enteropathy, and acute rejection of small bowel transplant [39, 43–46].

Radiologic Evaluation of Gut Failure

The radiologic evaluation of gut failure should be tailored to the etiology of the failure and considerations of the plan for future potential interventions. A multimodal imaging regimen to best evaluate remaining anatomy, inflammation, and other intra-abdominal abnormalities is often required. An attempt should be made to evaluate viable length of bowel. An upper gastrointestinal (UGI) series, with small bowel follow-through (SBFT), is the mainstay to evaluate length, gross structure of the small bowel mucosa, and presence of entero-entero fistulae. Fistulagrams should be part of any evaluation of enterocutaneous fistula. Fistulagrams can be extremely helpful in determining whether or not surgery, if any, will be of value in correcting some of the metabolic complications of gut failure. Whenever possible, these diagnostic radiologic studies should be done with a member of the primary team taking care of the

patient to ensure adequate communication of findings.

Many of the anatomical relationships noted earlier can also be seen on CT or CT enterography. It can be critical prior to any consideration for surgical exploration that all possible anatomic information be obtained. CT angiography may also help with surgery planning to identify altered arterial supply due to surgical division of proximal arterial pedicles, leading to enteric vascular supply from collateral vessels. MRI has been suggested in imaging of intestinal failure patients due to its sensitivity for detecting severe adhesive or inflammatory disease, but this is less common in clinical practice [47]. A thorough workup often includes both UGI with SBFT and CT enterography [48, 49].

Medical Management of Intestinal Failure

Medical management of intestinal failure is multifaceted and consists of fluid and electrolyte management, pharmacologic management, and nutrition including dietary modifications and enteral and/or parenteral nutrition therapies. Management strategies should be defined by the physiology and anatomy of the patient and their stage of intestinal adaptation.

Fluid and Electrolytes

After a massive enterectomy, or loss of large segments of mucosal absorptive surface, patients may experience extreme gastric hypersecretion resulting in significant fluid and electrolyte losses. Initial management of patients with gut failure primarily involves supportive care, including management of sepsis and postoperative complications. When stable from the initial phase of resuscitation, volume status and weight should be closely monitored (e.g., stomal, fecal, and urinary losses) to ensure optimal hydration and electrolyte balance status. Sodium chloride, potassium chloride, and magnesium are the primary ions likely to require replacement in the acute phase of intestinal resection.

Acid-reducing medications are integral in managing fluids and electrolytes by decreasing gastric hypersecretion. These medications may be needed in the acute phase and more chronically as gastric hypersecretion can persist up to 6 months post-intestinal resection [12]. Their use is described in more detail in the pharmacology section.

As adaptation occurs dependence upon parenteral fluid and electrolytes may improve however, for those with extensive resection or nonfunctional remaining bowel that lack a colon often suffer from dehydration and salt depletion. Fluids typically used include normal saline IV fluids parenterally, normal saline flushes enterally via feeding tubes, and oral rehydration solutions for patients consuming fluids orally. The oral rehydration solutions are glucose polymer-based where the glucose promotes salt and water absorption by solvent drag [50]. The optimal sodium concentration of the oral rehydration solutions should be at least 90 mmol/L, which is the concentration of the small bowel effluent [51]. Oral solutions with lower sodium concentration may result in increased sodium losses. For patients with a residual colon in continuity, oral rehydration solution may still be of value, but the amount of sodium in the solution may be not extremely critical, because the colon can absorb sodium and water against a steep electrochemical gradient [50]. Avoidance of hypertonic fluid is recommended becuase it will cause shifts of fluid for dilution from the intravascular space to the gut lumen. Similarly, if hypotonic solutions are consumed, electrolytes will be required to increase the solute composition for optimal absorption as the fluids travel through the GI tract.

In addition to sodium losses, large quantities of magnesium can be lost in the jejunal and ileal effluent [52]. There are two primary mechanisms responsible for hypomagnesemia in intestinal failure. Magnesium binds with unabsorbed fatty acids in the intestine and is lost in the effluent or stool output. The second, more indirect mechanism of magnesium loss is increased excretion

of magnesium by the kidneys as a result of secondary hyperaldosteronism. Secondary hyperaldosteronism occurs as the body attempts to retain sodium chloride and maintain water absorption [53].

Magnesium deficiency may result in secondary calcium deficiency, because hypomagnesemia impairs the release of parathyroid hormone [54]. These electrolytes, therefore, should be monitored and replaced as appropriate (Table 11.3). Chronic hypomagnesemia in intestinal failure can be difficult to replete due to the laxative effect of oral magnesium supplementation. Reducing intestinal secretion and stool output and maximizing intestinal absorption can improve overall fluid and electrolyte status for intestinal failure patients. Pharmacological strategies are discussed in the next section.

Pharmacology

Pharmacologic management during the acute phase generally involves decreasing gastric secretions and intestinal losses and maximizing intestinal fluid absorption. Antisecretory agents, antidiarrheal agents, and trophic agents have all been used in order to manage the severe malabsorption and diarrhea that result from intestinal failure. Patients may require or select combinations of agents for maximal response.

Antisecretory Agents

Histamine receptor antagonist (H2RA) or proton pump inhibitors (PPIs) are initially given intravenously to suppress hypergastrinemia-induced gastric acid hypersecretion and limit volume loss [15, 32, 55]. PPIs have been shown to be more effective than H2RA in decreasing gastric volume secretion. These are usually given at a dose higher than the routine acid reducing level (e.g., omeprazole 40 mg BID or rarely TID).

Octreotide, a long-acting analog of native somatostatin, is occasionally used in the acute setting for its antisecretory function. Octreotide inhibits the secretory stimulants of serotonin, gastrin, secretin, CCK, vasoactive intestinal polypeptide (VIP), and motilin [56]. Use of octreotide results in the reduction of fluid and electrolyte output [57], but octreotide and other somatostatin analogs also have several metabolic drawbacks. Octreotide has been known to increase gallbladder stasis, resulting in cholelithiasis [58]. Doses of octreotide (usually over 250 μg three times per day) cause alterations in blood glucose levels, due to inhibitory effects on insulin secretion. Though octreotide has been shown to reduce fluid and electrolyte output in SBS patients, it is also expensive, and its clinical effect is diminished over time [53]. It is most often used as a last-line agent in those who are unresponsive to other pharmacological strategies.

Clonidine, which acts via an alpha-adrenergic agonists mechanism, commonly used for blood pressure control, has also been shown to stimulate small bowel fluid absorption and inhibit anion secretion. It has limited benefit and must be used with caution in the intestinal failure population, as these patients commonly have hypovolemia, and the use could contribute to hypotension.

Antidiarrheals

Antidiarrheal agents slow transit and minimize diarrhea by increasing nutrient enterocyte contact time. Loperamide (Imodium) and diphenoxylate-atropine (Lomotil) are two of the most common antidiarrheal agents. They exert their effects on intestinal opioid receptors, slowing bowel transit through reduction of circular and longitudinal muscle activity.

Loperamide is the first-line anti-motility or antidiarrheal agent as it does not cross the blood-brain barrier, whereas diphenoxylate-atropine does lead to central nervous system side effects such as confusion, euphoria, lethargy, and dizziness [59]. In patients with ileostomies, loperamide has been shown to reduce stool output by approximately 20%; however some patients do not respond at all [60]. Doses can be titrated to a maximum of 32 mg per day. It is typically

administered 30–60 min prior to meals and at bedtime for maximal effect. Loperamide is available over the counter or as a prescription and is typically considered as the first-line antidiarrheal agent.

Diphenoxylate-atropine or Lomotil crosses the blood-brain barrier as mentioned previously and has potential for creating dependence. It requires a prescription and is a schedule V medication due to the possibility of dependence and potential for overdose. The maximum recommended dose is 30 mg/day. Some clinicians use diphenoxylate-atropine alone or in conjunction with loperamide as antidiarrheal agents. It is also important to remember that abruptly stopping diphenoxylate-atropine can result in withdrawal [57].

Bile acid-binding resins such as cholestyramine are bile acid sequestrants that will bind unabsorbed bile acids and prevent bile acid-induced (choleretic) diarrhea. In patients with less than 100 cm of ileum resected, unabsorbed bile acids pass on to the colonic lumen and are metabolized by bacteria to lithocholic acid, resulting in secretory diarrhea. In the patient with colon present and limited distal ileum, cholestyramine can be given at maximum doses of 24 g/day. In cases of more extensive ileal resection, patients may lose more bile acids than can be replaced through liver synthesis, and cholestyramine may exacerbate fat malabsorption and fat-soluble vitamin deficiencies. If cholestyramine is used, it is important to monitor for improvement in diarrhea and fat-soluble vitamin deficiency.

Narcotics are occasionally used in refractory diarrhea, as they can dramatically decrease transit time. Narcotic agents such as codeine, morphine, paregoric, and tincture of opium have been used with success and should be individualized as needed. Clinical considerations for narcotics include potential medical contraindications, cost, availability, and lack of insurance coverage. Often nonadherence to clinical treatment is related to the patient's inability to afford the treatment.

Pancreatic enzymes have limited to no benefit in intestinal failure, although they are occasionally tried if maldigestion is considered.

Glucagon-Like Peptide 2 Analogs

Glucagon-like peptide 2 analogs have recently been approved by the Food and Drug Administration for use in humans. They are marketed under the name teduglutide for patients with gut failure resulting from short bowel. GLP-2, which is secreted from the distal small bowel colon mucosa, has been shown to be the key agent in stimulating intestinal adaptation [61, 62]. Other GLP-2 agonists are in final stages of FDA approval. In 2005, Jeppesen examined the use of teduglutide for 21 days in SBS patients and reported a significant decrease in fecal wet weight and loss of nutrients in the stool while increasing villus height and crypt depth [62]. Jeppesen later carried out a 24-week, phase III, placebo controlled trial showing that teduglutide significantly increased rates of gut autonomy in intestinal failure. These results were maintained in a 2-year trial of teduglutide which also showed no realized adverse health effects of long-term teduglutide use [63]; continued long-term trials must be carried out to determine the effects of long-term teduglutide more definitively. A number of other studies have supported these claims, which resulted in fewer days of PN needed. Several potential side effects must be considered to include mucosal overgrowth at the ostomy site, potentially leading to bowel obstruction (reported from 4% to 9%). The potential promotion of other GI epithelial tumors must be considered. Fujioka et al. found that in two randomized, double-blind, phase III studies of patients administered teduglutide—a glucagon-like peptide 2 analog—patients who also received narcotics were more likely than those only receiving teduglutide to have abdominal complaints (pain, nausea, vomiting). There are, however, very few randomized controlled trials concerning narcotic use and intestinal failure [64]. Consequently, these should be used with caution, secondary to the significant side effects these narcotic agents have. Criteria for use of glucagon-like peptide analogs include patients with short bowel syndrome that require PN or IV fluids more than three times per week for greater than 1 year. Patients must be optimized

Table 11.5 Methods to control high ostomy or stool output (goal < 2.0 L/day)

Treatment	Result	Recommendations/guidelines
Antidiarrheal agents	Slows small bowel motility and decreases secretion, increases absorption, increases anal sphincter tone	Imodium (loperamide) Max dose 32 mg/day Does not cross blood-brain barrier
		Lomotil (diphenoxylate-atropine) Max 12 tabs/day Drowsiness (crosses blood-brain barrier) Anticholinergic side effect of dry mouth
		Codeine 15–60 mg PO QID Use with other antidiarrheal agents
		Tincture of opium (10 cm3 TID) Start 0.15 mg. 75 TID to QID, caution CNS side effects Regular dosing is key
Other		Clonidine (0.05 mg BID to 0.15 mg BID) Use with other antisecretory agents Alpha-2 adrenergic agonist
Histamine 2-receptor antagonists (H2RAs)	Reduces gastric secretions	Ranitidine 20–40 mg PO/IV/BID Famotidine 150–300 mg PO/IV BID
Proton pump inhibitors (PPIs)	Decreases gastric acid and indirectly biliopancreatic secretions	Doses up to 20–40 mg BID to TID
Antisecretory	Reduces GI secretions and motility	Octreotide 100–300 mg TID SQ Side effects rise with dose

medically and nutritionally and able to demonstrate adherence to therapies. Finally precautions to using these trophic agents include active GI malignancy, stricture, active Crohn's disease, biliary or pancreatic disease, etc. [65] (Table 11.5).

Nutritional Management

A comprehensive nutrition assessment in patients with intestinal failure should include a thorough review of weight changes, dietary history, medication usage, GI symptoms, signs of micronutrient deficiencies, lab data, and history of IV access or enteral feeding devices. GI and surgical history is imperative to maximize utility of nutrition therapies and patient outcomes. For patients with short bowel syndrome, diet modifications have been beneficial in terms of reducing stool output and improving nutritional status; however, it requires detailed education by the medical team and motivation and commitment on the part of the patient. Enteral and parenteral nutrition therapy play important roles in different stages of intestinal failure as well. Though the type of therapy can be very important, it is critical to weigh the clinical benefits of rigorous diet recommendations versus the potential consequences to the patient such as unpalatable diets, the cost, and the psychological, social, or cultural impact on the patient's life.

Dietary Management

Carefully planned dietary modifications can promote optimal intestinal function. Luminal nutrients increase splanchnic blood flow, upregulate nutrient transporters, stimulate digestive enzymes, and promote intestinal motility and

mucosal growth. The process of nutrient assimilation and absorption is highly regulated in the healthy GI tract. In cases of intestinal failure, the intestinal tract's reserve capacity and ability to assimilate nutrients is disrupted or reduced. However, the intestine capacity will adapt over time to endogenous and exogenous stimulation and develop a new nutritional homeostasis. Effective and timely diet therapy along with an understanding of the pathophysiology and phase of intestinal failure may decrease dependence upon parenteral nutrition therapy or IV hydration over time.

In general, patients with SBS-related intestinal failure will consume energy more than two times their basal energy expenditure. It is theorized that neuroendocrine signaling increases sense of appetite and thirst, resulting in hyperphagia, in order to compensate for intestinal insufficiency and malabsorption. Some patients have increased their oral intake by as much as four times their energy expenditure and are able to avoid parenteral nutrition support [66]. Though hyperphagia increases energy intake, it may also result in worsening diarrhea and excessive loss of nutrients. SBS patients are predicted to absorb approximately one-half to two-thirds as someone with normal bowel length and function. Ongoing assessment of dietary intake, stool output, and micronutrient levels is necessary.

Specific dietary recommendations are based on remnant intestinal anatomy, more specifically, the presence or absence of the terminal ileum and colon. Not only does the colon reabsorb fluids and electrolytes, it has an energy-recovering role as described earlier. The bacteria in the colon degrade complex carbohydrates into short-chain fatty acids that are then utilized by the body for energy. For these reasons, having 50% of the colon in continuity is equivalent to having an additional 50 cm small intestine [66]. In patients with short bowel syndrome and a preserved colon, a low-fat, carbohydrate-rich diet is recommended. Steatorrhea or fat malabsorption is common in intestinal failure. Steatorrhea also leads to loss of fat-soluble vitamins, calcium, magnesium, and zinc. Nordgaard et al. investigated the effect of a high-fat diet to a high-carbohydrate, low-fat diet on fecal energy loss. Absorption of energy increased 20%, while patients with colon in continuity were on the low-fat, carbohydrate-rich diet [18]. Patients with colon in continuity may also benefit from a low-oxalate diet. Oxalate is a natural substance found in many foods that can only be absorbed in the colon (Table 11.6).

Table 11.6 Foods rich in oxalates

Spinach
Bran flakes
Rhubarb
Beets
Potato chips
French fries
Nuts and nut butters

In normal absorptive physiology, oxalate binds tightly to dietary calcium in the proximal small bowel and is excreted in the stool as a relatively insoluble calcium oxalate. With fat malabsorption, however, dietary calcium preferentially binds to free fatty acids, allowing oxalate to pass into the colon, where it is taken up by the colonic mucosa, especially in the inflamed colon. Once absorbed and circulating, oxalate is filtered by the kidney, is concentrated, and results in nephrocalcinosis and nephrolithiasis [41]. This issue is made more severe when the urine is acidic causing the oxalate to precipitate. Acidic urine is common in short gut failure patients as a result of this population taking vitamin C supplements. Patients with SBS with colon continuity, therefore, should be on a low oxalate-containing diet and consume calcium-rich foods or take calcium supplements to reduce the risk of oxalate stone formation.

Conversely, patients without a colon in continuity (end jejunostomy) may be able to tolerate higher fat intake without compromising energy absorption, fluid, and monovalent electrolytes; however, there may be an increase in divalent cation losses such as calcium, magnesium, zinc, and copper [66]. The benefits of fat in the diet include improved palatability, intake of essential fatty acids, and higher energy density. Once diet recommendations have been provided, ongoing dietary surveillance is imperative to understand the impact on the patient. If a patient, who has a

colon in continuity, is attempting to follow a low-fat diet as recommended but is not able to consume adequate energy on a low-fat diet, the diet recommendations should be liberalized to include more fat. On the other hand, if a patient with an end jejunostomy is eating a high-fat diet, supplementation with calcium, magnesium, zinc, and copper will likely be necessary.

Lactose restriction is commonly recommended by medical providers in SBS; however, at least a small amount is often well tolerated by most patients. Restricting lactose eliminates many calcium-rich foods from the diet and significantly reduces overall calcium intake. Decreased calcium intake will contribute to the development of osteoporosis that is commonly seen in the SBS population. In addition, as mentioned previously, for patients with a colon in continuity, adequate calcium intake is important to reduce the risk of calcium oxalate stones. It is recommended to only restrict lactose in individuals who are known to be intolerant. See Table 11.7 for a summary of nutritional management principles.

Table 11.7 Nutritional management principles in chronic gut failure

GI anatomy	Dietary management principle
All patients with intestinal failure	Chew foods thoroughly
	Small frequent meals
	Minimize simple sugars or concentrated sweets (desserts, sodas, candies, pastries, etc.)
	Avoid sugar alcohols (sugar-free foods, liquid medications, sugar-free chewing gums)
	Consume high amount of complex carbohydrates, 50% or more of calories (pasta, rice, potatoes, breads, etc.)
	Consume high biological value protein, 20–30% of calories (eggs, dairy, meat, poultry, fish)
	Do not limit lactose unless necessary
Colon in continuity (Absorb more fluid and sodium than nutrients)	Oral rehydration solutions may be needed in some patients
	Low to moderate fat intake, less than 30% of total calories
	Low oxalate diet (see Table 11.6)
	Soluble fiber intake, 5–10 grams (oatmeal, oat cereal, oat bran, lentils, legumes, apples, psyllium, guar gum, pectin)
End jejunostomy or ileostomy (absorb more nutrients than fluids)	Limit fluids with meals to ~ 4 ounces
	Drink more fluids between meals
	Oral rehydration solutions as fluids to drink
	Avoid hypertonic fluids (soda, juices, sweetened beverages)
	Limit hypotonic beverages (coffee, tea, water, diet sodas, alcohol)
	Increase salt intake with salty foods, salt shaker
	Moderate to high fat intake, 30–40% of total calories
	Usual fiber intake

Micronutrient Supplementation

Micronutrient status should be carefully monitored and supplemented as appropriate. Water-soluble vitamins are primarily absorbed in the proximal jejunum, so it is unusual to have deficiencies, except in patients with relatively high jejunostomies or high-output proximal enterocutaneous fistulae. Thiamine deficiency has been reported in gut failure patients on PN and should be replaced to prevent Wernicke's encephalopathy and beriberi [67, 68]. Erythrocyte transketolase appears to be the most accurate biomarker for thiamine deficiency, and activity should be determined, although this requires the sample to be sent to regional labs, so if sent out for assay, the patient should be supplemented until results are returned. Empiric therapy should be started with 100 mg of thiamine daily [21]. In patients with >60 cm terminal ileum resection, vitamin B12 should be replaced at 300 μg/month either subcutaneously [69, 70] or intranasally. The intranasal supplement option has been approved but remains relatively expensive. Fat-soluble vitamin (A, D, E, and K) deficiencies are common in patients with gut failure, or for those having undergone surgically related bowel

malabsorptive procedures. This includes bariatric procedures, like duodenal switch or Roux-en-Y gastric bypass, where fat-soluble vitamin deficiency has been reported in up to 60% of patients. Besides the malabsorptive effect of resection or bypass, the short bowel patient may develop steatorrhea, which subsequently results in decreased micelle formation and fat digestion as a result of maldigestion and not true malabsorption [71]. Trace metals, such as zinc and selenium, are lost in the feces and will generally need replacement.

Enteral Nutrition

Though parenteral nutrition may be the primary treatment in the acute phase of intestinal failure, attempts at enteral nutrition should always be made when oral intake is not possible in efforts to decrease dependence on IV nutrition support. Enteral nutrition (EN), via feeding tube that terminates in the stomach, should be started gradually and administered continuously at first to optimize nutrient intestinal mucosa contact. Several publications have suggested a formula with partially hydrolyzed proteins or peptides may be of benefit, although no randomized clinical trials have proven benefit over a more complex formula with intact proteins. Elemental or semi-elemental formulas with hydrolyzed proteins also include medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) as the fat source. MCTs have the advantage of dual absorptive mechanisms, via the lymphatic system and directly into the portal vein by enterocyte mechanisms. Although beneficial in many malabsorptive etiologies, no significant study has shown dramatic benefit of specific nutrients in SBS or other etiologies of gut failure. In addition, semi-elemental or elemental formulas that contain hydrolyzed proteins and MCTs tend to have higher osmolality and are much more expensive than standard enteral formulas. Formulas with intact protein and a combination of MCT and LCTs as fat source in patients without a colon and in addition a soluble fiber supplement in patients with a colon in continuity may be beneficial [72].

Glutamine, considered a conditionally essential amino, has been shown to be the primary fuel for the small bowel enterocyte. As such, it has been subject to numerous clinical trials in various animal and human models of bowel compromise. It appears to be most beneficial when combined with human recombinant growth hormone and high-soluble fiber diets. The results of these studies suggest a positive influence of glutamine and human recombinant growth hormone on weight gain and energy absorption. This effect appears to be self-limited to short-term benefit while receiving this combination and rapidly returns to pretreatment status upon stopping the glutamine and growth hormone [73, 74]. The growth hormone studies with or without glutamine have been abandoned since the clinical use of GLP-2 derivatives has shown significantly greater benefits.

Parenteral Nutrition

Generally, most patients with massive enterectomy will need to be supported, at least initially, with PN. For normally nourished and active patients, PN should be given at roughly 25–30 kcal/kg/day, based on ideal body weight [21]. Initially, serum glucose should be monitored at least four times daily, and should have a goal between 120 and 180 mg/dL, with insulin added at an initial dose 0.1 U/g of dextrose as needed. Intravenous lipids are generally used to supply 20–30% of infused calories. Protein should be delivered in the range of 1.5–2.0 g/kg/day, based on ideal body weight. Initially, PN is infused continuously. PN should be considered a temporary fix, while all attempts to utilize the remaining viable intestine are made. The need for PN may be lifelong, if adaptation has not compensated for the loss of mucosal mass within 1–3 years. Once a patient is stable, PN should be infused intermittently over 10–16 h, with a 30–60 min taper, as tolerated by cardiac, renal, and volume status [75, 76].

The transition from hospital to home total PN should involve extensive education of the patients and their families, prior to hospital discharge

[76]. Instructions should be given not only for catheter care, but working knowledge of intravenous pump and sterile principles for dressing changes should be provided. In addition, the issues of maintaining hydration, glycemic control, and consequences of not maintaining electrolyte and volume appropriately should be addressed.

If the patient ultimately achieves gut autonomy and graduates to enteral nutrition, either via volitional oral intake or tube feedings, it is critical to develop an effective plan for weaning. The two most common PN weaning practices include maintaining daily durations of PN while decreasing the caloric content and volume, or maintaining the energy content and volume but decreasing the number of days of PN per week as the patient increases enteral intake. During the weaning period, it is especially critical to regularly monitor nutrition labs and stay in close contact with the patient and their care team to evaluate for signs of nutritional compromise or fluid and volume issues [77].

Complications of Long-Term Parenteral Nutrition

Hepatic Complications

Long-term PN use can result in a broad spectrum of liver conditions generally referred to as intestinal failure-associated liver disease (IFALD). Conditions associated with IFALD include steatosis, steatohepatitis, fibrosis, cholestasis, and ultimately biliary cirrhosis [78–80]. A report from France suggests that <50% of adult patients on PN for >5 years will develop complications [81]. In a report from the USA, as many as 15% of patients on PN >1 year will develop end-stage liver disease [82]. Recent studies suggested that liver disease associated with long-term PN is not likely caused by insufficient production of nutrients required for normal hepatic function but rather direct toxic effects of PN [83–86]. Several mechanisms have been suggested as the etiology including toxicity from phytosterols and chronic pro-inflammatory state secondary to sole source of soy-based lipid emulsions. The incidence of IFALD has been significantly decreased with the use of fish oil-containing lipid emulsions. These mixed lipid emulsions containing soy, MCT, olive oil, and fish oil are now available in the USA since 2016 [87]. No doubt the routine use of the newer intravenous lipid emulsions including the soy-olive oil emulsions and the soy-olive-MCT-fish oil as well as the pure fish oil emulsions used for rescue therapy will yield long-term improvements in correcting and preventing PNALD [88].

Catheter-Related Complications

Safe and accurate delivery of HPN relies upon PN administered via meticulously maintained central venous catheters by motivated patients and/or well-trained caregivers. To limit complications, patients and caregivers should have ready access to a multidisciplinary team of professionals to troubleshoot any problems before life-threatening situations occur. Early diagnosis and treatment of complications, including catheter-associated blood stream infection (reported incidence 0.14–0.83 episodes/patient-year on HPN) and central venous thrombosis (reported incidence 0.03 episodes/patient-year), is important to minimize morbidity and mortality. There is a significant variation in the reported incidence of both hepatobiliary complications (19–75%) and advanced liver disease (0–50%). In a 1994 report, The Oley Foundation registry indicated that PN patients were hospitalized approximately once per year for catheter-related complications [4]. Messing et al. found that among patients with intestinal failure requiring chronic PN, mortality was over 50% during a 64-month median follow-up, with more than 30% of those deaths related to sepsis [15]. This is very similar to what is reported today with 5-year survival rates in large HPN programs; results are reported as being between 60% and 78%, with survival primarily related to underlying diagnosis and sepsis [75].

Moukarzel et al. found that in long-term pediatric PN patients, the mean functional life span of

a central venous catheter was 22.4 months, with 25% of catheters being removed, secondary to thrombus [89]. In 1154 years of patient follow-up, the estimated incidence of catheter thrombosis is approximately 0.2 episodes per 1000 catheter days [90]. When all usual central veins have been clotted or become nonviable for PN infusion, alternatives include translumbar or transhepatic access to the inferior vena cava. Occasionally when local expertise is available, major venous occlusion can be cleared with interventional radiology techniques and stents.

Other Long-Term Parenteral Nutrition Complications

Renal dysfunction [91], metabolic bone disease [92], memory deficits [93], and biliary complications [15] have been reported among patients who require long-term PN and are beyond the scope of this brief review.

Microbiome in Intestinal Failure

It has now been well validated that intestinal microbiota influences the physiology, nutritional status, immune function, and overall health status of the host [94, 95]. Patients with intestinal failure have an extremely "artificial" microbiologic environment. Invasive techniques (which eliminate or dramatically alter natural barriers) and the use of multiple medications (which affect GI motility, luminal pH, bile acids, blood flow, and mucosal oxygenation) radically influence gut microbiota variety and the metabolic products of the microbiota such as the volatile organic acids. These changes in the gut microbiota accompany the often major changes in intravascular volume and blood flow to the GI tract, which commonly occur in the gut failure population. Therapeutic measures commonly involved and used in hospitalized and ICU patients can cause dramatic changes in the mucosal redox potential and pH at the gut epithelial interface.

In addition to the iatrogenic issues causing changes in the microbiome, the physiologic stress response of the host induced by illness, surgery, or trauma has been shown to cause significant changes on the mucosal microenvironment, through alterations in bile salts, pH, redox potential, and mucosal energy supply [96]. Several investigators have reported in a variety of stress models, including gastrointestinal failure, a rapid depletion in intestinal luminal phosphate. This luminal phosphate depletion induces normally nonpathogenic bacteria, viable in the intestinal lumen, to undergo a phenotypic change and become extremely pathogenic in some species. These stress-induced mucosal changes result in downregulation of mucus production and upregulation of virulence factors in the endogenous bacteria, which facilitate attachment and invasion of the host epithelial barrier [97, 98].

Microbiota presiding in the host GI tract are felt to interact not only between species but also with the intestinal mucosa of the host. Many of these effects yield benefits. The ability to manipulate and potentially exploit these microbial changes noted in intestinal failure has become the focus of research only in recent years [99, 100].

In intestinal failure, the potential to capitalize on the beneficial effects of the bacterial symbiotic relationships has significant possibilities to alleviate many of abnormalities seen in failure. These mechanisms of benefit include enhancement of the physical epithelial barrier, by increasing production of mucins (which adhere to intestinal mucosa), production of bacterial antimicrobial peptides inhibiting overgrowth of pathogens, concomitant inhibition of pathogen adhesion, and competitive exclusion of the pathogenic microorganisms [101]. Certain microbiota have been shown to aid specifically in maintaining integrity of gap junctions [102], while others enhance host-cell antimicrobial peptide production, which reduces epithelial adherence of pathogens [103]. Manipulation of the host microbiota in the ICU setting has been shown to modulate metabolic and immune responses [99]. Novel investigative approaches of the microbiome in intestinal failure may help shift the paradigm for the future.

The diagnostic utility of the microbiome is limited by the generally unclear results of

microbiome analysis. However, certain patterns in colonic bacterial diversity have been linked to intestinal failure. *Lactobacilli*, which make up a very small subset of the bacterial population in healthy patients, proliferate in the colon of the intestinal failure patient, dominating the typically predominant anaerobic strains; this microenvironment has been aptly referred to as a "lactobiome." The cause of this proliferation is likely multifaceted. One proposed explanation is short bowel length contributing to greater partial pressure of oxygen in the colon, resulting in a hostile environment for anaerobes [104]. The best clinical outcomes may include manipulations of gut bacteria in intestinal failure, not from attempting to kill gut bacteria, as is commonly done today. The concept of bioecological control in intestinal failure is currently in its infancy and will rapidly develop. Fecal microbial transplant may be an option in some pathologic states of SBS once the safety and physiology is worked out.

Surgery in Intestinal Failure

Surgery is rarely indicated in management of intestinal failure. Once sepsis is controlled and abscesses are drained, the need for surgery is for occasional access for EN support. Percutaneous endoscopic gastrostomy (PEG) is occasionally helpful for both feeding and in serving as a venting gastrostomy for chronic obstruction or pseudo-obstruction. If remaining colon or distal small bowel is present and not in continuity, one should consider restoring bowel continuity. Even placing short segments of colon back into continuity can aid tremendously with fluid and electrolyte balance. Bowel lengthening procedures, commonly used in short bowel patients in pediatrics, such as serial transverse enteroplasty (STEP) and the Bianchi procedure, have limited, if any, use in adults [105]. A newer alternative to these bowel lengthening procedures is spiral intestinal lengthening and tailoring (SILT), first described in 2011 [106]. The SILT procedure is similar to the STEP procedure in that it does not disrupt the orientation of the muscle fibers but has the advantage of minimal handling of the mesentery. However long-term data does not yet exist, and data in the adult population is far too scarce to determine the efficacy of this treatment with respect to gut autonomy [107]. Small bowel transplant is obviously the ultimate surgical option for intestinal failure and is reported with variable success, depending on populations involved [108, 109]. The frequency of bowel transplant as treatment for intestinal failure has decreased over the last decade as a result of improved nutritional, pharmacologic, and PN treatment. Intestinal transplant bears significant risk of complication, including extremely high likelihood of postoperative infection, acute cellular rejection, chronic kidney disease, posttransplant lymphoproliferative disease, and graft-versus-host disease [110]. The general consensus is now that small bowel transplant is reserved for those patients who develop life-threatening complications of PN.

Conclusions

1. Patient therapy and goals should be individualized to meet postsurgical intestinal anatomy or the extent of viable functional bowel following an insult and mucosal loss.
2. The introduction of oral nutrition or tube feeding into the lumen of the bowel is essential to maximize adaptation of remaining functional bowel.
3. The importance of patient and family education working closely with a multidisciplinary team cannot be overemphasized. This education needs to include the management of fluid and electrolyte imbalance, oral rehydration principles, the use of antimotility agents, the medications to optimize outcome and minimize readmissions, and the consequences for failing to comply with instruction.
4. Parenteral nutrition is a key element for almost all patients with gut failure, especially in the early phases. The majority of patients will attain gut autonomy and be able to liberate themselves from the need of PN within 1–3 years.

5. It is common for patients with gut failure to need occasional supplemental intravenous fluid and electrolyte supplementation, even when they are able to maintain body weight and nutrition status with EN or volitional oral intake. The appropriate and timely use of pharmacologic agents such as antimotility, antisecretory, mucosal growth stimulants, and less commonly surgery must be highly individualized due to the variety of etiologies and variable presentation of intestinal failure.

References

1. Fleming CR, Remington M. Intestinal failure. Nutrition and the surgical patient. Edinburgh: Churchhill Livingstone; 1981. p. 219–35.
2. Llyod DAJ, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence upon home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther. 2006;24:1231–40.
3. The Oley Foundation. Annual report with outcome profiles 1985–1992. North American Home Parenteral and Enteral Nutrition Patient Registry. Albany; 1994.
4. Mundi MS, Pattinson A, McMahon MT, Davidson J, Hurt RT. Prevalence of home parenteral and enteral nutrition in the United States. Nutr Clin Pract. 2017;32:799–805.
5. Joly F, Baxter J, Staun M, Kelly DG, Hwa YL, Corcos O, De Francesco A, Agostini F, Klek S, Santarpia L, Contaldo F, Jonker C, Wanten G, Chicharro L, Burgos R, Van Gossum A, Cuerda C, Virgili N, Pironi L, ESPEN HAN CIF group. Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure. Clin Nutr. 2018;37(4):1415–22.
6. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, Lal S. Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre. Clin Nutr. 2017;36(2):570–6.
7. Kappus M, Diamond S, Hurt RT, Martindale R. Intestinal failure: new definitions and clinical implications. Curr Gastroenterol Rep. 2016;18(9):48.
8. Sondheimer JM, Cadnapaphornchai M, Sontag M, Zerbe GO. Predicting the duration of dependence on parenteral nutrition after neonatal intestinal resection. J Pediatr. 1998;132(1):80–4.
9. Pironi L, Arends J, Baxter J, Bozzetti F. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171–80.
10. Pironi L, Konrad D, Brandt C, Joly F, Wanten G, Agostini F, Chambrier C, Aimasso U, Zeraschi S, Kelly D, Szczepanek K, Jukes A, Di Caro S, Theilla M, Kunecki M, Daniels J, Serlie M, Poullenot F, Wu J, Cooper SC, Rasmussen HH, Compher C, Seguy D, Crivelli A, Pagano MC, Hughes SJ, Guglielmi FW, Kozjek NR, Schneider SM, Gillanders L, Ellegard L, Thibault R, Matras P, Zmarzly A, Matysiak K, Van Gossum A, Forbes A, Wyer N, Taus M, Virgili NM, O'Callaghan M, Chapman B, Osland E, Cuerda C, Sahin P, Jones L, Lee ADW, Bertasi V, Orlandoni P, Izbéki F, Spaggiari C, Díez MB, Doitchinova-Simeonova M, Garde C, Serralde-Zúñiga AE, Olveira G, Krznaric Z, Czako L, Kekstas G, Sanz-Paris A, Jáuregui EP, Murillo AZ, Schafer E, Arends J, Suárez-Llanos JP, Shaffer J, Lal S. Clinical classification of adult patients with chronic intestinal failure due to benign disease: an international multicenter cross-sectional survey. Clin Nutr. 2018;37(2):728–38.
11. Shaffer J. Intestinal failure: definition and service development. Clin Nutr. 2002;1(21 Suppl):144–5.
12. O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol. 2006;4:6–10.
13. Fanucci A, Cerro P, Fraracci L, Ietto F. Small bowel length measured by radiography. Gastrointest Radiol. 1984;9:349–51.
14. Nightingale JM, Bartram CI, Lennard-Jones JE. Length of residual small bowel after partial resection: correlation between radiographic and surgical measurements. Gastrointest Radiol. 1991;16:305–6.
15. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117:1043–50.
16. Pironi L. Definitions of intestinal failure and the short bowel syndrome. Best Pract Res Clin Gastroenterol. 2016;30(2):173–85.
17. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124:1111–34.
18. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343:373–6.
19. Thompson JS, Rochling FA, Weseman RA, Mercer DF. Current management of short bowel syndrome. Curr Probl Surg. 2012;49:52–115.
20. Efsen E, Jeppesen PB. Modern treatment of adult short bowel syndrome patients. Minerva Gastroenterol Dietol. 2011;57:405–17.
21. American Gastroenterological Association. American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124:1105–10.

22. Jeong SH, Lee HJ, Bae HJ, Kim Y, Yoo MW, Yoon YK, et al. Factors affecting postoperative dietary adaptation in short bowel syndrome. Hepato-Gastroenterology. 2009;56:1049–52. 14.
23. Longshore SW, Wakeman D, McMellen M, Warner BW. Bowel resection induced intestinal adaptation: progress from bench to bedside. Minerva Pediatr. 2009;61:239–51.
24. De Francesco A, Malfi G, Delsedime L, David E, Pera A, Serra R, et al. Histological findings regarding jejunal mucosa in short bowel syndrome. Transplant Proc. 1994;26:1455–6.
25. Vanderhoof JA, Kollman KA, Griffin S, Adrian TE. Growth hormone and glutamine do not stimulate intestinal adaptation following massive small bowel resection in the rat. J Pediatr Gastroenterol Nutr. 1997;25:327–31.
26. Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. Nutrition. Nov-Dec. 2006;22(11–12):1210–3.
27. Goulet O, Baglin-Gobet S, Talbotec C, Fourcade L, Colomb V, Sauvat F, et al. Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. Eur J Pediatr Surg. 2005;15:95–101.
28. Goulet OJ, Revillon Y, Jan D, De Potter S, Maurage C, Lortat-Jacob S, et al. Neonatal short bowel syndrome. J Pediatr. 1991;119:18–23.
29. Dibaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. Clin Gastroenterol Hepatol. 2006;4:11–20.
30. Kaufman SS, Loseke CA, Lupo JV, Young RJ, Murray ND, Pinch LW, et al. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. J Pediatr. 1997;131:356–61.
31. Tappenden KA. Emerging therapies for intestinal failure. Arch Surg. 2010;145:528–32.
32. Jeppesen PB, Mortensen PB. Significance of a preserved colon for parenteral energy requirements in patients receiving home parenteral nutrition. Scand J Gastroenterol. 1998;33:1175–9.
33. Bohan R, Tianyu X, Tiantian Z, Ruonan F, Hongtao H, Qiong W, Chao S. Gut microbiota: a potential manipulator for host adipose tissue and energy metabolism. J Nutr Biochem. 2019;64:206–17.
34. Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, Gordon JI. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci U S A. 2008;105(43):16767–72.
35. Nightingale JM, Kamm MA, van der Sijp JR, Morris GP, Walker ER, Mather SJ, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a 'colonic brake. Gut. 1993;34:1171–6.
36. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. Gut. 1996;39:267–72.
37. Joly F, Dray X, Corcos O, Barbot L, Kapel N, Messing B. Tube feeding improves intestinal absorption in short bowel syndrome patients. Gastroenterology. 2009;136:824–31.
38. Gong JF, Zhu WM, Yu WK, Li N, Li JS. Role of enteral nutrition in adult short bowel syndrome undergoing intestinal rehabilitation: the long-term outcome. Asia Pac J Clin Nutr. 2009; 18:155–63.
39. Gutierrez IM, Fisher JG, Ben-Ishay O, Jones BA, Kang KH, Hull MA, Shillingford N, Zurakowski D, Modi BP, Jaksic T. Citrulline levels following proximal versus distal small bowel resection. J Pediatr Surg. 2014;49(5):741–4.
40. Kelly DG, Tappenden KA, Winkler MF. Short bowel syndrome: highlights of patient management, quality of life, and survival. JPEN J Parenter Enteral Nutr. 2014;38(4):427–37.
41. Nightingale JM, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. Gut. 1992;33:1493–7.
42. Sham J, Martin G, Meddings JB, Sigalet DL. Epidermal growth factor improves nutritional outcome in a rat model of short bowel syndrome. J Pediatr Surg. 2002;37:765–9.
43. Stultz JS, Tillman EM, Helms RA. Plasma citrulline concentration as a biomarker for bowel loss and adaptation in hospitalized pediatric patients requiring parenteral nutrition. Nutr Clin Pract. 2011;26(6):681–7.
44. Cynober L, Moinard C, De Bandt JP. The 2009 ESPEN Sir David Cuthbertson. Citrulline: a new major signaling molecule or just another player in the pharmaconutrition game? Clin Nutr. 2010;29:545–51.
45. Kaore SN, Amane HS, Kaore NM. Citrulline: pharmacological perspectives and its role as an emerging biomarker in future. Fundam Clin Pharmacol. 2013;27:35–50.
46. Piton G, Manzon C, Cypriani B, Carbonnel F, Capellier G. Acute intestinal failure in critically ill patients: is plasma citrulline the right marker? Intensive Care Med. 2011;37:911–7.
47. Smith J, Godfrey E, Bowden D, Hickman K, Sharkey L, Butler A, Upponi S. Imaging of adult intestinal failure. Clin Radiol. 2019;74(8):603–12.
48. Oliveira C, de Silva N, Wales PW. Five-year outcomes after serial transverse enteroplasty in children with short bowel syndrome. J Pediatr Surg. 2012;47:931–7.
49. Vantini I, Benini L, Bonfante F, Talamini G, Sembenini C, Chiarioni G, et al. Survival rate and prognostic factors in patients with intestinal failure. Dig Liver Dis. 2004;36:46–55.

50. Fordtran JS, Rector FC Jr, Carter NW. The mechanisms of sodium absorption in the human small intestine. J Clin Invest. 1968;47:884–900.
51. Ladefoged K, Olgaard K. Fluid and electrolyte absorption and renin-angiotensin-aldosterone axis in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1979;14:729–35.
52. Selby PL, Peacock M, Bambach CP. Hypomagnesaemia after small bowel resection: treatment with 1 alpha-hydroxylated vitamin D metabolites. Br J Surg. 1984;71:334–7.
53. Bechtold ML, McClave SA, Palmer LB, Nguyen DL, Urben LM, Martindale RG, Hurt RT. The pharmacologic treatment of short bowel syndrome: new tricks and novel agents. Curr Gastroenterol Rep. 2014;16(7):392.
54. Anast CS, Winnacker JL, Forte LR, Burns TW. Impaired release of parathyroid hormone in magnesium deficiency. J Clin Endocrinol Metab. 1976;42(4):707–17.
55. Jacobsen O, Ladefoged K, Stage JG, Jarnum S. Effects of cimetidine on jejunostomy effluents in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1986;21:824–8.
56. O'Keefe SJ, Peterson ME, Fleming CR. Octreotide as an adjunct to home parenteral nutrition in the management of permanent end-jejunostomy syndrome. JPEN J Parenter Enteral Nutr. 1994;18:26–34.
57. Nightingale JM, Walker ER, Burnham WR, Farthing MJ, Lennard-Jones JE. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. Aliment Pharmacol Ther. 1989;3:367–73.
58. Pazzi P, Gamberini S, Buldrini P, Gullini S. Biliary sludge: the sluggish gallbladder. Dig Liver Dis. 2003;35(Suppl 3):S39–45.
59. Karim A, Ranney RE, Evensen KL, Clark ML. Pharmacokinetics and metabolism of diphenoxylate in man. Clin Pharmacol Ther. 1972;13(3):407–19.
60. Kristensen K, Qvist N. The acute effect of loperamide on ileostomy output: a randomized, double-blinded, placebo-controlled, crossover study. Basic Clin Pharmacol Toxicol. 2017;121(6):493–8.
61. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. Gastroenterology. 2001;120:806–15.
62. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut. 2005;54:1224–31.
63. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, Li B, Youssef NN, Jeppesen PB. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol. 2016;7:e142.
64. Fujioka K, Jeejeebhoy K, Pape UF, Li B, Youssef NN, Schneider SM. Patients with short bowel on narcotics during 2 randomized trials have abdominal complaints independent of teduglutide. JPEN J Parenter Enteral Nutr. 2017;41(8):1419–22.
65. U.S. Food and Drug Administration. Center for drug evaluation and research, application number: 203441Orig1s000. Summary Review. November 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203441Orig1s000SumR.pdf
66. Jeppesen PB, Fuglsang KA. Nutritional therapy in adult short bowel syndrome patients with chronic intestinal failure. Gastroenterol Clin North Am. 2018;47:61–75.
67. Alloju M, Ehrinpreis MN. Shortage of intravenous multivitamin solution in the United States. N Engl J Med. 1997;337:54.
68. Schiano TD, Klang MG, Quesada E, Scott F, Tao Y, Shike M. Thiamine status in patients receiving long-term home parenteral nutrition. Am J Gastroenterol. 1996;91:2555–9.
69. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study. Clin Ther. 2011;33:358–71.
70. Lin J, Kelsberg G, Safranek S. Clinical inquiry: is high-dose oral B12 a safe and effective alternative to a B12 injection? J Fam Pract. 2012;61:162–3.
71. Edes TE, Walk BE, Thornton WH Jr, Fritsche KL. Essential fatty acid sufficiency does not preclude fat-soluble-vitamin deficiency in short-bowel syndrome. Am J Clin Nutr. 1991;53:499–502.
72. Dibaise JK, Decker GA. Enteral access options and managemtn in the patient with intestinal failure. J Clin Gastroenterol. 2007;41(7):647–56.
73. Wales PW, Nasr A, de Silva N, Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. Cochrane Database Syst Rev. 2010;6:CD006321.
74. Guo M, Li Y, Wang Z, Wu B, Wang J, Li J. Morphological adaptation in adult short bowel syndrome undergoing intestinal rehabilitation. J Investig Surg. 2013;26:1–5.
75. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther. 2013;37:587–603.
76. Kumpf VJ, Tillman EM. Home parenteral nutrition: safe transition from hospital to home. Nutr Clin Pract. 2012;27:749–57.
77. Kirby DF, Corrigan ML, Hendrickson E, Emery DM. Overview of home parenteral nutrition: an update. Nutr Clin Pract. 2017;32(6):739–52.
78. Bowyer BA, Fleming CR, Ludwig J, Petz J, McGill DB. Does long-term home parenteral nutrition in

adult patients cause chronic liver disease? JPEN J Parenter Enteral Nutr. 1985;9:11–7.
79. Briones ER, Iber FL. Liver and biliary tract changes and injury associated with total parenteral nutrition: pathogenesis and prevention. J Am Coll Nutr. 1995;14:219–28.
80. Stanko RT, Nathan G, Mendelow H, Adibi SA. Development of hepatic cholestasis and fibrosis in patients with massive loss of intestine supported by prolonged parenteral nutrition. Gastroenterology. 1987;92:197–202.
81. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132:525–32.
82. Chan S, McCowen KC, Bistrian BR, Thibault A, Keane-Ellison M, Forse RA, et al. Incidence, prognosis, and etiology of end-stage liver disease in patients receiving home total parenteral nutrition. Surgery. 1999;126:28–34.
83. Buchman AL, Ament ME, Sohel M, Dubin M, Jenden DJ, Roch M, et al. Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a placebo-controlled trial. JPEN J Parenter Enteral Nutr. 2001;25:260–8.
84. Buchman AL, Dubin M, Jenden D, Moukarzel A, Roch MH, Rice K, et al. Lecithin increases plasma free choline and decreases hepatic steatosis in long-term total parenteral nutrition patients. Gastroenterology. 1992;102:1363–70.
85. Buchman AL, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, et al. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. Hepatology. 1995;22:1399–403.
86. Xu ZW, Li YS. Pathogenesis and treatment of parenteral nutrition-associated liver disease. Hepatobiliary Pancreat Dis Int. 2012;11:586–93.
87. Cowan E, Nandivada P, Puder M. Fish oil-based lipid emulsion in the treatment of parenteral nutrition-associated liver disease. Curr Opin Pediatr. 2013;25:193–200.
88. Mundi MS, Martindale RG, Hurt RT. Emergence of mixed-oil fat emulsions for use in parenteral nutrition. JPEN J Parenter Enteral Nutr. 2017;41(1_suppl):3S–13S.
89. Moukarzel AA, Haddad I, Ament ME, Buchman AL, Reyen L, Maggioni A, et al. 230 patient years of experience with home long-term parenteral nutrition in childhood: natural history and life of central venous catheters. J Pediatr Surg. 1994; 29:1323–7.
90. Mailloux RJ, DeLegge MH, Kirby DF. Pulmonary embolism as a complication of long-term total parenteral nutrition. JPEN J Parenter Enteral Nutr. 1993;17:578–82.
91. Buchman AL, Moukarzel A, Ament ME, Gornbein J, Goodson B, Carlson C, et al. Serious renal impairment is associated with long-term parenteral nutrition. JPEN J Parenter Enteral Nutr. 1993;17:438–44.
92. Buchman AL, Moukarzel A. Metabolic bone disease associated with total parenteral nutrition. Clin Nutr. 2000;19:217–31.
93. Buchman AL, Sohel M, Brown M, Jenden DJ, Ahn C, Roch M, et al. Verbal and visual memory improve after choline supplementation in long-term total parenteral nutrition: a pilot study. JPEN J Parenter Enteral Nutr. 2001;25:30–5.
94. Morowitz MJ, Babrowski T, Carlisle EM, Olivas A, Romanowski KS, Seal JB, et al. The human microbiome and surgical disease. Ann Surg. 2011;253:1094–101.
95. Bengmark S. Nutrition of the critically ill; a 21st-century perspective. Nutrients. 2013;5:162–207.
96. Alverdy JC. During critical illness the gut does not pass the acid test. Crit Care. 2012;16:150.
97. Zaborina O, Zaborin A, Romanowski K, Babrowski T, Alverdy J. Host stress and virulence expression in intestinal pathogens: development of therapeutic strategies using mice and C elegans. Curr Pharm Des. 2011;17:1254–60.
98. Long J, Zaborina O, Holbrook C, Zaborin A, Alverdy J. Depletion of intestinal phosphate after operative injury activates the virulence of P aeruginosa causing lethal gut-derived sepsis. Surgery. 2008;144:189–97.
99. Morrow LE, Gogineni V, Malesker MA. Probiotics in the intensive care unit. Nutr Clin Pract. 2012;27:235–41.
100. Katayama M, Xu D, Specian RD, Deitch EA. Role of bacterial adherence and the mucus barrier on bacterial translocation: effects of protein malnutrition and endotoxin in rats. Ann Surg. 1997;225:317–26.
101. Turroni F, Ventura M, Butto LF, Duranti S, O'Toole PW, Motherway MO, et al. Molecular dialogue between the human gut microbiota and the host: a Lactobacillus and Bifidobacterium perspective. Cell Mol Life Sci. 2014;71(2):183–203.
102. 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.
103. Sherman PM, Johnson-Henry KC, Yeung HP, Ngo PS, Goulet J, Tompkins TA. Probiotics reduce enterohemorrhagic Escherichia coli O157:H7- and enteropathogenic E. coli O127:H6-induced changes in polarized T84 epithelial cell monolayers by reducing bacterial adhesion and cytoskeletal rearrangements. Infect Immun. 2005;73:5183–8.
104. Billiauws L, Corcos O, Joly F, et al. What's new in short bowel syndrome? Curr Opin Clin Nutr Metab Care. 2018;21:313–8.
105. Thompson J, Sudan D. Intestinal lengthening for short bowel syndrome. Adv Surg. 2008;42:49–61.
106. Cserni T, Takayasu H, Muzsnay Z, Varga G, Murphy F, Folaranmi SE, Rakoczy G. New idea of intestinal lengthening and tailoring. Pediatr Surg Int. 2011;27(9):1009–13.

107. Hommel MJ, van Baren R, Haveman JW. Surgical management and autologous intestinal reconstruction in short bowel syndrome. Best Pract Res Clin Gastroenterol. 2016;30(2):263–80.
108. Lauro A, Zanfi C, Pellegrini S, Catena F, Cescon M, Cautero N, et al. Isolated intestinal transplant for chronic intestinal pseudo-obstruction in adults: long-term outcome. Transplant Proc. 2013; 45:3351–5.
109. Yildiz BD. Where are we at with short bowel syndrome and small bowel transplant. World J Transplant. 2012;2:95–103.
110. Kesseli S, Sudan D. Small bowel transplant. Surg Clin Nutr Am. 2019;99:103–16.

Part III

Metabolic Support and Nutrition Repletion

Enteral Nutrition

12

Bryan Collier, Daniel I. Lollar, and Eric H. Bradburn

Basic Science of Enteral Feeding

Feeding the gut with enteral nutrition (EN) is beneficial and is the recommended approach for almost all disease states that surgeons encounter. The benefits of enteral feeding are both nutritional and immunologic. While parenteral nutrition may provide macro- and micronutrients, direct stimulation of the GI tract with enteral nutrition creates additional immunologic benefits beyond the provision of protein and calories.

Recent insights into the pathophysiology of the role of the intestine during the body's response to stress have highlighted three key mechanisms [1]. These include the loss of intestinal epithelial integrity, alterations in the microbiome [2], and reductions in the function of intestinal immune function. Under normal conditions, the intestinal crypts produce multipotent stem cells which differentiate during the migration toward the tip of the villus. Once at the tip, they are sacrificed via apoptosis or sloughing into the lumen. The entire process from creation to sacrifice takes less than a week. Gut mucosal defense mechanisms include luminal factors such as gastric acids and secretory IgA and IgM, antimicrobial factors which prevent colonization of pathogens, physical barriers such as mucous layers and tight junctions, and mechanical factors such as desquamation and peristalsis [3]. During physiological stress or gut disuse, the system begins to become compromised. This time- and severity-dependent process leads to an environment for systemic inflammation, infection, and ultimately multi-organ failure [3, 4]. In addition, the systemic inflammatory response and its associated hormone milieu increases total body protein breakdown [5]. This catabolism also drives ongoing acute and chronic inflammation which continues for a minimum of 4–6 weeks after the initial physiologic insult [6].

Nutritional Assessment

Management of all surgical patients should include a nutritional plan, ideally in the preoperative period regardless of the urgency of the procedure. The first step in any nutritional plan should be a nutritional assessment. While there are multiple assessment scores described [7], guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend using the

B. Collier
CNSC Surgical Nutrition, Trauma Center, Virginia Tech Carilion School of Medicine, Carilion Roanoke Memorial Hospital, Roanoke, VA, USA

D. I. Lollar (✉)
Virginia Tech Carilion School of Medicine, Carilion Roanoke Memorial Hospital, Roanoke, VA, USA
e-mail: dilollar@carilionclinic.org

E. H. Bradburn
Penn Medicine Lancaster General Health, Lancaster, PA, USA

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_12

NRS-2002 score for assessment of elective surgical patients [8]. This scoring system evaluates body mass index (BMI), nutritional intake, weight loss, and severity of illness to quantitate nutritional risk as mild, moderate, or severe. ASPEN guidelines [9] recommend the NRS-2002 or NUTRIC score to assess critically ill patients. Each of these take into account not only patient comorbidities but also the degree of inflammation or critical illness.

Patients at high nutritional risk should be considered for more "intense" nutritional intervention. This includes the use of early (at times intraoperative) nasoenteric or even surgically placed feeding access. Early nutritional support has found to be effective reducing complications, decreasing hospital length of stays, and being cost-efficient [10]. Additionally, limiting the fasting period prior to anesthesia induction (preoperatively or between operative procedures) leads to better outcomes by decreasing the glycemic response to stress. Clinically, patients require fewer units of insulin to achieve glycemic control and have lower instances of postoperative nausea and vomiting [11] and decreased rates of ileus. This effect is particularly pronounced in the diabetic and geriatric patient populations. Current recommendations are for those without an increased risk of aspiration to receive clear liquids (containing glucose) up to 2 hours before induction of anesthesia in the preoperative period [12].

Furthermore, there is evidence that minimal stoppage of enteral feeds in the preoperative period or even feeding during an operation is safe for nutritionally high-risk patients. No increase in adverse outcomes were noted, and increased nutritional content was provided [13, 14]. Though beyond the scope of this chapter, the nutritional components of enhanced recovery programs utilized in almost all departments of surgery can be applied to patients receiving enteral nutrition.

Feeding Access

Ideally, all patients would be able to take in all necessary nutrients by eating a standard diet composed of adequate macro- and micronutrients from whole foods. However, this is frequently not possible for a variety of reasons. Anticipating who will be able to consume sufficient nutrients postoperatively can be challenging though certain high-risk patients can be identified preoperatively regardless of the urgency of the intervention required. Part of the preoperative nutrition evaluation should be addressing the means by which nutrition will be provided and anticipating the time for which supplemental nutrition will be needed.

Aspects to consider include the patient's preoperative nutritional status, pre-existing comorbidities such as facial fractures or other alterations in normal facial anatomy, oropharyngeal dysphagia or esophageal motility disorders, gastroparesis, paraesophageal hernias (especially types III and IV), or other pathologies that might limit the ability to place bedside feeding access. As we have seen with prior assessment scores, the underlying pathology with which they present will also affect which options may be available for perioperative nutritional supplementation.

Patients who are identified as being malnourished preoperatively should be given strong consideration for at least 7–10 days of prehospital nutritional repletion prior to elective procedures [9]. This may take the form of nutritional supplementation, tube feeding via nasoenteric access, or even parenteral nutrition. Patients at high nutritional risk who must undergo urgent or emergent operations should be strongly considered for surgical feeding access to minimize the potential time period of nutritional deficiency postoperatively. Recognizing this cohort at the time of presentation can facilitate the discussion of feeding access prior to operation and set expectations for the postoperative period.

Nasoenteric feeding tubes can be utilized for most patients who may otherwise not be able to take nutritional orally, namely, those with anorexia or dysphagia. However, consideration for those who may have relative or absolute contraindications to nasoenteric access should be considered prior to operation. Frequently those with significant maxillofacial fractures, esophageal varices, severe PEH, obstruction or ileus,

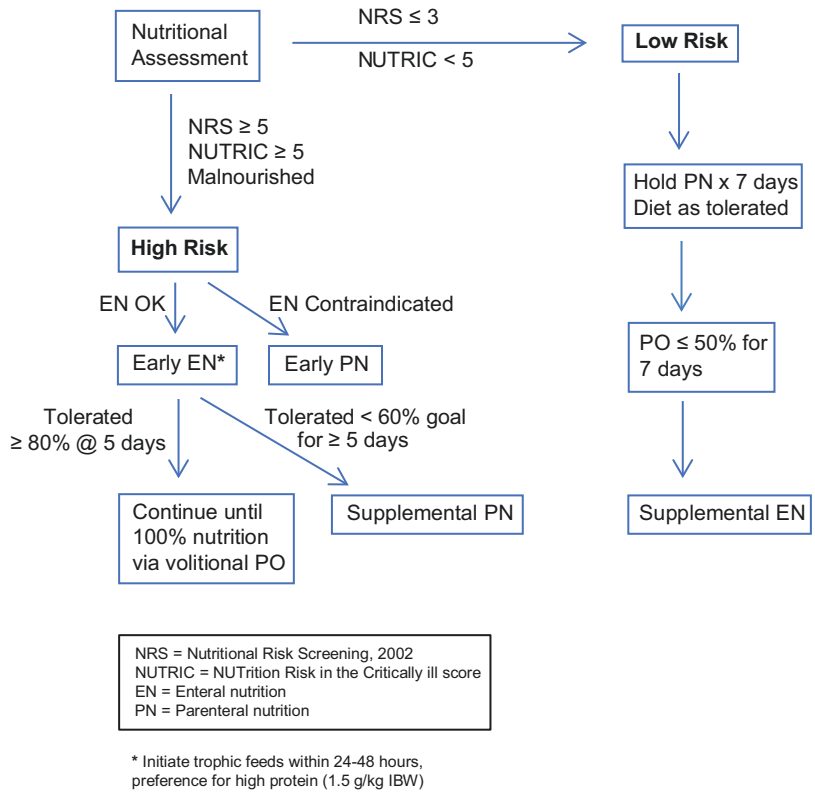

Fig. 12.1 Initiating enteral nutrition

severe shock, intestinal ischemia, high-output enterocutaneous fistula (ECF), or severe intestinal hemorrhage are contraindicated from enteral feeding and should be considered for early nutritional therapy such as PN while the feasibility of enteral nutrition is being evaluated and reevaluated on a daily basis.

The debate between nasogastric and nasojejunal placement of a feeding tube should not delay initiation of enteral feeding. While nasojejunal placement may decrease the risk of gastric intolerance and pneumonia rates in critically ill patients, nasogastric tube placement is frequently easier and more efficient. Nasogastric tubes can easily be placed intraoperatively or at the bedside. However, with nearly 1000 patients, 12 studies, over 20 years, and a moderate to high recommendation from the ASPEN guidelines, small bowel feedings were favored with a lower rate of pneumonia. Interestingly, initial feeds can and should be started in the stomach. However some of the evidence suggests we should pursue distal feeds. How hard and how long we should spend to accomplish this is not clear. Therefore, the concept of aspiration or aspiration risk should be considered when deciding the need for distal access and enteral nutrition (Fig. 12.1).

Prior to initiation of tube feeding, confirmation of blindly placed feeding access is required. Appropriate positioning of enteral access can be confirmed using portable X-ray, fluoroscopy, or proprietary electromagnetically guided placement device (EMPD) technology. Any of these devises can be used to reduce potential feeding access placement into the airway or confirm which portion of the gastrointestinal tract the access resides.

Recently, the use of EMPD has been safely trialed for the placement of post pyloric feeding tubes. Powers et al. demonstrated a 97.2% success rate using EMPD with a nurse-driven protocol [15]. Only 8% of the 904 feeding tubes placed in this study required X-ray confirmation. In another study by the same authors, the rate of agreement between EMPD and X-ray confirmation achieved a 99.5% agreement rate [16]. The

advantages of a protocol using EMPD include immediate recognition of misplaced feeding tube, reduction in radiation exposure, possible earlier initiation of tube feeds, and reduced cost [17]. Though the placement of blind, endoscopic, fluoroscopic, and now EM-guided placements have all been described, local practice patterns will frequently determine which method is most efficient. Ultimately, all techniques should be in the surgeon's armamentarium to facilitate adequate, safe enteral access.

Nutritional Intervention

Early feeding provides numerous benefits to the surgical patient. This benefit is reflected in the ASPEN guidelines from 2016 which recommend initiation of enteral feeding in most critically ill patient populations within 48 hours of admission. "Can this patient eat?" should be the first question regarding nutritional repletion. To judge the appropriateness of initiating enteral nutrition (PO or tube feed) the "CAN WE FEED" mnemonic can be helpful to bring to mind the relevant questions regarding feeding a surgical patient [18] (Table 12.1).

Is there a benefit to feeding early versus allowing a short period of limited nutrition postoperatively? Recently the concept of autophagy has suggested that there may be a beneficial effect of limiting nutrition to upregulate the body's ability to process large damaged proteins (such as mitochondrial structures) that may accumulate from critical illness. While there are no clinical markers of autophagy currently available, the mechanisms underlying this process are well described.

Table 12.1 Mnemonic "CAN WE FEED?" to facilitate safe initiation of enteral nutrition

*C*ritical illness severity
*A*ge
*N*utrition risk screening
*W*ait for resuscitation
*E*nergy requirements
*F*ormula
*E*nteral access
*E*fficacy
*D*etermine tolerance

However, the concern for downregulating the processes of autophagy is balanced by the benefits to the immunity of the patient. Robust clinical trials have confirmed that outcomes are improved with early feeding. A recent meta-analysis of feeding within 24 hours of critical illness confirmed that when comparing early enteral feeding to delayed enteral feeding, early enteral feeding leads to decrease mortality and pneumonia rates [19]. Lower infection rates, for example, pneumonia, clinically support the theory of gut stimulation and suppression of the systemic inflammatory response. ESPEN and ASPEN guidelines also reinforce early feeding but define "early" as within 48 hours of admission.

The effects of early enteral feeding are not limited to critically ill patients. Multiple studies have demonstrated the benefit of feeding postoperative patients early without an increased risk of feeding-related complications. The effect was most recently confirmed in a systematic review of 879 patients from nine studies that showed a decrease in colorectal anastomotic leaks on univariate analysis [20]. While this effect did not persist on multivariate evaluation, there is likely no increased risk to anastomotic integrity with early feeding.

The goal of most nutritional plans is to achieve near-target caloric goals. Obstacles to achieving the full intake required for nutritional repletion include access, feeding intolerance, gastric dysmotility, ileus, diarrhea, and feeding interruptions for procedures. It is unclear what the relationship between these complications and the amount of enteral feeding provided may be. Data supports the hypothesis that provision of full macronutrient requirements is no better than hypocaloric or trophic feeds (approximately 60–70% of goal) in critically ill patients. The EDEN trial [21] found that trophic feeding did not increase mortality, infections, or ventilator days. The full nutrition group had more episodes of emesis, high gastric residual volumes (GRV), and constipation. While full caloric provision may not improve outcomes, repletion of protein may be more important than calories. Nicolo [22]

demonstrated that after adjusting for confounders, protein intake >80% goal was associated with improved 60-day mortality. Energy or calorie intake >80% of goal after adjustment did "not" demonstrate that same benefit. The emerging theory is that high-protein, hypocaloric nutrition may be the best approach for critically ill patients; however this theory has not been tested in an adequately powered prospective trial [23].

The role for immune-enhancing formulas has become potentially narrower after recent publications failed to show benefit, and suggested potential harm, in critically ill patients fed with a glutamine and/or omega-3 fatty acid supplement [24]. However, a role for immune modulating formulas does exist for malnourished patients undergoing major cancer surgery. This recommendation is based on a number of meta-analyses that demonstrate decreased infectious complications and shortened length of stay utilizing these formulas in patients undergoing major surgery on the GI tract with or without a cancer diagnosis [25–27]. Additionally, parenteral glutamine supplementation received a Grade B recommendation from ESPEN for patients who cannot be fed enterally and require PN. Part of this recommendation was based on work by Zeigler et al. [28], which demonstrated safety with glutamine. On the other hand, the REDOX study examined glutamine and antioxidants in patients with severe sepsis [29]. Because of the negative results, much less enthusiasm for these individual components of immune-enhancing formulas has been expressed. This has resulted in even less use of immune-enhancing formulas in all patient populations despite the REDOX negative results being applicable to sepsis patients with already established organ failure. Other patient populations who may benefit have yet to be completely elucidated.

Complications of Enteral Nutrition

The benefits of enteral nutrition are many but must be weighed against the possibility of complications. Most complications of enteral nutrition are relatively minor but dramatic responses such as aspiration or mesenteric ischemia can create provider reticence. As with any therapy, nutritional support must be managed actively to avoid potential morbidity. However, this process should not dissuade providers from providing a therapy that can dramatically improve outcomes.

Aspiration

Aspiration is a feared complication of enteral feeding as it can lead to sudden and impressive patient morbidity and mortality, specifically aspiration pneumonitis precipitating rapid cardiovascular collapse. Pneumonia from silent aspiration is another important cause of prolonged hospital stay and poor discharge disposition. Risk factors include advanced age, neurologic pathology, prolonged intubation, and gastroesophageal reflux. Patients at risk for aspiration should be assessed at the bedside by a nurse or speech language pathologist. Those patients with dysphagia that preclude oral intake should have feeding access established for nutritional therapy. Ironically, any tube, including the smallest caliber tubes that pass from the esophagus to the stomach, can increase reflux by creating an incompetent lower esophageal sphincter. Furthermore, it is difficult to predict which patients may aspirate and which will not. The practice of using gastric residual volumes as a predictor of who is at risk for complications from aspiration or regurgitation, while common, is not supported with literature [30]. This does not mean that one should be apathetic with respect to managing patients at high risk for aspiration. Simple maneuvers can have profound effects, especially in combination. Protocols or bundles that include elevating the head of bed to at least 30 degrees at all times and providing oral hygiene are useful and should be applied broadly. Additional interventions can be utilized based on the patient's condition. Speech therapists should be utilized for patients taking an oral diet, while subglottic suctioning will be useful for an intubated patient. A full rendering of these approaches is beyond the scope of this chapter.

Bowel Dysmotility

Tube feed intolerance can be related to dysfunction of the stomach (gastroparesis), small bowel

(ileus), or even the colon (pseudo-obstruction). After operative intervention, altered gastric emptying and discoordinated bowel motility can increase the risk of enteral feeding. An element of these syndromes is universal; however the degree can vary greatly based on the patient, the hormonal milieu created postoperatively, anesthetic agents, and pre-existing conditions. Waiting for return of bowel function before initiating any enteral nutrition is, as previously discussed, to be avoided unless that patient is actively nauseated or vomiting or has a nasogastric tube for decompression with high outputs. Patients who are clinically obstructed prior to operative intervention may also benefit from a delay in initiation of nutrition.

However, in the absence of a strong indication to withhold nutrition, the gut may take feedings before clinical return of bowel function. In fact, early initiation of enteral nutrition may improve return of bowel function and decrease anastomotic leak rate [31–33].

Pharmacologic support has been shown to have a modest improvement in treating feeding intolerance in patients with functional slowing of the GI tract [34]. The two agents used most frequently are metoclopramide and erythromycin. Data suggests that the two agents work best when used in combination. In fact their mechanisms of action are complementary. Metoclopramide is a dopamine antagonist and decreases elevated dopamine levels associated with depressed gastric emptying [35]. Erythromycin acts on motilin receptors in the small bowel to improve motility [36]. While these agents can have side effects, in particular QTc prolongation, a trial for patients with feeding intolerance can improve nutritional administration.

Diarrhea

Diarrhea is common in the hospitalized patient and can have many causes. Typical definitions of diarrhea in noncritically ill patients are more than three bowel movements a day or a measured volume greater than 250 cc. Definitions in ICU patients are more variable resulting in an incidence that ranges between 2% and 63% [37]. Initial steps in management include ruling out an infectious etiology (e.g., *Clostridium difficile*) and looking for reversible causes. Common iatrogenic causes of diarrhea include antibiotics; medications which may contain sorbitol, magnesium or lactose; and H2 blockers [38]. If a reversible cause is not immediately apparent, diarrhea often can be related to incomplete absorption by the recovering bowel. This inability to fully absorb nutrition may be due to a number of causes. Tube feeds are often hyperosmolar, and the GI tract may be incapable of handling the osmotic load. Endothelium damaged by sepsis or starvation may have damaged the cellular transporters involved in appropriate nutrient absorption at the brush border. While severe diarrhea must be considered a sign of enteral nutrition intolerance, ongoing stimulation of the bowel should continue. Fluid and electrolyte corrections should occur; adjustment of enteral nutrition rates and a daily evaluation of "tolerance" should ensue to optimize the calorie and protein provision in these critically ill patients. Additionally, consideration should be made for adding fiber supplementation in hemodynamically stable patients with persistent diarrhea. While routine use of fiber in the ICU is a matter of debate, switching to a mixed fiber (soluble and insoluble) or adding a fermentable soluble fiber supplement (such as inulin or fructooligosaccharides) in noncritically ill patients without another cause of diarrhea may be beneficial.

Nonocclusive Mesenteric Ischemia

One of the most dreaded yet rare (0.14–3.5%) complications of enteral feeding is nonocclusive mesenteric ischemia (NOMI) leading to small bowel or more specifically jejunal necrosis [39, 40]. Enteral nutrition of any kind places an additional metabolic load on the bowel. In most cases, the increased cellular metabolism is inconsequential, and the benefits of nutrition outweigh any risk. However patients with shock may not be able to tolerate any additional metabolic burden. To help avoid the risk of NOMI in patients with shock of any etiology, tube feeding should be held until the patient is properly resuscitated. Though beyond the scope of this chapter, defined endpoints of resuscitation for specific patient

populations should be selected. When these points of resuscitation are reached, early enteral nutrition should be started. Both the events should be able to occur within 24–48 hours for the vast majority of patients.

Patients with distributive (particularly septic) and cardiogenic shock may require vasopressor support for prolonged periods. Determining the appropriate time to initiate enteral nutrition is ultimately at the judgment of the provider, but the astute clinician should consider the physiology of the shock state in relation to the additional metabolic load placed on the bowel [41]. In septic shock, some data suggests a trophic amount of nutrition will stimulate vasoconstriction counteracting the pathologic mesenteric vasoplegia of the disease state. However, patients in cardiogenic shock may have a fixed cardiac output and may not be able to compensate for any additional metabolic load placed upon the tenuous blood flow to the bowel [42]. When the decision to initiate enteral nutrition in a patient with shock is made, we recommend monitoring for bowel ischemia with clinical examination and adjuncts such as serial lactate measurements or more advanced techniques such as gastric tonometry.

Failure of Enteral Nutrition

When do we consider a patient to have failed EN and start PN? This is an unfortunately common situation where a surgical patient who is at high nutritional risk does not seem to be taking adequate volitional intake despite return of bowel function and an intact swallow mechanism. Attempts to determine precise amounts of caloric intake are fraught with challenges, and the patient is reticent to increase the intensity of nutritional supplementation to a more invasive means. Many patients can be identified as high risk preoperatively. European guidelines recommend initiating early EN with 24 hours of surgical intervention for patients anticipated to take less than 50% PO for 7 days. High-risk patients are those undergoing major head and neck or GI cancer surgery, those with severe trauma especially with a traumatic brain injury, and those with preoperative malnutrition. If the duration of decreased oral intake is expected to last at least 4 weeks (severe TBI), surgical gastrostomy tube placement is recommended. If the patient is unable to tolerate 60% or greater energy and protein requirements within 7–10 days, consideration for initiation of supplemental PN should be discussed. Typically patients that will benefit from PN should anticipate receiving it for at least a week. For patients with contraindications to volitional oral intake postoperatively, nutritional risk will determine the aggressiveness of post-op PN. In those with normal nutrition entering the operation (Nutritional Risk Screening [NRS] 2002 score of $\leq$3 or Nutrition Risk in Critically Ill [NUTRIC] score $\leq$5), PN should be withheld until the seventh postoperative day. Studies [43] have demonstrated a decrease in infectious morbidity with delayed PN initiation. However patients with a high nutritional risk (NRS 2002 score $\geq$5, NUTRIC score $\geq$5, or severely malnourished) should have PN started as soon as possible in the postoperative period. Patients receiving supplemental nutrition via tube or vein should have their nutritional goal reassessed regularly, and supplementation should continue until the patient's protein and calorie goals are met via volitional PO intake. An algorithmic approach may be helpful as a general tool to assist with decision-making in challenging patient populations (Fig. 12.1).

Pancreatitis

Patients with acute pancreatitis should be identified by the severity of disease. The majority of patients (80%) will have mild pancreatitis, defined as pancreatitis without systemic signs of inflammation. These patients typically have a self-limited course and require no specific nutritional intervention or consideration. An oral diet is preferred. Patients with more severe disease such as SIRS, organ failure, or pancreatic necrosis on imaging are considered moderate (organ failure resolves <48 hours) or severe (organ failure persists beyond 48 hours.) While less common, these patients require special nutritional

consideration. There are multiple scoring systems that have been studied to predict those with worse outcomes from pancreatitis. While a full discussion is outside the scope of this chapter, it behooves the provider to utilize these tools to help determine those with more severe disease. Frequent reassessment of disease severity is advised as patients with initially mild symptoms may progress to develop more severe disease. Also, it should be noted that patients with pancreatitis and alcohol use disorder have a high prevalence of being malnourished at baseline and providers should have a lower threshold for an aggressive approach to nutrient repletion in this patient population.

For patients with moderate to severe pancreatitis, the standard paradigm for nutritional therapy has traditionally been nil per os status and parenteral nutrition. The guiding principle for this approach was the belief that stimulation of pancreatic enzymes by enteral nutrients will exacerbate the cascade of enzyme activation leading to worsening pancreatic injury. Further clarification has revealed that certain constituents are responsible for inducing additional injury. These elements include meat protein, long-chain fatty acids, calcium, and magnesium, and exposure of these substances into the duodenum should be avoided.

When enteral feeding is compared to the typical approach of NPO plus PN, the data are more clear. The recent ASPEN guidelines recommend EN over PN for patients with moderate to severe acute pancreatitis. While the quality of evidence is low, the recommendation is supported with three meta-analyses of ten randomized trials. Benefits of EN over PN include decreased mortality, decreased infectious complications and multi-organ failure, reduced need for surgical intervention, and therefore not surprisingly, decreased hospital LOS.

Does this mean that all patients with pancreatitis requiring nutritional support should be feed into the jejunum? In a small prospective trial, 35 patients with mild to moderate pancreatitis were randomized to receive nasogastric feeding versus NPO status. Utilizing the Gastroparesis Cardinal Symptom Index questionnaire, patients were found to have similar scores; however the patients fed via NGT experienced earlier return of appetite [44]. Similarly, in a study that directly compared nasojejunal to nasogastric tube feeding placement in patients with severe pancreatitis, 90% of patients were found to reach their target nutrient delivery regardless of the placement of the feeding tube. These support the concept that feeding pancreatitis patients enterally is safe and the specific route is less important [45]. In fact, patients with pancreatitis are conceptually similar to other patient populations: nutrition for pancreatitis patients should be started within 48 hours of hospital admission, and initial feeding intolerance does not mandate discontinuation of EN for PN. Patients who fail nasogastric feeding should have attempts made to establish jejunal access and should be considered for a low-fat, peptide-based formula with medium-chain triglycerides versus a standard formula. Criteria for starting PN on patients with pancreatitis are similar to other patient populations: failure to tolerate >50% of nutrient goals for a week should prompt initiation of PN supplementation.

Conclusion

Patients undergoing surgical interventions should have their nutrition status regularly assessed using a standardized tool. Perioperative fasting in the elective setting should be limited, and ideally patients would follow a standardized enhanced recovery pathway. Postoperatively, nutrition should be emphasized, and those deemed high nutritional risk should have appropriate feeding access established early. While achieving full caloric intake in the early postoperative period is not necessary and may be harmful, patients should have PO or enteral feeds started at a set rate, and frequent monitoring for complications should be maintained. Patients found not to meet appropriate protein and calorie goals should have an escalation in nutritional intervention.

References

1. Meng M, Klingensmith NJ, Coopersmith CM. New insights into the gut as the driver of critical illness and organ failure. Curr Opin Crit Care. 2017; 23(2):143–8.
2. Alverdy JC, Chang EB. The re-emerging role of the intestinal microflora in critical illness and inflammation: why the gut hypothesis of sepsis syndrome will not go away. J Leukoc Biol. 2008;83(3):461–6.
3. 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.
4. Dobbins WO 3rd. Gut immunophysiology: a gastroenterologist's view with emphasis on pathophysiology. Am J Phys. 1982;242(1):G1–8.
5. Ljungqvist O, Khan A, Ware J. Evidence of increased gluconeogenesis during hemorrhage in fed and 24-hour food-deprived rats. J Trauma. 1989;29(1):87–90.
6. Wischmeyer PE. Are we creating survivors...or victims in critical care? Delivering targeted nutrition to improve outcomes. Curr Opin Crit Care. 2016;22(4):279–84.
7. Mueller C, Compher C, Ellen DM, American Society for P, Enteral Nutrition Board of D. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. JPEN J Parenter Enteral Nutr. 2011;35(1):16–24.
8. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36(3):623–50.
9. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, 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.). Crit Care Med. 2016;44(2):390–438.
10. Zhang H, Wang Y, Jiang ZM, Kondrup J, Fang H, Andrews M, et al. Impact of nutrition support on clinical outcome and cost-effectiveness analysis in patients at nutritional risk: a prospective cohort study with propensity score matching. Nutrition. 2017;37:53–9.
11. McCracken GC, Montgomery J. Postoperative nausea and vomiting after unrestricted clear fluids before day surgery: a retrospective analysis. Eur J Anaesthesiol. 2018;35(5):337–42.
12. Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Soreide E, et al. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2011;28(8):556–69.
13. Parent BA, Mandell SP, Maier RV, Minei J, Sperry J, Moore EE, et al. Safety of minimizing preoperative starvation in critically ill and intubated trauma patients. J Trauma Acute Care Surg. 2016;80(6):957–63.
14. Pousman RM, Pepper C, Pandharipande P, Ayers GD, Mills B, Diaz J, et al. Feasibility of implementing a reduced fasting protocol for critically ill trauma patients undergoing operative and nonoperative procedures. JPEN J Parenter Enteral Nutr. 2009;33(2):176–80.
15. Powers J, Fischer MH, Ziemba-Davis M, Brown J, Phillips DM. Elimination of radiographic confirmation for small-bowel feeding tubes in critical care. Am J Crit Care. 2013;22(6):521–7.
16. 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.
17. Bear DE, Champion A, Lei K, Camporota L, Barrett NA. Electromagnetically guided bedside placement of post-pyloric feeding tubes in critical care. Br J Nurs. 2017;26(18):1008–15.
18. Miller KR, Wischmeyer PE, Taylor B, McClave SA. An evidence-based approach to perioperative nutrition support in the elective surgery patient. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl): 39S–50S.
19. Tian F, Heighes PT, Allingstrup MJ, Doig GS. Early enteral nutrition provided within 24 hours of ICU admission: a meta-analysis of randomized controlled trials. Crit Care Med. 2018;46(7):1049–56.
20. Smeets BJJ, Peters EG, Horsten ECJ, Weijs TJ, Rutten HJT, Buurman WA, et al. Effect of early vs late start of oral intake on anastomotic leakage following elective lower intestinal surgery: a systematic review. Nutr Clin Pract. 2018;33(6):803–12.
21. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Rice TW, Wheeler AP, Thompson BT, Steingrub J, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795–803.
22. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study. JPEN J Parenter Enteral Nutr. 2016;40(1):45–51.
23. Hoffer LJ. High-protein hypocaloric nutrition for non-obese critically ill patients. Nutr Clin Pract. 2018;33(3):325–32.
24. van Zanten AR, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA. 2014;312(5):514–24.
25. Marimuthu K, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients

undergoing major open gastrointestinal surgery. Ann Surg. 2012;255(6):1060–8.
26. Zhang Y, Gu Y, Guo T, Li Y, Cai H. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. Surg Oncol. 2012;21(2):e87–95.
27. Wong CS, Aly EH. The effects of enteral immunonutrition in upper gastrointestinal surgery: a systematic review and meta-analysis. Int J Surg. 2016;29:137–50.
28. Ziegler TR, May AK, Hebbar G, Easley KA, Griffith DP, Dave N, et al. Efficacy and safety of glutamine-supplemented parenteral nutrition in surgical ICU patients: an American multicenter randomized controlled trial. Ann Surg. 2016;263(4):646–55.
29. 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.
30. 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.
31. Braga M, Gianotti L, Gentilini O, Liotta S, Di Carlo V. Feeding the gut early after digestive surgery: results of a nine-year experience. Clin Nutr. 2002;21(1):59–65.
32. Gianotti L, Nespoli L, Torselli L, Panelli M, Nespoli A. Safety, feasibility, and tolerance of early oral feeding after colorectal resection outside an enhanced recovery after surgery (ERAS) program. Int J Color Dis. 2011;26(6):747–53.
33. 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.
34. Lewis K, Alqahtani Z, McIntyre L, Almenawer S, Alshamsi F, Rhodes A, et al. The efficacy and safety of prokinetic agents in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized trials. Crit Care. 2016;20(1):259.
35. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of G. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013;108(1):18–37; quiz 8.
36. MacLaren R, Kiser TH, Fish DN, Wischmeyer PE. Erythromycin vs metoclopramide for facilitating gastric emptying and tolerance to intragastric nutrition in critically ill patients. JPEN J Parenter Enteral Nutr. 2008;32(4):412–9.
37. Ringel AF, Jameson GL, Foster ES. Diarrhea in the intensive care patient. Crit Care Clin. 1995;11(2):465–77.
38. Wiesen P, Van Gossum A, Preiser JC. Diarrhoea in the critically ill. Curr Opin Crit Care. 2006;12(2):149–54.
39. Melis M, Fichera A, Ferguson MK. Bowel necrosis associated with early jejunal tube feeding: a complication of postoperative enteral nutrition. Arch Surg. 2006;141(7):701–4.
40. Spalding DR, Behranwala KA, Straker P, Thompson JN, Williamson RC. Non-occlusive small bowel necrosis in association with feeding jejunostomy after elective upper gastrointestinal surgery. Ann R Coll Surg Engl. 2009;91(6):477–82.
41. 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.
42. Bendjelid K. Five recurrent misconceptions regarding cardiogenic shock management. Cardiol Rev. 2014;22(5):241–5.
43. 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.
44. Ma J, Pendharkar SA, O'Grady G, Windsor JA, Petrov MS. Effect of nasogastric tube feeding vs nil per os on dysmotility in acute pancreatitis: results of a randomized controlled trial. Nutr Clin Pract. 2016;31(1):99–104.
45. Chang YS, Fu HQ, Xiao YM, Liu JC. Nasogastric or nasojejunal feeding in predicted severe acute pancreatitis: a meta-analysis. Crit Care. 2013; 17(3):R118.

Parenteral Nutrition

13

Vivian M. Zhao, Thomas R. Ziegler, and Kimberly A. Davis

Introduction

Protein–calorie malnutrition (PCM), which encompasses major loss of lean body mass and body fat stores, with or without concomitant depletion of essential micronutrients (vitamins, minerals, trace elements) remains common, as >1 in every 3 hospitalized patients are malnourished at hospital admission [1]. Recent data from the Healthcare Cost and Utilization Project indicates that only 3% are recognized as malnourished and treated. The lack of treatment of malnourishment is associated with a fivefold increase in mortality in patients who are malnourished relative to patients who are well-nourished (11.7% vs. 2.4%) [2].

While the majority of surgical patients will advance to oral diet shortly after operation and require minimal nutritional intervention, major surgery or postoperative complications can delay advancement to a full oral diet. The degree of PCM is worsened by the stress of operation, increased nutritional needs for wound healing, and increased metabolic rate related to postoperative recovery, insufficient food intake, and repeated catabolic insults [3, 4]. PCM prior to and during hospitalization are each associated with increased morbidity and mortality, length of hospital stay, and added cost of care [4–7].

Preoperative weight loss significantly increased postoperative morbidity and mortality in patients undergoing gastric surgery, independent of age, impaired cardiovascular and respiratory function, and type of operation [8]. Various pathophysiologic factors contribute to nutritional deficiencies among patients undergoing elective or major surgery (Table 13.1) [9]. Acute and chronic illness, trauma, and inflammation induce stress-related catabolism, and drug-induced adverse effects may reduce appetite or increase nausea and vomiting. In addition, patient management in the intensive care unit (ICU) may also interrupt feeding routines [10]. Identifying malnourished surgical patients and provision of proper nutritional support has long been a key focus of surgical patients. Research has emphasized methods of delivery to minimize surgery-associated metabolic changes. Nutrition support can be delivered safely with specialized enteral and/or parenteral nutrition [11]. This chapter will focus on parenteral nutrition (PN), which provides fluid, calories, carbohydrate, essential and

V. M. Zhao
Nutrition and Metabolic Support Service, Emory University Hospital, Atlanta, GA, USA

T. R. Ziegler (✉)
Division of Endocrinology, Metabolism and Lipids, Emory University Hospital Research Unit, Atlanta Clinical and Translational Science Institute (ACTSI), ACTSI Clinical Research Network, Atlanta, GA, USA
e-mail: tzieg01@emory.edu

K. A. Davis
Department of Surgery, Yale University School of Medicine, New Haven, CT, USA

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_13

Table 13.1 Pathophysiologic factors that contribute to malnutrition in surgical patients

Diminished dietary intake prior to or after surgery (e.g., anorexia, pain, altered gastrointestinal function awaiting for bowel function to return, NPO status)
Increased catabolic hormones and cytokine concentrations (e.g., catecholamines, cortisol, interleukins, tumor necrosis factor-α)
Decline in anabolic hormones levels (e.g., insulin-like growth factor-I, testosterone)
Resistance to anabolic hormones with subsequent underutilization of substrate (e.g., resistance to insulin)
Abnormal nutritional losses (e.g., diarrhea, surgical drainage, emesis, polyuria, renal replacement therapy, wounds)
Decreased protein synthesis secondary to decreased physical activity (e.g., bed rest, deceased ambulation, chemically induced paralysis)
Medication–nutrient interactions (e.g., corticosteroids, diuretics, vasopressors)
Increased requirements for calories, protein, and/or specific micronutrient (e.g., with infection, oxidative stress, trauma, large wounds)
Iatrogenic factors (e.g., prolonged suboptimal enteral or parenteral nutrition provision in relation to metabolic requirements)

NPO nil per os

nonessential amino acids, essential fats, vitamins, trace elements, and minerals.

Current Clinical Practice Guideline Overview

There is limited published data from well-designed, adequately powered intent-to-treat randomized control trials (RCTs) on PN efficacy in hospital settings [12, 13]. Therefore, current PN utilization is largely based on international guidelines by major professional societies [14–16]. A caveat regarding efficacy of current PN practices is that no rigorous RCT has featured an unfed or minimally fed control group; thus the safe duration for minimal to no feeding in surgical patients is unknown [17]. In addition, many of the earlier studies were conducted with excessive PN caloric doses and liberal blood glucose control strategies compared to current practice today, in which lower caloric doses (20–25 kcal/kg/day) and stricter blood glucose control (140–180 mg/dL) are the standards of care. Nonetheless, current research suggests that patients with moderate to severe generalized malnutrition benefit from PN in terms of overall morbidity and possibly mortality if enteral nutrition (EN) is not possible [8, 18].

Major professional societies have outlined clinical practice guidelines for calorie and protein (as amino acids in PN) intake in hospitalized adult medical and surgical patients [14–16]. Guidelines for pediatric patients have been published but are beyond the scope of this chapter [19, 20]. It is important to recognize that caloric needs in hospitalized surgical patients, especially those with critical illness, can vary significantly secondary to serial changes in clinical conditions [14, 15]. Optimal caloric and protein intake in surgical patients are not well-defined due to a lack of current rigorous, randomized, controlled clinical trials [14, 16, 17, 21].

Nutritional Assessment

Complete nutritional status assessment requires incorporation of medical and surgical history, current clinical and fluid status and tempo of illness, dietary intake history, body weight history, gastrointestinal and functional status, physical examination, and selected biochemical tests (Table 13.2) [9]. Serum levels of albumin and prealbumin can be helpful in outpatient setting; however, they are not reliable in the postoperative patient because inflammation, infection, lowered hepatic synthesis, changes in volume status, and/or increased clearance can markedly alter blood concentrations. On the other hand, serum albumin level can be an excellent prognostic indicator, with an inverse correlation between postoperative morbidity and mortality compared with preoperative serum albumin level [22, 23]. Concentrations of specific vitamin and trace elements are useful to follow in certain at-risk patients; however their levels can fluctuate secondary to volume status, inflammation, and interorgan shifts that require serial levels to guide repletion strategies. In addition, body weight often changes markedly in relation to volume status [23].

Table 13.2 Important steps in nutritional assessment of hospitalized surgical patients

Assess past medical and surgical history, tempo of current illness, and expected hospital/perioperative course
Evaluate dietary intake history and previous specialized nutrition support utilization
Review body weight changes (e.g., % weight loss from usual body weight, rate of loss)
Complete physical examination with attention to fluid status, organ functions, and evidence of protein–calorie malnutrition and skin/conjunctival/tongue lesions consistent with vitamin–mineral deficiency
Evaluate gastrointestinal tract status to assess feasibility and tolerance for enteral feeding
Determine ambulatory capacity, mental status
Serial evaluation of standard blood tests (organ function indices, electrolytes, pH, triglycerides, and selected vitamins and minerals if at risk for deficiency)
Assess calorie and protein needs
Determine enteral and parenteral access for nutrient delivery

Patients weighing less than 90% of their ideal body weight, those with involuntary body weight loss of >5–10% of usual body weight in the previous several weeks or months, and patients or those with a body mass index (BMI) less than 18.5 kg/m^2 should be carefully evaluated for malnutrition

A simple and practical bedside method known as subjective global assessment (SGA) has been validated for nutritional assessment and used as prognostic indicator of clinical outcomes in stable patients without significant fluctuation in fluid status [24, 25]. The SGA integrates various components, such as history of weight loss and food intake, functional capacity, gastrointestinal symptoms that continued >2 weeks (e.g., diarrhea, nausea, and vomiting), and physical examination (e.g., muscle or fat mass wasting, edema/ascites, wounds, hair loss, skin breakdown), to categorize the degree of malnutrition (e.g., well-nourished, mildly malnourished, moderately malnourished, or severely malnourished) [24, 25]. Another method commonly used in European hospitals for evaluation of nutritional risk calculates a nutritional risk score accordingly to body mass index (BMI), percent reduction in usual food intake, body weight history, age, and severity of illness [25]. Clinical practice guidelines for the identification and documentation of adult malnutrition are published by the Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition which consider key elements such as percent weight loss history, dietary energy intake history, loss of skeletal muscle and fat mass, functional status, and presence of inflammation [14].

Nutrition Support Goals

Resting energy expenditure (REE) is most commonly calculated using traditional predictive equations although may over- or underestimate REE in surgical patients secondary to changes in clinical conditions and/or fluid status [9, 26]. Current American and European clinical practice guidelines suggest an approximate caloric goal of 25 kcal/kg/day for most surgical patients, which is approximately 1–1.2 times of the measured or estimated REE. For severely stressed patients, estimated caloric needs may range higher, from 25 to 30 kcal/kg/day. Prehospital and preoperative body weight should be used for calculating caloric needs because measured body weight in the hospital (especially in the ICU) may be influenced by fluid status and can be much higher than recent "dry" weight. Ideal body weight (IBW) derived from routine tables or equations can be used as an alternative when recent dry weight is not available and to determine calorie need for obese and morbidly obese patients [9].

The provision of adequate amino acides (protein equivalents) in PN is crucial for cell and tissue function, wound healing, and improving net protein balance, especially after major operation. The commonly recommended protein dose is between 1.2 and 1.5 g/kg/day for most surgical patients with normal renal and hepatic function (i.e., 50–100% above the recommended daily allowance (RDA) of 0.8 g/kg/day); however, a dose range of 2.0–2.5 g/kg/day is currently recommended in patients with certain severely catabolic conditions such as burns, those with large wounds, and those receiving continuous renal replacement therapy (CRRT) [9, 21]. Administered doses of amino acids may need to be adjusted downward to 0.6–0.8 g/kg/day in relation to the extent and progression of renal

dysfunction in the absence of dialysis treatment. In the event of acute hepatic dysfunction and hyperbilirubinemia, patients are at risk for developing amino acid-induced hyperammonemia, and it may be prudent to administer lower doses of amino acids (0.6–1.2 g/kg/day) in relation to the degree of acute hepatic dysfunction [9, 21]. Protein restriction is generally not necessary in patients with stable chronic hepatic dysfunction, but clinical judgment is required.

Timing of Parenteral Nutrition Support

The 2016 Society of Critical Care Medicine (SCCM)/ASPEN guidelines state: "We recommend that, in patients at either low or high nutrition risk, use of supplemental PN be considered after 7–10 days if unable to meet 60% of energy and protein requirements by the enteral route alone." Initiating supplemental PN prior to this 7- to10-day period in critically ill patients on some EN does not improve outcomes and may be detrimental to the patient [14]. The 2017 ESPEN guideline for clinical nutrition in surgery (recommendation 8) states: "If the energy and nutrient requirements cannot be met by oral and enteral intake alone (<50% of caloric requirement) for more than 7 days, a combination of enteral and parenteral nutrition is recommended." [16]

Diminished caloric intake for 10–14 days after major surgery can significantly increase morbidity and mortality [9, 16]. Current guidelines recommend starting nutrition support within 3–5 days of operation if the patients were nutritionally at risk preoperatively and are unlikely to achieve desired oral intake or enteral nutrition [14, 27].

In elective surgery, while there is limited evidence to support preoperative PN in severely malnourished patients, some data suggest that adequate feeding for at least 7–10 days prior to surgery and continued after surgery may decrease postsurgical morbidity [23, 28]. Delaying elective surgery for preoperative nutritional support is recommended for patients with one or more of the following conditions: lost more than 10–15% of actual body weight within 3–6 months, BMI <18.5 kg/m^2, SGA score grade C (severe malnutrition), serum albumin <30 g/L without hepatic or renal dysfunction, or an ideal body weight <90% [4, 27].

Indications

In settings when EN either not feasible or tolerated, PN is indicated for the following patients: (1) after major upper GI surgery when the GI tract is not accessible or not functioning (e.g., mechanical obstruction, paralytic ileus); (2) after extensive small bowel resection with or without colonic resection; (3) with perforated small bowel; (4) with high-output (>600 mL) and/or proximal fistulas that necessitate bowel rest; and (5) other conditions leading to prolonged EN intolerance (e.g., severe diarrhea, persistent emesis, significant abdominal distention, acute GI bleeding, hemodynamic instability, impaired gastric emptying, or paralytic ileus) preventing sufficient EN provision for >3–7 days [9, 14]. PN is contraindicated (not evidence based) for the following patients: (1) those with functional GI tract and accessibility for EN; (2) fluid-restricted patients who cannot tolerate the intravenous fluid load provided for PN; (3) those with severe hyperglycemia or electrolyte abnormalities at the planned day of PN initiation; (4) PN therapy is unlikely to be given for >5–7 days; and (5) if new access line placement solely for PN causes unnecessary risks [9, 14] (Table 13.3).

Table 13.3 Parenteral nutrition (PN) indications in relation to the feasibility of enteral nutrition (EN)

Absolute contraindications for EN
Intestinal obstruction
Ischemic bowel
Acute peritonitis
Relative contraindications for EN (use PN if EN deemed to be not feasible)
High output fistulas
Severe malabsorption
Septic shock with impaired splanchnic perfusion
Fulminant sepsis

Administration

PN solutions can be administered either peripherally through an IV or through a centrally placed catheter. These catheters can be placed peripherally (peripherally inserted central catheter "PICC line") or in a non-tunneled fashion percutaneously directly into a central vein. The types of PN solutions vary. Peripheral PN (PPN) is of lower osmolarity that centrally delivered PN (CPN) which must be delivered into a central vein. For short-term PN needs (<14 days), peripheral intravenous IV lines can be used for 10–14 days if the patient can tolerate the required fluid load to meet amino acid and energy needs. If central vein PN is required and is deemed to be needs for 30 days or less, a percutaneous non-tunneled central venous catheter (PICC) can be used [4, 23]. When long-term PN is required, a tunneled, cuffed, silicone catheter is preferred (not evidence based). Table 13.4 outlines a comparison of peripheral and central vein PN, as well as fluid, macronutrient, and micronutrient content. Due to risk of phlebitis with hypertonic central vein-type PN formulations, peripheral vein PN (PPN) provides low amount of dextrose (5%; dextrose = 3.4 kcal/g) and amino acids (≤3%; 4 kcal/g) and a larger proportion of calories as lipid emulsion (≤5%; 10 kcal/g; 50–60% of total calories) [4, 23]. PPN usually requires a 2–3 L/day fluid volume to provide adequate protein and calorie needs (based on patient body size), which limits its use for ICU patients and those require fluid restriction due to cardiac, hepatic, and/or renal dysfunction. In contrast, central venous PN (CPN) is delivered through the superior vena cava, which permits hypertonic CPN infusions. Thus, CPN can be the concentrated complete solutions (1–1.5 L/day), while meeting caloric and protein need for vast majority of patients. Non-PN hydration fluid rate should be proportionally adjusted in accordance of fluid status when PN is initiated [29–31].

Table 13.4 Sample formulations of typical peripheral and central parenteral nutrition

Component	Peripheral vein PN	Central vein PN
Volume (L/day)	2–3	1–1.5
Dextrose (%)	5	10–25
Amino acids (%)	2.5–3.0	3–8
Lipid (%)	2.5–5.0	2.5–5.0
Sodium (mEq/L)	50–150	50–150
Potassium (mEq/L)	20–35	30–50
Phosphorus (mMol/L)	5–10	10–30
Magnesium (mEq/L)	8–10	10–20
Calcium (mEq/L)	2.5–5	2.5–5
Multivitamins (mL/day)[a]	10	10
Trace elements/minerals (mL/day)[b]		

[a]Multivitamins are consisted of vitamins A, B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), B_9 (folate), B_{12} (cobalamin), C, D, E, biotin, and with or without vitamin K. Specific vitamins such as vitamin B_1, B_6, B_9, B_{12}, C, and K are available as individual supplement

[b]Trace elements/minerals consisted of chromium, copper, manganese, selenium, and zinc in various concentrations. Only copper, selenium, and zinc are available as individual supplement

PN electrolyte dosing is adjusted as needed to maintain normal serially measured serum levels. With high and/or low blood levels of specific electrolytes, daily dose adjustment may be required until serum levels are within the normal range. Higher dextrose concentrations in CPN may result in increased requirements for potassium, magnesium, and phosphorus [4, 23]. The most recent clinical practice guidelines recommend a glycemic goal range in hospitalized adult patients receiving nutrition support to be 140–180 mg/dL (7.8–10 mmol/L). Separate intravenous insulin drips are commonly utilized to prevent hyperglycemia in ICU settings [9, 23, 32].

Commercially available amino acid formulation used in PN provides all nine essential and several nonessential amino acids [9]. The addition of glutamine, once thought to be of benefit, has been demonstrated to provide no additional outcome benefit in multiple RCTs [33–35]. Amino acid concentration in PN may need to be adjusted for azotemia or hyperbilirubinemia in patients with renal and hepatic dysfunction, respectively. PN also contains intravenous lipid emulsions (LE) as a source of both energy and essential linoleic and α-linolenic fatty acids [23]. Soybean oil-based LE is the long-standing commercially available formulation in the USA,

although a mixed lipid emulsion containing 80% olive oil and 20% soybean oil was recently approved for adults requiring PN. In Europe and other countries, intravenous soybean oil/medium-chain triglyceride mixtures, fish oil, olive oil/soybean oil mixtures, and combinations of oils are available for use in PN. A recent double-blind, randomized, controlled study in 100 mixed medical and surgical ICU patients found no differences in clinical outcomes in patients receiving PN containing soybean oil-based lipid emulsion versus the group receiving PN containing the recently approved olive/soybean oil product [36].

Lipid is typically mixed with dextrose and amino acids in the same PN infusion bag ("all-in-one" solution) and given with PN over 16–24 h [23]. Lipid emulsions may also be used as a separate infusion over 10–12 h. The maximal recommended dose of lipid emulsions infusion is 1.0–1.3 g/kg/day, with monitoring of blood triglyceride levels at baseline and then approximately weekly and as indicated to assess clearance of intravenous fat [4, 9, 17]. Triglyceride levels should be maintained below 400–500 mg/dL by lowering lipid emulsion concentration in PN to decrease risk of pancreatitis and diminished pulmonary diffusion capacity in patients with severe chronic obstructive lung disease. A typical central venous PN provides 60–70% of nonprotein calories as dextrose and 30–40% of nonprotein calories as LE [8, 9, 17, 23].

Specific needs for intravenous vitamins and minerals have not been rigorously defined for hospitalized patients [9, 18, 23]. Therefore, standardized intravenous preparations of combined vitamins and minerals have been added in PN to maintain normal blood levels in most stable patients (Table 13.3). However, several studies show that a significant proportion of critically ill patients receiving standard nutrition support may variously experience zinc, copper, selenium, vitamin C, vitamin E, and vitamin D deficiencies [23]. Low micronutrient levels can be related to pre-ICU depletion, increased requirements possibly secondary to oxidative stress associated with critical illness, and increased excretion and/or tissue redistribution [23]. Depletion of these essential nutrients may impair antioxidant capacity, immunity, wound healing, and other important body functions. Thus, as with electrolytes, therapy is directed at maintaining normal blood levels, with serial measurements in blood as clinically and biochemically indicated.

Supplemental Parenteral Nutrition

The body of evidence that examines the practice of supplemental PN (SPN or PN in combination with EN) is limited. A recent Cochrane review found insufficient evidence to determine whether the combination of EN and PN impacted hospital mortality, ventilator-free days, or adverse events [10].

Complications and Monitoring

Administration of PN has been associated with infectious, mechanical, and metabolic complications [9, 18, 23, 27]. Catheter-related bloodstream infections can occur. Mechanical complications are mainly related to insertion and use of central venous catheters, such as pneumothorax, hemothorax, thrombosis, and bleeding. Proper and safe administration of both peripheral and central vein PN requires strict catheter care protocols, including the use of designated catheter ports for PN administration and subclavian vein insertion sites for central venous PN [4, 9, 18, 23, 27].

Potential metabolic and clinical consequences of overfeeding and refeeding syndrome during PN in critically ill patients are shown in Table 13.5 [9, 23]. Risk factors for PN-associated hyperglycemia include (1) use in obese, diabetic, and/or septic patients; (2) poorly controlled blood glucose at PN initiation; (3) initial use of high dextrose concentrations (>10%) or dextrose load (>150 g/day); (4) insufficient insulin administration and/or inadequate monitoring of blood glucose; and (5) concomitant administration of corticosteroids and vasopressor agents.

Overfeeding can induce several metabolic complications of varying degrees of severity affecting several organ systems (Table 13.5)

Table 13.5 Potential complications of overfeeding and refeeding syndromes in patients receiving parenteral nutrition

Intracellular shift of magnesium, phosphorus, and/or potassium (due to excess dextrose; refeeding hyperinsulinemia)
Immune cell dysfunction and infection (due to hyperglycemia)
Cardiac dysfunction or arrhythmias (due to excess fluid, sodium, and other electrolytes; intracellular/extracellular shift of electrolytes related to refeeding)
Neuromuscular dysfunction (due to thiamine deficiency; electrolytes shifts due to refeeding)
Renal dysfunction or azotemia (due to excess amino acid; inadequate caloric provision relative to amino acid dose)
Edema or fluid retention (due to excess fluid and/or sodium; refeeding hyperinsulinemia)
Elevated liver function tests and/or hepatic steatosis (due to excessive calorie, dextrose, or fat content)
Increased blood ammonia levels (due to excessive amino acids provision with hepatic dysfunction)
Hypercapnia (due to excessive total caloric provision)
Respiratory insufficiency (due to refeeding-associated hypophosphatemia; excess fluid, calorie, carbohydrate, or fat content)
Hypertriglyceridemia (due to excessive carbohydrate or fat provision; carnitine deficiency)

[9, 23]. A recent large study found that overfeeding and sepsis were the major risk factors for liver dysfunction in critically ill patients [37]. Thus, PN should be advanced carefully to goal rates and the composition adjusted as appropriate based on the results of close metabolic and clinical monitoring performed daily. The calories provided by dextrose present in non-PN intravenous fluids, the soybean oil lipid emulsion carrier of propofol, a commonly used ICU sedative, and the nutrients provided in any administered EN must be taken into account in the PN prescription to avoid overfeeding [23].

Refeeding syndrome is well recognized and relatively common in at-risk patients (preexisting malnutrition or electrolyte depletion; prolonged periods of intravenous therapy alone) [9, 38, 39]. Refeeding syndrome is triggered by excessive intravenous dextrose (>150–250 g or 1 L of PN with 15–25% dextrose) which stimulates insulin release, rapidly decreases blood potassium, magnesium, and especially phosphorus concentrations due to intracellular shift and utilization in metabolic pathways. High doses of carbohydrate increase thiamine utilization and can precipitate symptoms of thiamine deficiency. Hyperinsulinemia may cause sodium and fluid retention by the kidney. This, together with decreased blood electrolytes (which can cause cardiac arrhythmias), can result in heart failure, especially in patients with preexisting heart disease [38, 39]. Prevention of refeeding syndrome requires identification of at-risk patients; use of initially low PN dextrose concentrations (e.g., 1 L of PN with 10% dextrose); provision of higher PN doses of potassium, magnesium, and phosphorus, based on initial and adjusted on serial blood levels within the first several days of PN administration; and renal function and supplemental PN thiamine (e.g., 100 mg/day for 3–5 days) [9, 38, 39].

Consultation with an experienced multidisciplinary nutrition support team for recommendations is ideal. Nutrition support team daily monitoring has been shown to reduce complications and costs and to decrease inappropriate use of PN [39, 40]. Team approach results in improved patient care and therapeutic and economic benefits. PN therapy requires monitoring. Blood glucose should be monitored several times daily, and blood electrolytes and renal function tests should be determined generally daily [9, 23]. Blood triglyceride levels should be measured at baseline and then weekly until stabile. Liver function tests should be measured at least a few times weekly. pH should be monitored generally daily in ventilated patients when arterial blood gas pH measurements are available [9, 23].

Home Parenteral Nutrition

Home parenteral nutrition (HPN) was introduced as treatment option primarily for patients with long-term intestinal failure [41]. The goal of HPN is to prevent and/or correct malnutrition for a period of months or the rest of one's life. HPN is commonly indicated for patients with Crohn's disease, mesenteric vascular disease, cancer, intestinal failure, and radiation

enteritis who cannot meet their nutritional needs by EN and who can be treated outside the acute care setting [42, 43]. Intestinal failure in surgical patients can be caused by obstruction, dysmotility, and surgical resection. Current practice guidelines do not recommended HPN for patients with a short life expectancy for at least 40–60 days [42]. HPN is delivered via subcutaneously tunneled catheters or implanted ports.

HPN therapy is not without risks. Thrombosis and catheter occlusion occur while patients receive HPN, but catheter-related infections are most problematic. Liver dysfunction and metabolic bone disease are also common complications related to long-term PN. The prevalence of catheter-related bloodstream infections ranges between 0.16 and 1.09 episodes per catheter years, as much as 13.2 episodes per 1000 catheter days [34]. Recent data strongly suggest that ethanol locks, which must be administered via a silicone catheter (i.e., not via a plastic PICC), may markedly reduce PN-associated bloodstream infections, presumably by clearing microbe-containing biofilm on the catheter [44]. All available guidelines recommend routine monitoring by a multidisciplinary nutrition support team to minimize complications [42].

Conclusion

Recommendations for the optimal timing for PN intervention in surgical patients are consensus driven, based on best available evidence. PN is an essential and often life-saving treatment for patients who cannot tolerate enteral feeding. However, PN is not without risk, which can be mitigated by meticulous attention to detail, establishment of multidisciplinary nutritional support teams, appropriate balance of components, and strict hygiene measures to decrease catheter infections. Clinicians should be constantly vigilant about the resumption of enteral nutrition when feasible.

References

1. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system. Int J Environ Res Public Health. 2011;8(2):514–27.
2. Weiss AJ, Fingar KR, Barrett ML, et al. Characteristics of hospital stays involving malnutrition, 20131. Statistical Brief #210. Healthcare Cost and Utilization Project (HCUP). Rockville: Agency for Healthcare Research and Quality; 2016. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb210-Malnutrition-Hospital-Stays-2013.jsp.
3. Pirlich M, Schütz T, Norman K, Gastell S, Lübke HJ, Bischoff SC, et al. The German hospital malnutrition study. Clin Nutr. 2006;25(4):563–72.
4. 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):255–9.
5. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNMC, Delarue J, Berger MM. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24(4):502–9.
6. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L. Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. Clin Nutr. 2007;26(6):1S–138S.
7. Schneider SM, Veyres P, Pivot X, Soummer AM, Jambou P, Filippi J, et al. Malnutrition is an independent factor associated with nosocomial infections. Br J Nutr. 2004;92(1):105–11.
8. Studley HO. Percentage of weight loss - a basic indicator of surgical risk in patients with chronic peptic ulcer. JAMA. 1936;106:458–60.
9. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med. 2009;361(11):1088–97.
10. Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. Cochrane Database Syst Rev. 2018(6):CD012276. https://doi.org/10.1002/14651858.CD012276.pub2.
11. Seike J, Tangoku A, Yuasa Y, Okitsu H, Kawakami Y, Sumitomo M. The effect of nutritional support on the immune function in the acute postoperative period after esophageal cancer surgery: total parenteral nutrition versus enteral nutrition. J Med Invest. 2011;58(1–2):75–80.
12. 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.
13. Doig GS, Simpson F, Sweetman EA. Evidence-based nutrition support in the intensive care unit: an update

on reported trial quality. Curr Opin Clin Nutr Metab Care. 2009;12(2):201–6.
14. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the critically ill adult 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. 2016;40(2):159–1211.
15. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian 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):355–1373.
16. Weimann A, Braga M, Carli F, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36(3):623–50.
17. Ziegler TR. Nutrition support in critical illness–bridging the evidence gap. N Engl J Med. 2011;365(6):562–4.
18. 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.
19. Koletzko B, Goulet O, Hunt J. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). 2. Energy (vol 41, pg S5, 2005). J Pediatr Gastroenterol Nutr. 2013;56(4):460.
20. Mehta NM, Compher C. A.S.P.E.N. Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr. 2009;33(3):260–76.
21. Yarandi SS, Zhao VM, Hebbar G, Ziegler TR. Amino acid composition in parenteral nutrition: what is the evidence? Curr Opin Clin Nutr Metab Care. 2011;14(1):75–82.
22. Kudsk KA, Tolley EA, DeWitt RC, Janu PG, Blackwell AP, Yeary S, King BK. Preoperative albumin and surgical site identify surgical risk for major postoperative complications. JPEN J Parenter Enteral Nutr. 2003;27(1):1–9.
23. Brown RO, Minard G, Ziegler TR. Parenteral nutrition. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, editors. Modern nutrition in health and disease. 11th ed. Philadelphia: Lippincott Williams and Wilkins; 2012. p. 1136–61.
24. Norman K, Schütz T, Kemps M, Josef Lübke H, Lochs H, Pirlich M. The subjective global assessment reliably identifies malnutrition-related muscle dysfunction. Clin Nutr. 2005;24(1):143–50.
25. Rasmussen HH, Holst M, Kondrup J. Measuring nutritional risk in hospitals. Clin Epidemiol. 2010;2:209–16.
26. Anderegg BA, Worrall C, Barbour E, Simpson KN, Delegge M. Comparison of resting energy expenditure prediction methods with measured resting energy expenditure in obese, hospitalized adults. JPEN J Parenter Enteral Nutr. 2009;33(2):168–75.
27. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN guidelines on parenteral nutrition: surgery. Clin Nutr. 2009;28(4):378–86.
28. 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.
29. 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.
30. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381(9864):385–93.
31. 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.
32. McMahon MM, Nystrom E, Braunschweig C, Miles J, Compher C. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), Board of Directors; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. clinical guidelines: nutrition support of adult patients with hyperglycemia. JPEN J Parenter Enteral Nutr. 2013;37(1):23–36.
33. Grau T, Bonet A, Miñambres E, Piñeiro L, Irles JA, Robles A, et al. The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. Crit Care Med. 2011;39(6):1263–8.
34. 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.
35. Ziegler T, May A, Hebbar G, Kudsk K, Sax H, Blumberg H, Easley K, Wischmeyer P. Glutamine dipeptide-supplemented parenteral nutrition in surgical ICU patients: results of an American randomized, double-blind, multicenter trial. Clin Nutr Suppl. 2012;7(1):265.
36. Umpierrez GE, Spiegelman R, Zhao V, Smiley DD, Pinzon I, Griffith DP. A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. Crit Care Med. 2012;40(6):1792–8.
37. Grau T, Bonet A, Rubio M, Mateo D, Farré M, Acosta JA, Blesa A, Montejo JC, de Lorenzo AG, Mesejo A, Working Group on Nutrition and Metabolism of

the Spanish Society of Critical Care. Liver dysfunction associated with artificial nutrition in critically ill patients. Crit Care. 2007;11(1):R10.
38. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, Lobo DN. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62(6):687–94.
39. Kennedy JF, Nightingale JM. Cost savings of an adult hospital nutrition support team. Nutrition. 2005;21(11–12):1127–33.
40. Trujillo EB, Young LS, Chertow GM, Randall S, Clemons T, Jacobs DO, Robinson MK. Metabolic and monetary costs of avoidable parenteral nutrition use. JPEN J Parenter Enteral Nutr. 1999; 23(2):109–13.
41. Shils ME, et al. Long-term parenteral nutrition through an external arteriovenous shunt. N Engl J Med. 1970;283(7):341–4.
42. Dreesen M, Foulon V, Vanhaecht K, De Pourcq L, Hiele M, Willems L. Guidelines recommendations on care of adult patients receiving home parenteral nutrition: a systematic review of global practices. Clin Nutr. 2012;31(5):602–8.
43. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F. ESPEN guidelines on parenteral nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr. 2009;28(4):467–79.
44. Oliveira C, Nasr A, Brindle M, Wales PW. Ethanol locks to prevent catheter-related bloodstream infections in parenteral nutrition: a meta-analysis. Pediatrics. 2012;129(2):318–29.

14 Immunonutrition and Supplementation: Pathways, Promise, and Pessimism

Andy Tully, Kristina Z. Kramer, and Stathis Poulakidas

Introduction

Throughout this textbook, the reader is impressed with the critical role nutrition plays in the neuroendocrine immunoinflammatory supersystem. The ever-expanding network of links, levers, inhibitions, cross talk, and feedback governing the healthful recovery of the patient is underpinned by proper nutrition. But what if the clinician could use proper nutrition as more than just an essential support for recovery, more than just a workbench? What if nutrition actively became a precision tool to effect recovery? By tugging just a few well-chosen strings upstream in the system—and what could be more upstream than food?—a malfunctioning neuroendocrine immunoinflammatory supersystem could be made to pivot on its axis like a puppet and restored to a healthy phenotype.

Using food as a tool to shift this system has long been an appealing, elegant solution to a complex problem. In Greece in the fifth century BC, Hippocrates of Cos has been credited with the dictum "Let food be thy medicine and medicine be thy food." Although this phrase may not actually appear in the Hippocratic Corpus, attending to the nutrition of the patient was clearly essential in the Hippocratic Oath: "I will apply dietetic measures for the benefit of the sick, according to my ability and judgement." A sober understanding of the limits of modulating nutrition was also present, "In food excellent medication, in food bad medication, bad and good relatively" [1]. Across time and geography, food is an integral remedy in humoral theories of medicine. "Hot" diseases can be treated by eating "cold" foods or at least abstaining from "hot" foods. Such ideas can be found in the writings of Galen of Pergamum (Rome, second century AD), Ho the Physician (China, sixth century BC), and Ibn Sina also known as Avicenna (Persia, tenth century AD) [2].

With the work of Antoine Lavoisier in the eighteenth century, nutrition began to be examined from a more molecular scientific perspective. Prevention of infection became an intense surgical focus thanks to the efforts of Sir Joseph Lister in the nineteenth century. Using bacterial populations as supplements to modulate health—today known as probiotics—was first promoted by immunologist and discoverer of phagocytosis Ilya Ilyich Metchnikoff in the

A. Tully
Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA

K. Z. Kramer
John H. Stoger, Jr. Department of Trauma and Burn Surgery, Hospital of Cook County, Chicago, IL, USA

S. Poulakidas (✉)
Department of Trauma & Burns, Cook County Health and Hospital Systems, Chicago, IL, USA
e-mail: spoulakidas@cookcountyhhs.org

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_14

1900s [2]. The 1930s work of Isidor Schwaner Ravdin at the University of Pennsylvania on nutritional prevention of laparotomy dehiscence in dogs marks the increasing attraction of this idea to the surgical community [3]. Further popularization ensued with Francis D. Moore's highly influential 1959 *Metabolic Care of the Surgical Patient* and the editions that followed.

With the advent of immunosuppression therapies for transplant in the 1980s, immunologic research began to blossom. By the 1990s, research began to more clearly define immunology cell signaling and transduction pathways, and it became apparent that immunology is intimately intertwined with basic biochemistry, cellular metabolism, and nutrition. By the late 1990s and early 2000s, many investigators were eager and incentivized to apply these new bench science insights directly to patient care. With the worldwide attention garnered by the 2002 inception of the Surviving Sepsis Campaign, a broad patient population was defined. An outpouring of funded research took place, geared to use nutrition to restabilize the critically dysregulated immune system. Thus evolved our current concept of immunonutrition. Immunonutrition is the use of nutritional intervention, either enterally or parenterally, to produce effects beyond the basic nutrient value and modulate a malfunctioning neuroendocrine immunoinflammatory supersystem.

Immunonutrition as currently described focuses on five components, arginine, glutamine, omega-3 fatty acids, nucleotides, and antioxidants, and there is a strong argument to include probiotics and prebiotics as immunonutrition. The administration of probiotics and prebiotics is occasionally cited as ecoimmunonutrition. This chapter begins with a brief overview of these seven components and mechanistic rationales why each is a potential immunomodulator. The chapter continues with a summary of the mixed clinical evidence for immunonutrition interventions in particular patient populations where it might benefit. The chapter concludes with a summary of current therapeutic guidelines with an eye to future developments.

L-Arginine

Arginine (Fig. 14.1) is one of the six conditionally essential amino acids; in infancy and during times of stress, the body cannot supply enough new arginine quickly enough to meet the demand. On the supply side, arginine is not well absorbed from the intestine, where it is likely degraded by intraluminal arginase, leading to a bioavailability of 21–68% [4, 5]. Arginine can be synthesized de novo from citrulline. Citrulline is synthesized mostly from glutamine by the intestine and then sent to the kidney to produce arginine in a so-called intestinal-renal axis. However, citrulline sources also only account for 10–15% of total body arginine production. Accordingly, most of the body's arginine comes from endogenous protein catabolism (80%) [6].

Arginine demand can be quite high, given its participation in multiple biochemical pathways. Arginine is key to production of urea, creatinine, creatine phosphate, and polyamides like putrescine and spermidine useful for cell proliferation

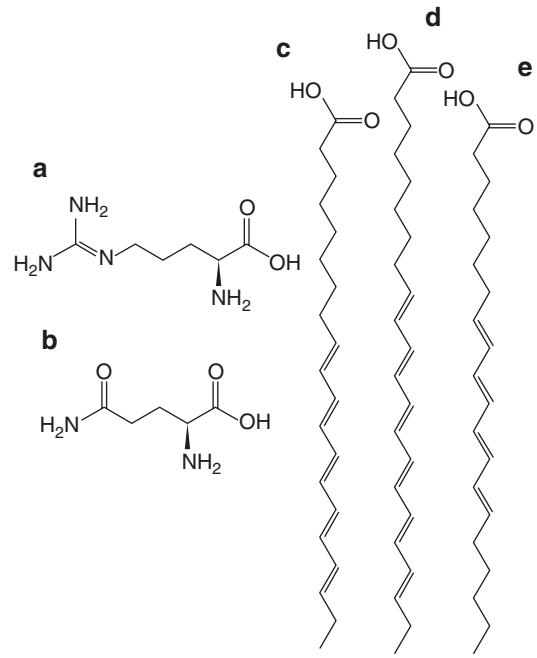

Fig. 14.1 (**a**) L-arginine. (**b**) L-glutamine. (**c**) Eicosapentaenoic acid (EPA) (20: 5n-3). (**d**) Docosahexaenoic acid (DHA) (22: 6n-3). (**e**) Arachidonic acid (ARA) (20: 4n-6)

and proline for collagen synthesis and wound healing. Most importantly, arginine is the direct precursor to nitric oxide (NO), a crucial molecule for inflammation and hemostasis. NO produced by macrophages and neutrophils is a free radical, directly toxic to pathogens but also to human cells in the setting of asthma and other airway diseases. As a vasodilatory molecule, NO is released at a constant low level to maintain the body's basal resting vascular tone, opposing the pro-inflammatory effect of cell-free hemoglobin. Basal NO has been shown to inhibit platelet activation and adhesion. With higher inflammatory levels of NO, further vasodilation occurs, recruiting more cells to the site of injury. The highest levels of NO underpin the vasoplegia of septic shock [6].

Arginine administration has been shown to induce wider system-level effects. Through inhibition of somatostatin, arginine increases secretion of growth hormone and insulin-like growth factor-1 (IGF-1). Arginine is a potent secretagogue for glucagon, pancreatic polypeptide, and insulin; it also may decrease leptin levels and inhibit angiotensin-converting enzyme (ACE). Accordingly, there is some older evidence for improved blood pressure and insulin sensitivity with arginine administration. The arginine to polyamide pathway has been linked to autoimmune disease [7]. Arginine has been shown to improve wound healing through increased collagen deposition and NO activity [8]. As precursor to NO, arginine increases macrophage and natural killer cell function, but it also has been shown to enhance B cell differentiation and T cell mitogenesis, possibly even independently of the thymus. Independently of NO, arginine itself serves as an antioxidant, a stimulant of fibrinolysis, and an inhibitor of thromboxane B2 and reduces the viscosity of the blood [5].

It should be noted arginine plays a complex role in tumor biology. Not only is NO a possible direct carcinogen as a free radical, but NO also plays a role in tumor angiogenesis and inhibition of p53, a well-known tumor suppressor gene. Arginine may be necessary for the continued expansion of some tumors, but it also may sensitize other tumors to the immune system and chemoradiotherapy [5]. The role of immunonutrition in the treatment of cancer patients is explored below, but the prudent clinician should be aware that unintended effects are possible with such pleotropic molecules.

L-Glutamine

Glutamine (Fig. 14.1), not to be confused with glutamate, is cited as the most abundant amino acid in the body, composing 20% of the free amino acid pool and 60% of the intracellular pool in muscles and the liver, which is 10–100-fold greater than any other amino acid. Glutamine is readily absorbed by the small intestine, but up to 30% of dietary glutamine will be retained by the small intestine endothelial cells as a primary energy source [9, 10]. Glutamine is also synthesized de novo by adipose, lung, and muscle tissues, which can produce 50–80 gm/day for healthy adults [11]. Surprisingly, despite what would seem an abundant supply, glutamine—like arginine—becomes conditionally essential in times of stress. This conditionally essential status can be explained both by decreased supply from diminished muscle production and increased demand for glutamine as an intermediate in numerous biochemical pathways and as "the fuel of the immune system."

Glutamine participates in multiple crucial biochemical pathways; only a brief summary will be possible here. The clinician will recall glutamine is a precursor to purines, pyrimidines, gluconeogenesis, amino sugars, glutathione (the preeminent antioxidant), the gamma aminobutyric acid (GABA) cycle, and the tricarboxylic acid (TCA) cycle also known as the Krebs cycle. The TCA cycle provides energy to the cell in the form of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2); it is the starting point for acetyl-coenzyme A and lipid synthesis. Glutamine serves as an ammonia shuttle used by the liver to synthesize urea and by the kidney to maintain pH homeostasis. Glutamine has also been shown to be involved in extracellular matrix synthesis, the ubiquitin pathway, the heat shock protein response, and apoptosis [12].

Since the 1980s, glutamine has been dubbed "the fuel of the immune system," at least equal to and possibly greater than glucose [13]. Partly this reflects the need of any rapidly dividing cell population for a versatile energy source and building block for nucleic acids. But glutamine also directly activates extracellular signal-related kinase (ERK) and c-Jun N-terminal kinase (JNK) to increase cell proliferation through the mitogen-activated protein kinase (MAPK) and activator protein-1 (AP-1) pathways. It is also involved in the mammalian target of rapamycin (mTOR) and nuclear factor kappa-light chain-enhancer of activated B cells (NFκB) pathways. Different branchpoints of immune cell subset differentiation appear to regulate glutamine metabolism differently, such as M1 and M2 macrophages. T cell differentiation into Th1, Th17, and T regulatory subsets can be influenced by manipulating aspects of glutamine metabolism and availability. Glutamine is also required for B cell transformation into plasma cells [13].

Similar to arginine, glutamine plays a complex role in cancer biology and is also necessary for tumor growth in vitro [14]. In the past, storage and administration of glutamine as an isolated amino acid were impractical due to molecular instability. One solution has been to administer glutamine as a dipeptide. Combinations of alanine-glutamine, glycine-glutamine, and arginine glutamine have been used in humans [13].

Omega-3 (n-3) Fatty Acids

Omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids (Fig. 14.1) are the two major families of polyunsaturated fatty acids (PUFA). They are so named for the position of the first double bond of the fatty acid backbone, counting from the methyl end. Two such examples are linoleic acid (18: 2n-6) and α-linolenic acid (18: 2n-3), named for their 18-carbon backbone with two total double bonds. These two PUFAs and their derivatives are considered essential fatty acids produced by plants but not by animals to any efficient, appreciable extent, and their derivatives have wide biological significance, of which only a small part will be summarized here [15].

Several cell signaling pathways are regulated by the PUFA-derived phospholipids of the cell membrane. The type of phospholipid in the membrane influences the fluidity, and the fluidity determines how quickly membrane-embedded signaling molecules can co-localize to perform their function. Furthermore, several signaling pathways cleave off pieces of membrane phospholipid, and both portions can serve as signals. The most prevalent cell membrane PUFA in humans on a typical Western diet is an omega-6 fatty acid, arachidonic acid (ARA) (20: 4n-6). When arachidonic acid is freed from the membrane, enzyme families like cyclooxygenase (COX) and lipoxygenase (LOX) use arachidonic acid to produce eicosanoids, a broad class of inflammatory mediators. Eicosanoids include the pro-inflammatory prostaglandins, thromboxane A2, leukotrienes, hydroxyeicosatetraenoic acid (HETE), and anti-inflammatory prostacyclins and lipoxins [16, 17].

The types of eicosanoids produced are altered by dietary omega-3 PUFA. Two members of the omega-3 PUFA family are eicosapentaenoic acid (EPA) (20: 5n-3) and docosahexaenoic acid (DHA) (22: 6n-3). EPA and DHA are produced by algae and plankton before ascending the food chain to deep sea fish and humans. When EPA and DHA become more abundant in the diet, more cells start to preferentially utilize them for membrane phospholipid synthesis and reduce the prevalence of arachidonic acid. The COX and LOX enzymes are not restricted to omega-6 ARA; they also act on the omega-3 EPA and DHA, but the mediators produced by omega-3 reactions are far less biologically potent than arachidonic-derived mediators. Additionally, some COX and LOX isoforms use omega-3 PUFAs to produce unique anti-inflammatory mediators: protectins, resolvins, and maresins [16, 17].

EPA and DHA have other mechanisms to modulate the immune system. Omega-3 PUFAs decrease production of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) even after stimulation with lipopolysaccharide (LPS). EPA and DHA decrease expression of immune cell adhesion molecules such as intracellular adhesion

molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). EPA and DHA have been shown to inhibit the pro-inflammatory NFκB pathway and stimulate the anti-inflammatory peroxisome proliferator-activated receptor-γ (PPAR-γ) transcription pathway [16, 17].

Several pathways modulated by omega-3 fatty acids are also affected by arginine, and some researchers have hypothesized potential synergism with co-supplementation [18].

At an ecological level, there exists a hypothesis that since humans evolved in the rift valley in Africa, where omega-3 fatty acids exist in greater prevalence than elsewhere in the world, perhaps the human genome is more adapted to certain omega-3 ratios in the diet [19].

Nucleotides

Nucleotides are the basic building blocks of DNA and RNA as well as the cellular energy equivalents NADH and FADH2. Under normal healthy conditions, humans absorb adequate nucleotides from a typical diet of 1–2 g/day. Additional nucleotides are supplied by de novo synthesis, which depends on glutamine or several "salvage pathways." As discussed above, during times of stress immune cells undergo frequent, rapid division, generating high demand for nucleotides. Studies as early as the 1980s document impaired leukocyte function without adequate nucleotides [15]. At an organismal level, it remains unclear whether the demand can truly exceed the plentiful supply, even in critically ill patients. However, an unintended consequence of processing techniques used in manufacturing commercial enteral and parenteral nutrition may inadvertently deplete these products of nucleotides. Accordingly, some formulations of immunonutrition supplement nucleotides to compensate for this possible deficit [20].

Antioxidants

Oxidants and free radicals have long been known to inflict damage on the cellular and organismal level, as early as 1957. Free radicals are molecules with unpaired electrons, making them unstable, readily engaging in redox reactions. Recall that in redox reactions, the oxidizing agent is itself reduced; that is, it gains an electron. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) can be free radicals or non-free radicals, which are prone to form free radicals [21].

Antioxidants terminate or prevent redox reactions via a variety of biochemical mechanisms. Antioxidants can be enzymes whose products quench free radicals. Examples include catalase, superoxide dismutase (SOD), and glutathione peroxidase with its associated supporting enzymes like glutathione reductase. Antioxidants can also be nonenzymes which quench redox reactions directly. Examples include flavonoids (found in cranberries and chocolate), thiols (including glutathione), vitamin A (retinol), vitamin E (tocopherols), vitamin C (ascorbic acid), melatonin, carotenoids, catechins (found in green tea and papaya), uric acid, coenzyme Q10, and polyphenols (found in red wine, onions, and thyme). Transition metals can serve as antioxidants because they readily accept or donate electrons. Selenium, copper, manganese, and zinc function as antioxidants alone or embedded in an enzyme, such as copper and zinc embedded in SOD. Synthetic antioxidants which protect food from spoilage such as BHT and BHA (butylated hydroxytoluene and butylated hydroxyanisole, respectively) are components of the contemporary Western diet [21, 22].

In the healthy state, cells depend on redox reactions for diverse essential functions. Redox reactions underpin the mitochondrial electron transport chain, providing energy for the cell. ROS and RNS interact with protein tyrosine phosphatases and kinases in multiple signaling networks, including the MAP kinase pathway, AP-1, NFκB, and nuclear factor erythroid-derived 2-related factor 2 (Nrf2) pathways. ROS have been shown to activate microRNAs [23]. Simultaneously, cells maintain an elaborate synergy of antioxidants to control redox collateral damage in each cell compartment. The cytosol is protected by the glutathione system, whereas fat-soluble vitamin E and beta-carotene protect the

hydrophobic membranes. The mitochondria rely on coenzyme Q10, while the extracellular space is protected by a multi-antioxidant system: albumin, uric acid, lactoferrin, ceruloplasmin, vitamin C, as well as catalase and SOD, both in the red blood cells. Only about 1% of ROS normally escapes these control systems [21].

This balance is upended in the stressed state. Cellular resources are diverted from maintaining the antioxidant system, which in turn cannot keep up with increased redox output from five sources: the mitochondrial electron transport chain, xanthine oxidase, phagocytes, arachidonic acid pathways, and free transition metals. The electron transport chain contains semi-ubiquinone in complex I which reacts with O_2 and produces O_2^- (superoxide). Increased superoxide, NO, and other ROS inhibit components downstream of complex I. This causes upstream buildup of more superoxide, a cascade thought to underpin septic shock [24]. Another stress state, ischemic reperfusion injury, has been tied to overactivity of xanthine oxidase. Xanthine oxidase functions in the purine nucleotide degradation pathway which leads to uric acid production. Uric acid itself is an antioxidant, but the xanthine oxidase reaction produces superoxide as a by-product. Normally, the superoxide by-product is safely oxidized via freely available NAD^+. During ischemia, however, fresh NAD^+ is not regenerated by aerobic metabolism, and the uncompensated superoxide levels rise. Stressed ischemic cells also break down more damaged nucleotides, which further increases uncompensated xanthine oxidase output of superoxide. Another source of ROS is phagocytes such as macrophages and neutrophils. In any stress state, phagocytes have a capacity for "respiratory burst" in which they use the enzyme NADPH oxidase and myeloperoxidase to produce multiple ROS, which aid in the destruction of pathogens. When overstimulated, phagocytes produce an overabundance of ROS [21, 25]. Arachidonic acid was discussed above as a producer of inflammatory mediators; additionally, arachidonic acid trans isomers can lead to increased ROS, probably through a conversion of xanthine dehydrogenase to xanthine oxidase [26]. Lastly, as discussed above, transition metals accept or donate electrons and are ready participants in redox reactions. In healthy cells, transition metals are closely regulated and contained in protein structures which control their availability for reaction. In times of stress, however, these structures are poorly maintained or degraded, leaving free metallic ions free for unregulated redox. Iron, copper, and some forms of selenium can cause redox damage.

It should be noted that intensive care unit (ICU) treatments may disturb the balance of the redox/antioxidant system during stress. Mechanical ventilation with high FiO_2, renal replacement therapy, blood and iron transfusions, and crystalloid administration associated with neutrophil activation all add redox stress to a sick patient. The standard dietary intake of ICU patients minus their substantial outputs including drains may result in a net loss of micronutrients and inadequate antioxidant power to meet their demands [21].

Uncontrolled redox reactions have many ways of damaging the cell and increasing inflammation. ROS and RNS degrade important structural proteins such as collagen and hyaluronic acid. ROS and RNS damage phospholipid membranes covering mitochondria, lysosomes, and the cell itself. Leaking mitochondria and lysosomes promote further amplification of the damage. ROS interfere with other critical proteins, such as the Na^+/K^+ ATPase and the Ca^{2+} ATPase essential for maintaining gradients that underpin all basic cell machinery. ROS interfere with glutamine synthetase. If ROS damage to DNA or to mitochondrial membranes is extensive enough, apoptotic pathways are activated. Moreover, ROS activate the NFκB pathway and are chemotactic to immune cells, which amplify the inflammatory cascade to the tissue level [27].

Some investigators have advocated rebalancing the redox/antioxidant system during physiologic stress by providing supplemental antioxidants. Trials have focused on selenium, copper, zinc, vitamin A, vitamin C, vitamin E, and N-acetyl cysteine. The strategy seems rational given the above discussion, but the clinical trials have been disappointingly mixed. This is probably reflective of the current knowledge gap

regarding complex antioxidant chemistry. Redox reactions occur on a spectrum; the molecules considered to be antioxidants actually become prooxidants in some conditions and concentrations. Current assays for analyzing these conditions are also limited. Consider the problem of analyzing the free radical NO. Its half-life is less than a few seconds in an aqueous environment, but in a low oxygen tension environment perhaps more consistent with distressed tissue, its half-life has been measured at greater than 15 s [23]. On an ecological scale, world distributions of antioxidants can vary widely. The case of selenium is one such example where European selenium deficiencies compared to North American levels may help explain some clinical trial discrepancies [28]. Attempting to reset the redox balance may be more complex than currently realized.

Probiotics

Probiotics are currently classified under the 2001 joint definition by the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO), as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [29]. Any discussion of modulating the neuroendocrine immunoinflammatory supersystem would be gravely incomplete without considering the microbiome. Healthy humans live with 40 trillion bacterial cells inside the gut representing 1000 species spread out over a gut surface area of 32 m^2, the size of half a badminton court. These bacteria are in constant interaction with 80% of the entire host lymphocyte population [30]. Science is only just beginning to measure the wide-reaching effects of these commensals interacting with their particular human host since birth. The lungs, liver, kidneys, and brain have all been found to have phenotypes regulable by the microbiome, and in turn the microbiome is dynamically sensitive to the host. Within 6 h of a sudden physiologic stress such as trauma or cardiac arrest, 90% of the normal anaerobic gut flora has dissipated, allowing ecologic space for the rise of a "pathobiome" [31]. Unlike the microbiome whose survival interests are aligned with the host, the pathobiome can sense a weak host on the verge of death, which may trigger an overall increased virulence to parasitize every last survival advantage from a "bad investment."

As noted above, the idea of modulating bacterial populations by using other bacterial populations was first popularized by Metchnikoff in the 1900s [2]. The idea has recently gained wider traction in traditional medical circles as well as popular culture. *Lactobacillus* and *Bifidobacterium* species are "generally regarded as safe" by US and European food regulatory agencies. These two genera form the backbone of the probiotic food industry which is expected to reach over $46 billion dollars in value by 2020 [29]. The phyla *Bacteroidetes* and *Firmicutes* compose the majority of healthy flora but generally require more research and characterization as stably nonpathogenic before they can be used as probiotics. It remains a concern that some nonpathogenic bacteria can increase their virulence under certain conditions. Current recommendations are to avoid probiotic supplementation in critically ill patients, but as discussed below, some surgical patient populations may benefit. The case of fecal transplant in *Clostridium difficile* infection is one case in point.

Prebiotics

Manipulation of the bacterial flora can be taken a step further upstream, hence the term prebiotics. Prebiotics, scientifically described since at least 1921, are substrates often indigestible by the host but "selectively used by host microorganisms conferring a health benefit" [32]. Prebiotics can be indigestible carbohydrates such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), human milk oligosaccharides, and inulin which promote gut motility and the growth of favorable flora such as *Bifidobacterium* and *Lactobacillus*. Some groups have even tried administering enteral bovine-derived IgG targeting certain enteral bacteria [33]. Other compounds such as plant polyphenols are also being

investigated. Currently, prebiotics are not recognized as a class by the US Food and Drug Administration (FDA) and are classified under fiber, either soluble, insoluble nondigestible, lignin, or synthetic nondigestible.

Clinical Evidence

The above discussion has focused on a basic science theoretical overview of why immunonutrition interventions are potentially useful. In vitro and animal experiments suggest immunonutrition could work. The clinical evidence in humans, however, is disappointingly mixed, with most trials and meta-analyses showing minimal to no overall benefit. Some immunonutrition interventions have even appeared to cause harm. The discrepancy between theory and empiric evidence has been attributed to multiple flaws: underpowered study populations, imprecise or conflicting interventions, few standardized dosings or formulations, heterogenous inclusion/exclusion of the seven components of immunonutrition, variance in the timing of intervention, wide alterations in nutritional standards for the control arms, industrial conflicts of interest, inadequate patient selection, improving critical care standards over the past two decades, and overall immature understanding of the complexities of manipulating the neuroendocrine immunoinflammatory supersystem [19, 20, 34, 35].

One proposed solution to the literature's heterogeneity has been to focus future research on targeted immunonutrition interventions and dosages for particular patient populations, a concept called pharmaconutrition [36, 37]. Accordingly, instead of examining all pieces of a conflicting literature of over 200 clinical trials and over 16 meta-analyses capably reviewed elsewhere [20], here will be presented an overview of the clinical evidence for immunonutrition for patient populations treated by surgeons. The elective surgical patient population has accrued the most data. Studies in the critically ill have been published to a lesser extent. Patients with cancer, trauma, traumatic brain injury, burns, obesity, pancreatitis, transplant, inflammatory bowel disease, as well as pediatric patients have also been studied.

After surveying the evidence, the chapter concludes by examining the current guidelines for immunonutrition from the Society of Critical Care Medicine (SCCM), the American Society for Parenteral and Enteral Nutrition (ASPEN), the European Society for Clinical Nutrition and Metabolism (ESPEN), and the Canadian Critical Care Practice Guidelines (CCCPG) [38–40].

Elective Surgery

The best data supporting the use of immunonutrition come from elective surgical patients, especially for gastrointestinal surgeries. Pancreatic, cardiac, and head and neck surgery cohorts have also been studied in the elective setting. Perhaps this segment of the literature is strongest because the patients have all suffered a fairly well-defined insult, and the interventions are mostly confined to synergistic combinations of arginine and omega-3 fatty acids. Study populations have included patients in the hundreds, with meta-analyses often citing over 2000 patients [20]. Until 2014, the literature seemed to support a consensus that immunonutrition with arginine and omega-3 fatty acids in elective surgery patients leads to (1) a substantial decrease in infectious complications, (2) a decreased hospital length of stay, (3) possibly a decreased rate of anastomotic dehiscence, but (4) no change in mortality [41–47]. These benefits appeared to be largest when supplementation was provided both pre- and postoperatively and smallest when the patient was already well nourished. As an example, one widely cited meta-analysis compared arginine-supplemented enteral nutrition to standard enteral nutrition. This study showed infectious complications significantly reduced to a risk ratio (RR) of 0.59 with 95% confidence interval (CI) 0.50–0.70 with $p < 0.00001$, and hospital stay decreased by a weighted mean difference (WMD) of −2.38 days (95% CI −3.42 to −1.34, $p < 0.00001$) [47]. The meta-analysis is also notable for the fact that its first author received a research grant as principal investigator

from Nestlé, and the fifth author was medical director for Nestlé, which manufactured an immunonutrition supplement favored heavily in the analysis.

As optimistic as the above data appear at first glance, there is reason for continued skepticism, as highlighted by a smaller meta-analysis from 2014 [48]. Reduced in scope to include only trials examining preoperative interventions with control groups having either standard diet or standard diet plus an oral nutrition supplement, the 2014 meta-analysis concluded that the benefit signal for immunonutrition disappeared when the control was a non-immunomodulating nutrition supplement. Immunonutrition was associated with all infectious complications by an odds ratio (OR) of 0.71 (95% CI 0.30–1.68, $p = 0.44$) and hospital length of stay by WMD 0.07 days (95% CI −2.29 to 2.43, $p = 0.96$). The benefit for immunonutrition reappeared compared with controls of standard diet, no supplement. This suggests that giving any protein containing supplement preoperatively may help prevent infection and that no special immune-modulating properties were responsible for the benefits seen in other studies. Alternatively, many non-immunomodulating supplements already contain variable concentrations of antioxidants and amino acids, and except in a few instances, there are no clear threshold dosages at which immunonutrients begin to be effective. Similar to other studies, the 2014 meta-analysis was notable for author involvement with industry. The third author received educational grants from both Nestlé and Abbott Laboratories. The first and second authors were full-time employees of Abbott Laboratories. Each company produces both immunonutrition and non-immunomodulating oral nutrition supplements.

At the individual trial level, there are further criticisms of this literature. Few trials report follow-up to 30 days, a relevant time point considering the primary outcome of infectious complications [46]. Similarly sparse is the reporting of how much intervention and/or control nutrition was actually tolerated by gastrointestinal surgery patients, who are often intolerant of early diets [46]. Many trials used in these meta-analyses have not well delineated the preoperative nutrition status of the patient, and since gastrointestinal surgery is often performed in context of cancer, some authors have characterized these trials as nutrition vs malnutrition, with obvious result [48]. The nutrition vs malnutrition signal is only amplified by trials which did not use isocaloric, isonitrogenous control groups. Lastly, there was a particularly active research group in Europe characterized as having a disproportionate influence on the meta-analyses. The group was suspected of publishing multiple reports on the same patients to the extent several of their trials were excluded from at least one meta-analysis [49].

Critical Illness and Sepsis

The immunonutrition literature in critical illness shares many of the weaknesses as the elective surgery literature. Early small, single-center studies seemed to show immunonutrition administration improved length of stay and infection rate, with no change in mortality; later studies seem to show no benefit, even suggesting harm [20]. Indeed, in critically ill patients when the immune system is most dysregulated is where the physiologic effects of immunonutrition are least understood and their overall effects most debated. An exhaustive review is beyond the scope of this chapter, but it is useful to examine four prominent examples which frame this debate.

The REDOXS (REducing Deaths due to Oxidative Stress) trial [50], published in the New England Journal of Medicine in 2013, was a large blinded, randomized controlled trial of 1223 patients from 40 ICUs in Europe and North America which found increased mortality with glutamine supplementation. Patients on mechanical ventilation with two or more failing organ systems were eligible and randomized within 20 h of ICU admission to receive (1) glutamine, (2) antioxidants, (3) both, or (4) placebo. Glutamine was given intravenously (IV), as was the antioxidant selenium. Other antioxidants were given enterally: vitamin E and C, beta-carotene, selenium, and zinc. Patients received

supplemental intervention along with standard enteral nutrition according to Canadian guidelines in just over 20 h from the first organ dysfunction. Although the intervention and control groups were similar, the patients underlying disease were heterogenous. The diseases were mostly medical (79%), with shock etiology primarily septic (68%) and then cardiac (20%). There were no differences in primary outcome of mortality at 28 days for any intervention. However, glutamine was associated with significantly increased mortality at 6 months (44% vs 37% $p = 0.02$) and increased time to discharge alive (median 51.0 days vs 40.1 days $p = 0.03$), which was not due to infections or organ failure. Plasma levels of glutamine and selenium were tested only for a subset of 66 patients. Plasma levels were normal before the intervention (contrary to contemporary hypotheses in sepsis) and increased with supplementation but still within normal ranges. This trial has been discussed extensively. Criticisms include supplement dosing at the high end of therapeutic range and not accounting for increased amino acid loads on failing organs in shock, particularly the liver and kidneys [19]. After REDOXS, in 2014 the European randomized controlled trial METAPLUS [51] on mechanically ventilated patients detected increased 6-month mortality with enteral supplementation of glutamine, antioxidants, and omega-3 fatty acids. Although REDOXS and METAPLUS focused on glutamine, selenium, and omega-3 fatty acids, since the publication of these two trials, clinicians have since been wary of initiating all types of immunonutrition for patients in shock [52].

The OMEGA trial [53] published in the *Journal of the American Medical Association* in 2011 was a large double-blinded randomized controlled trial of 272 patients in 44 ICUs from the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. This trial administering omega-3 fatty acids was stopped early for futility and increased mortality. Patients on mechanical ventilation meeting criteria for ARDS and in need of enteral nutrition were eligible. In addition to standard enteral nutrition, within 6 h of randomization, patients were to receive twice daily a bolus of either (1) omega-3 fatty acids, antioxidants, and gamma linolenic acid (a complementary omega-6 fatty acid) or (2) an isocaloric isovolumic control composed of carbohydrates, not lipids. The leading etiologies for ARDS were pneumonia followed by sepsis (52% and 23%, respectively). The omega-3 group spent more time on the ventilator compared with the control patients; the omega-3 group had 3.2 fewer ventilator-free days (95% CI −5.8 to −0.7, $p = 0.02$), which was the primary endpoint. The omega-3 group also spent more time in the ICU, with 2.7 fewer ICU-free days (95% CI −5.1 to −0.3, $p = 0.04$), and experienced a non-statistically significant increased mortality before discharge (27% vs 16%, $p = 0.054$, adjusted for ARDS covariates 25% vs 18%, $p = 0.11$). The omega-3 group showed an expected eightfold increased concentration in plasma omega-3 levels, but no change in inflammatory biomarkers. There were no differences in infectious complications, but omega-3 patients did experience significantly more diarrhea. Similar to the REDOXS trial, the OMEGA trial called previous findings into question. It had been shown that patients with ARDS have omega-3 extremely low levels to 6% of normal, and basic science data suggested there would be a benefit to improving those levels in ARDS [53]. Prior to the OMEGA trial, three smaller trials had found multiple benefits for ARDS patients given omega-3 supplements, including improved oxygenation, ventilator time, ICU time, and mortality. However, the control groups in these three prior trials were administered nutrition containing omega-6 and omega-9 fatty acids. Theoretically, omega-6 and omega-9 fatty acids can be converted into pro-inflammatory mediators, potentially making the control groups sicker, giving the omega-3 intervention an apparent advantage. On the other hand, the three prior trials supplied their supplement continuously as opposed the OMEGA trial where the twice-daily boluses may have resulted in an inadvertent negative effect. Furthermore, on closer inspection, the control supplement in the OMEGA trial contained a larger quantity of protein (20 g vs 4 g) which may have given the control group an unintended

health benefit over the omega-3 group. Until more data accrue, clinicians should remain cautious with lipid supplementation for patients at risk for ARDS.

Probiotics in critical illness have been gaining traction. A recent meta-analysis in a diverse group of ICU patients showed no influence on mortality, mechanical ventilation, or length of stay but were associated with reduced ICU-acquired pneumonia (OR 0.58; 95% CI 0.42–0.79) and decreased ICU stay by 1.49 days (95% CI −2.12 to −0.87) [54]. However, the most cited reason for caution using probiotics in critically ill patients is concern for infectious complications. There has been no cited bacteremia with the use of probiotics, but a particular strain of yeast, *Saccharomyces boulardii*—a subset of *Saccharomyces cerevisiae*—was associated with several episodes of fungemia in the late 1990s [55]. In the most commonly cited series from France, patients with a mean age of 65 (range 50–82) who received *Saccharomyces boulardii* treatments between 4 and 14 days experienced fungemia between days 8 and 35 with a mean fever of 39.3 °C. One patient developed fungemia without receiving the probiotic treatment, but it was hypothesized that caregivers opening the probiotic packets contaminated their hands and subsequently manipulated the patient's central line. Three of the seven patients died, but the team could not directly attribute their deaths to the fungemia. Besides direct central line contamination, patient colonization and gut translocation were proposed as possible mechanisms. This complication of fungemia, although confined to a particular strain and case series, ensures that probiotic administration will probably face a higher burden of proof before its use becomes more widespread for critically ill patients. Prebiotics such as fiber, on the other hand, are already being recommended for critically ill patients, even if only for their effects on feeding tolerance and diarrhea. In the latest ASPEN guidelines, three of the five small randomized controlled trials of fiber-supplemented enteral nutrition found decreased diarrhea in the fiber group [38]; one of the studies found mean frequency of diarrhea days as low as 8.8 ± 10.0% vs 32.0 ± 15.3% ($p = 0.001$) [56].

Pharmacological use of the antioxidant vitamin C in sepsis is still under early investigation, a full review of which is beyond the scope of this chapter. It is worthwhile to refer readers to three commonly cited, intriguing studies. The first study was a phase 1 safety trial in 24 severely septic patients showing tolerability and reduced inflammatory biomarkers with IV vitamin C [57]. The second study was a nonsequential, retrospective study of 47 patients administered with hydrocortisone, vitamin C, and thiamine showing improved mortality, organ failure scores, and vasopressor weaning [58]. The third study was a double-blind randomized controlled trial in 28 patients who received either IV vitamin C or placebo which showed improvement in primary endpoint of vasopressor requirements and the secondary endpoint 28-day mortality [59].

Although not a component of immunonutrition per se and also beyond the scope of this chapter, glucose should not be omitted in a discussion of immunomodulatory molecules. It is well documented that hyperglycemia impairs multiple aspects of the immune system. After several landmark studies, the standard of care for hospitalized patients rightfully prioritizes avoidance of hypoglycemia and errs toward hyperglycemia. However, any clinician prescribing nutrition, much less trying to use immunonutrition strategies, would do well to avoid hypercaloric alimentation. The excess glucose will surely be counterproductive to whatever other immunotherapeutic strategies may be attempted. A target blood glucose level below 180 mg/dL is recommended [60].

Cancer

The immune system in cancer patients is impaired both from being unable to recognize and fend off the cancer and secondarily suppressed from anticancer therapies, especially chemoradiation. Often cancer patients suffer from malnutrition and cachexia from a dysregulated immunoinflammatory system, so correcting two problems at

once with immunonutrition is appealing. At the same time, the biology of cancer is complex, and despite newer evidence, some practitioners continue to have concerns that interventions to boost the immune system may aid rapidly dividing cancer cells, especially considering their known avidity for supplemental glutamine in vitro [14, 61].

Immunonutrition during chemoradiation has been studied in four trials in head, neck, and esophageal cancer [62–65]. Various combinations of arginine, glutamine, antioxidants, and omega-3 fatty acids were used, but the outcome measures were confined to biomarkers of immune function. Only one examined higher level clinical outcomes; in the immunonutrition vs standard nutrition arm, weight increased by 2.1 kg and performance status remained stable instead of declining. A recent meta-analysis found no overall benefit of immunonutrition in head and neck cancer patients, except for a weak association with reduced fistula formation [66]. There have been multiple trials using glutamine to reduce stomatitis during chemotherapy with apparently no adverse effects; there is some conflicting evidence that parenteral glutamine is more effective than enteral [14]. Fatty acid supplement composition for cancer patients has not yet been examined in clinical trials [67]. Trials of vitamin, mineral, and antioxidant supplementation at high dosage have been conducted in cancer patients with no benefit and occasional harm, such as with selenium increasing mortality by 2.6 in early prostate cancer patients and beta-carotene and tocopherol increasing lung cancer incidence in smokers [67]. The best evidence for immunonutrition in cancer patients is probably from the elective GI surgery literature, which, as discussed above, remains conflicted.

Trauma

The neurohormonal changes of the trauma patient, the inflammatory cytokine milieu, and the susceptibility to infection have given investigators reason to hope immunonutrition would be effective therapy in the trauma patient population. The data for elective surgical patients are relevant but may not be directly extrapolated to trauma surgical patients. A randomized controlled trial won attention in 1998 showing a statistically significant decrease in pneumonia, bacteremia, and sepsis in 29 trauma patients on enteral nutrition supplemented with glutamine versus 31 patients on standard enteral feeding [68]. A later 2008 meta-analysis of eight studies with a total of 372 trauma patients in the intervention groups from 1994 to 2005 showed no effect on mortality, new infection, or length of hospital stay. This study faced the common criticism that a variety of combinations of arginine, glutamine, and fish oils were being compared. In contrast, antioxidants and trace minerals do appear to be associated with a reduction in mortality in the trauma subgroup of the recent ASPEN meta-analysis (RR 0.8; 95% CI 0.7–0.92, $p = 0.001$) [69], and the benefit may be seen more clearly when administered early. Prophylactic alpha-tocopherol and ascorbic acid administration within 24 h of injury decreased organ failure (RR 0.43; 95% CI 0.19–0.96) in a 2002 randomized controlled trial of over 540 trauma patients [70]. Probiotics seem to provide some benefit. In a heterogenous trauma population in a 2013 meta-analysis of five trials, various combinations of probiotics were associated with reduced nosocomial infections (RR 0.65; 95% CI 0.45–0.94, $p = 0.02$), ventilator-associated pneumonia, and ICU stay, but no change in mortality [71]. In trauma as elsewhere for immunonutrition, the data are conflicted, and more are needed. Current clinical guidelines are summarized below [38–40].

Traumatic Brain Injury

Traumatic brain-injured patients often have a plethora of other injuries which confound analysis of this subgroup. One small trial of 20 patients supplemented with glutamine and probiotics found a reduction in infections, mechanical ventilation, and length of stay [72]. There is preclini-

cal evidence for the role of omega-3 fatty acids in neurological inflammation, particularly in their transformation to resolvins. However, the clinical evidence has been mostly case reports. Although omega-3 fatty acids appear to be safe even in anticoagulated patients, clinicians should remain alert for hemorrhagic stroke in this population [73]. ASPEN guidelines state that based on expert consensus, arginine or fish oils should be considered for traumatic brain-injured patients; ESPEN guidelines do not detail this population as a subgroup [38, 39].

Burns

The largest research focus on immunonutrition in burns has been on supplementary glutamine, where in small trials evidence has been largely positive. A commonly cited example is a 2003 Canadian single-center double-blind randomized control trial of 45 patients who were randomized to receive enteral glutamine supplement every 4 h or an isonitrogenous control of asparagine, aspartic acid, and glycine [74]. The average total body surface area burn was around 40%, and the average age was close to 40 years old. Patients receiving glutamine had decreased bacteremia (1.2 vs 4.3 days/patient, $p < 0.05$) and decreased mortality (2 vs 12, $p < 0.05$), despite no changes detected in serum glutamine concentration, neutrophil phagocytosis function, or biomarkers. The authors believed glutamine's main effect was on the gut mucosa. Other small trials more or less echo these positive results; a Cochrane review of seven such trials suggests glutamine can reduce both length of stay and mortality ($p < 0.0001$ and $p = 0.002$, respectively). However the study populations are so small the Cochrane authors suggest the evidence is too weak to recommend routine use [75], leaving burn practitioners to choose between a small body of literature suggesting benefit for burn patients and a larger body of literature suggesting glutamine can harm critically ill patients. To help solve this dilemma, the authors of the REDOXS trial are recruiting for the RE-ENERGIZE trial (RandomizEd trial of ENtERal Glutamine to minimIZE thermal injury) expected to accrue by 2021. The planned study is an international 80-center double-blind randomized controlled trial of 2700 patients with deep second- or third-degree burns of greater than 10–20%, depending on the patient age, to receive either enteral glutamine or isocaloric maltodextrin. The study is powered for a primary endpoint of 6-month mortality and will likely carry important implications for the future of immunonutrition in general [76].

Antioxidants have some literature supporting their use for burn patients. Due to massive potential for exudative losses, burn patients often have clinical deficiencies of selenium, iron, copper, and zinc. Supplementing these trace minerals and antioxidants has shown benefit in small studies [27, 77]. Vitamin C infusion IV was shown in a small non-blinded study of 37 patients of total body surface area burns >30% to reduce initial 24 h fluid resuscitation requirements compared to controls [3.0 ± 1.7 mL/kg per percentage of burn area vs 5.5 ± 3.1, respectively ($p < 0.01$)] [78]. Fluids were titrated to hemodynamic stability and urine output 0.5–1.0 cc/kg/h. This difference in fluid requirement was observed until the third 24-h period, but the difference in body weight continued to increase until day 7, giving control patients a threefold greater weight gain than the vitamin C infusion patients. Further work has been done in animals but apparently not in humans, perhaps awaiting greater clarity from the literature on the use of vitamin C in septic patients.

In the 1990s there was interest in the use of ornithine alpha-ketoglutarate (OKG) as immunonutrition for burn patients. Theoretically OKG can serve as a substrate to make either glutamine, arginine, or proline. Since proline hydroxylation is the rate-limiting step for collagen synthesis, which is especially important in burn patients, it was reasonable to hope OKG administration would be useful [79]. However, after three randomized trials from 1998 to 2000 which showed improved wound healing but no change in mortality, ornithine alpha-ketoglutarate has not

sparked any new trials or changes in recommendations [40].

Obesity

Obesity implies a neuroendocrine dysregulation at baseline. Some have suggested that with increased inflammatory markers, obesity represents a low-level systemic inflammatory response syndrome (SIRS) state. The microbiome in obesity is known to be dysregulated from classic experiments in mice, wherein microbiota transplanted from obese mice to normal mice recapitulated the obese phenotype [80]. The rationale for immunonutrition in obese patients has been reviewed [81], but dedicated inpatient clinical data have yet to accrue for this population [82].

Pancreatitis

Pancreatitis represents as a wide spectrum of disease. Patients with moderate to severe acute pancreatitis often fall into the category of critical illness. Given the concerns for critically ill patients discussed above, impetus to trial pancreatitis patients with immunonutrition is currently limited. However, with the shift to early enteral feeding in acute pancreatitis in the 2000s, some trials of immunonutrition in acute pancreatitis were performed which showed some benefit. One randomized controlled trial of 31 patients with acute pancreatitis which administered arginine, glutamine, and antioxidants noted nonsignificant improvement in biomarkers ($p = 0.220$) and a 2-day decrease in enteral feeding time ($p = 0.332$) [83]. Another randomized controlled trial of 28 patients using omega-3 immunonutrition found that enteral feeding decreased by 7 days ($p < 0.05$) and hospital stay decreased by 6 days ($p < 0.05$) [84]. A larger double-blinded randomized controlled trial in China in 2013 of 183 patients found two species probiotic supplementation plus standard enteral nutrition significantly reduced pancreatic sepsis by 5%, multiple organ failure by 8%, and mortality by 2% compared to enteral nutrition alone [85]. However this report must be tempered by the earlier 2008 PROPATRIA study (PRObiotics in PAncreatitis TRIAl) a multicenter double-blinded randomized controlled trial of twice-daily six species probiotic vs placebo [86]. PROPATRIA investigators found no decrease in the primary outcome of infections, but instead found substantially increased mortality in the probiotics group (RR 2.53; 95% CI 1.22–5.25) as well as increased bowel ischemia (9/152 vs 0/144, $p = 0.004$). Explanations for these alarming results include administering the probiotic too late after organ failure onset (up to 72 h), underdosing the probiotic, and inclusion of a fermentable carbohydrate supplement. The carbohydrate was originally intended to help establish the probiotic colonies, but instead it may have resulted in increased acidosis [87]. In acute pancreatitis where enteral nutrition is not an option, parenteral nutrition containing glutamine or omega-3 fatty acids may be superior to standard parenteral nutrition in terms of infectious complications, length of stay, and mortality, according to the most recent meta-analysis of 7 studies with a total 266 patients [88]. Further data are needed.

Solid Organ Transplant

Immunonutrition in transplant could provide obvious theoretical benefits boosting the immune suppression to reduce infection but is complicated by the competing priority of intentional immunosuppression. Immunonutrition data in transplant patients are small in scale at present. Liver transplant patients have been the predominant focus given their preoperative immunocompromised, complex malnutritional state and predisposition to infections postoperatively. A Cochrane review in 2012 for nutritional interventions in liver transplantation patients found the literature too limited to make recommendations or a meta-analysis [89]. Regarding

immunonutrition, 3 studies were identified with a total 150 patients. Two showed slightly decreased length of stay for glutamine and omega-3 supplementation, and the third showed no increased risk of rejection for an omega-3 supplement [89]. Since that publication a double-blind randomized controlled trial of perioperative arginine, omega-3 fatty acids, and nucleotides in 120 liver transplantation patients showed no interventional benefit [90]. A retrospective study of pre- and probiotics has detected reduced infectious complications (3/34 vs 10/33, $p = 0.03$) in liver transplant patients [91]. Immunonutrition has been studied to a greater extent in bone marrow transplant patients, with some benefits such as decreased graft versus host disease in one meta-analysis [92], but these patients are not usually under the care of a surgical team. With the current state of immunonutrition literature in nontransplant critically ill and elective surgery patients, there is little impetus to trial immunonutrition in the context of transplant, where long-term outcomes are just as crucial as short-term outcomes.

Inflammatory Bowel Disease

The pathogenesis of the inflammatory bowel diseases Crohn's disease (CD) and ulcerative colitis (UC) is complex and springs from the interplay of genetics, immunity, diet, and the microbiome. Nutritional strategies to manipulate this interplay have been successful in animal models but have had more equivocal results in humans [93]. At least twelve Cochrane meta-analyses with one or two revisions apiece have been published on immunonutrition efficacy at induction of remission or maintenance of remission in CD or UC. Therapies have included glutamine [94], omega-3 fatty acids [95–97], probiotics [98–101], fecal transplant [102], and even helminths [103]. Small studies of low signal lead these meta-analyses when they can be performed to echo the same conclusions seen above: immunonutrition does not appear to provide benefit, or there are too few data to show a clear benefit. Results with non-immunonutrition diets such as low-calcium diet, highly restricted organic diet, and low-refined-carbohydrate diet are also equivocal [104]. Similarly, elemental or semi-elemental enteral nutrition does not result in a significant difference inducing CD remission in pediatric patients, but it might still be a reasonable option if these children cannot tolerate steroids according to one meta-analysis [105].

Pediatric Population

The same inconclusive results of immunonutrition interventions are seen in the general pediatric population. At least nine studies have been conducted to date, each with varying combinations of glutamine, arginine, omega-3 fatty acids, antioxidants, or fibers. They have been mostly underpowered and only show a difference in inflammatory biomarkers without any clinical differences in the intervention arms [106]. In 1 trial of 293 pediatric patients using glutamine and antioxidants versus whey protein, an immunocompromised subgroup experienced reduced infection [107, 108]. Citing this lack of data and a potential for harm, ASPEN and the SSCM in 2017 issued a "strong" recommendation on "moderate evidence" that immunonutrition not be administered to critically ill pediatric patients [106].

Current Guidelines and Recommendations

As befitting such a mixed body of clinical evidence, the current guidelines and recommendations for use of immunonutrition are still guarded. The reader should note that the bulk of these guidelines are geared toward critically ill patients, though some crossover with other patient populations is appropriate. As emphasized by the guideline-making organizations themselves, these

guidelines are not a substitute for the educated judgment of the onsite provider on behalf of a specific patient.

For critically ill adult patients in the United States, the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) periodically update their guidelines every 3–5 years [38, 109]. The latest guidelines were published in 2016 using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system to define level of evidence. The relevant sections regarding immunonutrition are summarized as follows.

ASPEN/SCCM 2016 Summarized Recommendations for Immunonutrition (*Level of Evidence*)

- Routine use of specialty formulas should be avoided (*Expert consensus*).
- Immunonutrition (including arginine, glutamine, nucleic acids, and omega-3 fatty acids) should not be routinely used in the medical ICU (*Very low*).
- Immunonutrition (including arginine, glutamine, nucleic acids, and omega-3 fatty acids) should not be routinely used in severe sepsis (*Moderate*).
- Immunonutrition may benefit obese patients, but no recommendation is possible with lack of data (*Expert consensus*).
- Immunonutrition with arginine and fish oils should be considered for postoperative surgical ICU patients on enteral nutrition (*Moderate to low*).
- Immunonutrition with arginine and/or fish oils appears promising in moderate to severe pancreatitis, but data are insufficient to make recommendation at this time (*Very low*).
- Immunonutrition with arginine and fish oils should be considered in severe trauma (*Very low*).
- Immunonutrition with arginine or fish oils should be considered in traumatic brain injury (*Expert consensus*).
- Neither enteral nor parenteral glutamine should be used routinely (*Moderate*).
- Antioxidants and fish oils supplementation in ARDS has too much conflicting literature to make a recommendation (*Low to very low*).
- Antioxidant vitamins and trace minerals should be provided to patients on enteral nutrition (*Low*).
- Selenium, zinc, and antioxidant supplementation in severe sepsis has too much conflicting literature to make a recommendation (*Moderate*).
- Probiotics appear to be safe but should only be used in the patient populations where studies show benefit. Routine use cannot be recommended at this time (*Low*).
- Probiotics should be considered for patients with severe acute pancreatitis on enteral nutrition (*Low*).
- Hemodynamically stable MICU and SICU patients on enteral nutrition should be considered for 10–20 gm/day of soluble fiber supplementation (*Expert consensus*).

In Europe, the European Society for Clinical Nutrition and Metabolism (ESPEN) last updated their guidelines in 2018 for critically ill patients and in 2017 for surgical patients. Unlike ASPEN, ESPEN does not use the GRADE system for level of evidence; the Scottish Intercollegiate Guidelines Network (SIGN) system is used instead. Relevant sections regarding immunonutrition are summarized as follows [39, 60].

ESPEN 2018 Summarized Recommendations for Immunonutrition in Critical Illness (*Level of Evidence*)

- Glutamine should not be given to ICU patients except burn and trauma patients (*Grade B*).
  - Burn patients with >20% total body surface area burns should receive 0.3–0.5 g/kg/day for 10–15 days (*Grade B*).
  - Trauma patients should receive 0.2–0.3 g/kg/day for 5 days, extended to 10–15 days for prolonged wound healing (*Grade 0*).

  - Parenteral glutamine should not be given to unstable patients with renal or liver failure (*Grade A*).
- Omega-3 fatty acids should not be given routinely and should not be given by bolus (*Grade B*).
- Omega-3 fatty acids can be provided both enterally and parenterally (*Grade 0*).
- Antioxidants at high dose should not be given without first proving a deficiency, but micronutrients and vitamins should be routinely given in parenteral nutrition (*Grade B*).

ESPEN 2017 Summarized Recommendations for Immunonutrition in Surgical Patients (*Level of Evidence*)

- Nutrition with supplemental arginine, omega-3 fatty acids, and nucleotides should be provided at least postoperatively if the patient is malnourished and if the surgery is a major cancer surgery (*Grade B*).
- Preoperatively, immunonutrition supplements alone have no clear demonstrated advantage over standard supplements, but they can be administered 5–7 days before operation (*Grade 0*).
- Arginine-supplementation alone either enterally or IV has insufficient evidence to recommend use (*Grade 0*).
- Glutamine supplementation IV may be considered if the patient requires parenteral nutrition (*Grade B*).
- Glutamine supplementation alone given orally has insufficient evidence to recommend use (*Grade 0*).
- Omga-3 fatty acids should be given IV only if the patient requires parenteral nutrition (*Grade B*).

The CCCPG for Nutrition in critically ill patients were first published in 2003 and were updated in 2013 and 2015; relevant sections regarding immunonutrition are summarized as follows [40, 110, 111].

CCCPG 2015 Summarized Recommendations for Immunonutrition

- Arginine: Do not recommend for critically ill patients.
- Glutamine: Do not give enteral or IV glutamine to critically ill patients.
- Fish oils: Insufficient data to recommend fish oils alone in critically ill patients. An enteral formula with fish oils and antioxidants should be considered in patients with ALI and ARDS.
- Selenium: Do not recommend administering on its own or with other antioxidants for critically ill patients.
- IV vitamin C: Insufficient data to make recommendation for critically ill patients.
- Probiotics: Should be considered for critically ill patients.

The story of immunonutrition is incomplete without considering the influence of cost and commercial interests, especially given the nutrition industry's pervasive participation in the literature above. Eleven of the sixteen meta-analyses reviewed by Roehl had notable nutrition industry conflicts of interest [20]. Much of the interest and investment in immunonutrition was to cut down on hospital stay, infections, and overall cost, but commercial immunonutrition products are often more expensive than standard formulae. Table 14.1 is an update from multiple summaries of commercially available immunonutrition products in alphabetical order [20, 112, 113]. Prices where available were obtained directly from the company websites during March 2019. In the case of Abbott Laboratories, the prices cited are from the Medicare rates sheet. The product list is not exhaustive. It should also be noted that for every brand name, multiple variations of the product are also currently on the market. Several products unable to be found on the manufacturer's website were included for their prior appearance in the literature; historical composition is from sources [20, 112, 113]. For

Table 14.1 Commercially available and historical immunonutrition products

Product	kcal/mL	Arginine (g/L)	Glutamine (g/L)	EPA + DHA (g/L)	Nucleotides (g/L)	Fiber (g/L)	Selenium (mcg/L)	Selected antioxidants	Cost per 1000 kcal (USD)
Abbott AlitraQ	1.0	2.6	14.2	0	0	0	50	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin	Not available in the USA
Abbott Oxepa	1.5			6.5			74	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin, beta-carotene	12.22
Abbott Perative	1.3	8				6.5	63	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin, beta-carotene	19.10
Abbott Pivot 1.5	1.5	13	7.6	3.7		7.5	70	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin, beta-carotene	19.10
Abbott Vital AF 1.2	1.2			3.8		5.1	68	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin	19.10
Fresenius-Kabi Intestamin	0.5		60			0	600	Vitamins C, E, zinc, beta-carotene	Not available in the USA
Fresenius-Kabi Reconvan	1.0	6.7	10	2.5		0			Not available in the USA
Fresenius-Kabi Supportan	1.5			5.0		12	135	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, beta-carotene	Not available in the USA
Nestlé Impact	1.0	12.5		1.7	1.2		100	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin, beta-carotene	40.00
Nestlé Peptamen AF	1.2			2.4		6	80	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin, beta-carotene	27.22
Nestlé Tolerex	1.0	2.4	3.5	3.7			39	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin	24.11
Nestlé Vivonex Plus	1.0	5	10				40	Vitamins A, E, C, zinc, copper, molybdenum, chromium, manganese, riboflavin	35.19
Nutricia Pro-Stat Sugar Free AWC	3.3	110						Vitamin C, zinc	16.99
Abbott Optimental	1.0	5.5	0	3.26	0				Discontinued?
McGraw Inc. Immun-Aid	1.0	15	12	0	1.0		100		Discontinued?
Nutricia Stresson	1.25	9	13.4	1	0		140		Discontinued?

currently available products, only information available to the general public on the company website is presented.

Conclusion

Looking toward the future, it is possible that all nutritional intervention will be reshaped by the growing knowledge of the host/microbiome interaction. It is possible that immunonutrition as a separate entity will be subsumed into this wider view of the problem, and when immunonutrition concepts are applied, they will be applied more selectively to a particular patient's situation. For the present, clinical applications remain guarded. The prudent clinician should remain skeptical, still echoing Hippocrates, "In food excellent medication, in food bad medication, bad and good relatively" [1]. But if the past is any guide, clinical interest in trying to modulate a malfunctioning neuroendocrine immunoinflammatory supersystem will cycle back in vogue at least once during the reader's career.

References

1. Cardenas D. Let not thy food be confused with thy medicine: the Hippocratic misquotation. e-SPEN J. 2013;8(6):e262.
2. Gratzer WB. Terrors of the table: the curious history of nutrition. Oxford: Oxford University Press; 2006.
3. Arnold M, Barbul A. Nutrition and wound healing. Plast Reconstr Surg. 2006;117(7 Suppl):58S.
4. Grimble GK. Adverse gastrointestinal effects of arginine and related amino acids. J Nutr. 2007;137(6 Suppl 2):1701S.
5. Tong BC, Barbul A. Cellular and physiological effects of arginine. Mini Rev Med Chem. 2004;4(8):823–32.
6. Wijnands KA, Castermans TM, Hommen MP, Meesters DM, Poeze M. Arginine and citrulline and the immune response in sepsis. Nutrients. 2015;7(3):1426–63.
7. Hesterberg RS, Cleveland JL, Epling-Burnette PK. Role of polyamines in immune cell functions. Med Sci. 2018;6(1):22.
8. Witte MB, Barbul A. Arginine physiology and its implication for wound healing. Wound Repair Regen. 2003;11(6):419–23.
9. Altman BJ, Stine ZE, Dang CV. From Krebs to clinic: glutamine metabolism to cancer therapy. Nat Rev Cancer. 2016;16(10):619–34.
10. Smith RJ. Glutamine metabolism and its physiologic importance. JPEN J Parenter Enteral Nutr. 1990;14(4 Suppl):44S.
11. Kreider ME, Stumvoll M, Meyer C, Overkamp D. Steady-state and non-steady-state measurements of plasma glutamine turnover in humans. Am J Physiol. 1997;35(4):E621.
12. Curi R, Lagranha CJ, Doi SQ, Sellitti DF, Procopio J, Pithon-Curi TC, et al. Molecular mechanisms of glutamine action. J Cell Physiol. 2005;204(2):392–401.
13. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients. 2018;10(11):1564.
14. Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. Eur J Nutr. 2010;49(4):197–210.
15. Suchner U, Kuhn KS, Fürst P. The scientific basis of immunonutrition. Proc Nutr Soc. 2000;59(4):553–63.
16. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochem Soc Trans. 2017;45(5):1105–15.
17. Calder PC. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. Lipids. 2003;38(4):343–52.
18. Bistrian BR. Practical recommendations for immune-enhancing diets. J Nutr. 2004;134(10 Suppl):2872S; discussion 2895S.
19. Soeters P, Bozzetti F, Cynober L, Elia M, Shenkin A, Sobotka L. Meta-analysis is not enough: the critical role of pathophysiology in determining optimal care in clinical nutrition. Clin Nutr. 2015;35(3):748–57.
20. Roehl K. Immunonutrition in 2016: benefit, harm, or neither? Pract Gastroenterol. 2016;40(8):27–40.
21. Berger MM. Can oxidative damage be treated nutritionally? Clin Nutr. 2005;24(2):172–83.
22. Carocho M, Ferreira IC. A review on antioxidants, prooxidants and related controversy: natural and synthetic compounds, screening and analysis methodologies and future perspectives. Food Chem Toxicol. 2013;51:15–25.
23. Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. Nutr J. 2016;15(1):71.
24. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219–23.
25. Victor VM, Rocha M, De la Fuente M. Immune cells: free radicals and antioxidants in sepsis. Int Immunopharmacol. 2004;4(3):327–47.
26. Sakuma S, Kitamura T, Kuroda C, Takeda K, Nakano S, Hamashima T, et al. All-trans Arachidonic acid generates reactive oxygen species via xanthine

dehydrogenase/xanthine oxidase interconversion in the rat liver cytosol in vitro. J Clin Biochem Nutr. 2012;51(1):55–60.
27. Berger MM. Antioxidant micronutrients in major trauma and burns: evidence and practice. Nutr Clin Pract. 2006;21(5):438–49.
28. Rayman MP. Selenium and human health. Lancet. 2012;379(9822):1256–68.
29. Tan H, Zhai Q, Chen W. Investigations of Bacteroides spp. towards next-generation probiotics. Food Res Int. 2019;116:637–44.
30. Meng M, Klingensmith NJ, Coopersmith CM. New insights into the gut as the driver of critical illness and organ failure. Curr Opin Crit Care. 2017;23(2):143–8.
31. Alverdy J, Krezalek M. Collapse of the microbiome, emergence of the pathobiome, and the immunopathology of sepsis. Crit Care Med. 2017;45(2):337–47.
32. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14:491–502.
33. McClave SA, Martindale RG. Why do current strategies for optimal nutritional therapy neglect the microbiome? Nutrition. 2019;60:100–5.
34. Bertolini G, Luciani D, Biolo G. Immunonutrition in septic patients: a philosophical view of the current situation. Clin Nutr. 2006;26(1):25–9.
35. Yeh D, Heyland D. Immune-enhancing diets: what is the final answer? Curr Trauma Rep. 2016;2(2):79–87.
36. Jones NE, Heyland DK. Pharmaconutrition: a new emerging paradigm. Curr Opin Gastroenterol. 2008;24(2):215–22.
37. Dupertuis Y, Meguid M, Pichard C. Advancing from immunonutrition to a pharmaconutrition: a gigantic challenge. Curr Opin Clin Nutr Metab Care. 2009;12(4):398–403.
38. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, 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. 2016;40(2):159–211.
39. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2018;38(1):48–79.
40. CCCS/CCCTG Committee on Knowledge Translation Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients 2015. Available at: https://www.criticalcarenutrition.com/resources/cpgs/past-guidelines/2015. Accessed 3 Nov 2019.
41. Waitzberg DL, Saito H, Plank LD, Jamieson GG, Jagannath P, Hwang TL, et al. Postsurgical infections are reduced with specialized nutrition support. World J Surg. 2006;30(8):1592–604.
42. Zheng Y, Li F, Qi B, Luo B, Sun H, Liu S, et al. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr. 2007;16(Suppl 1):253–7.
43. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. JPEN J Parenter Enteral Nutr. 2010;34(4):378–86.
44. Cerantola Y, Hubner M, Grass F, Demartines N, Schafer M. Immunonutrition in gastrointestinal surgery. Br J Surg. 2011;98(1):37–48.
45. Zhang Y, Gu Y, Guo T, Li Y, Cai H. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. Surg Oncol. 2012;21(2):87.
46. Marimuthu K, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery. Ann Surg. 2012;255(6):1060–8.
47. 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(3):99, 399.e1.
48. Hegazi RA, Hustead DS, Evans DC. Preoperative standard oral nutrition supplements vs immunonutrition: results of a systematic review and meta-analysis. J Am Coll Surg. 2014;219(5):1078–87.
49. Osland E, Hossain MB, Khan S, Memon MA. Effect of timing of pharmaconutrition (immunonutrition) administration on outcomes of elective surgery for gastrointestinal malignancies: a systematic review and meta-analysis. JPEN J Parenter Enteral Nutr. 2014;38(1):53–69.
50. 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.
51. van Zanten AR, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA. 2014;312(5):514–24.
52. van Zanten ARH, Hofman Z, Heyland DK. Consequences of the REDOXS and METAPLUS trials. J Parenter Enter Nutr. 2015 Nov;39(8):890–2.
53. Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA. 2011;306(14):1574–81.
54. 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.

55. Lherm T, Monet C, Nougiere B, Soulier M, Larbi D, Le Gall C, et al. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. Intensive Care Med. 2002;28(6):797–801.
56. Spapen H, Diltoer M, Van Malderen C, Opdenacker G, Suys E, Huyghens L. Soluble fiber reduces the incidence of diarrhea in septic patients receiving total enteral nutrition: a prospective, double-blind, randomized, and controlled trial. Clin Nutr. 2001;20(4):301–5.
57. Fowler AA, Syed AA, Knowlson S, Sculthorpe R, Farthing D, Dewilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014;12:32.
58. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest. 2017;151(6):1229.
59. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract. 2016;5(2):94–100.
60. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, Laviano A, Ljungqvist O, Lobo DN, Martindale R, Waitzberg DL, Bischoff SC, Singer P. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36(3):623–50.
61. Prieto I, Montemuiño S, Luna J, de Torres MV, Amaya E. The role of immunonutritional support in cancer treatment: current evidence. Clin Nutr. 2016;36(6):1457–64.
62. Machon C, Thezenas S, Dupuy A, Assenat E, Michel F, Mas E, et al. Immunonutrition before and during radiochemotherapy: improvement of inflammatory parameters in head and neck cancer patients. Support Care Cancer. 2012;20(12):3129–35.
63. Vasson MP, Talvas J, Perche O, Dillies AF, Bachmann P, Pezet D, Achim AC, Pommier P, Racadot S, Weber A, Ramdani M, Kwiatkowski F, Bouteloup C. Immunonutrition improves functional capacities in head and neck and esophageal cancer patients undergoing radiochemotherapy: a randomized clinical trial. Clin Nutr. 2013;33(2):204–10.
64. Talvas J, Garrait G, Goncalves-Mendes N, Rouanet J, Vergnaud-Gauduchon J, Kwiatkowski F, Bachmann P, Bouteloup C, Bienvenu J, Vasson MP. Immunonutrition stimulates immune functions and antioxidant defense capacities of leukocytes in radiochemotherapy-treated head & neck and esophageal cancer patients: a double-blind randomized clinical trial. Clin Nutr. 2014;34(5):810–7.
65. Sunpaweravong S, Puttawibul P, Ruangsin S, Laohawiriyakamol S, Sunpaweravong P, Sangthawan D, et al. Randomized study of anti-inflammatory and immune-modulatory effects of enteral immunonutrition during concurrent chemoradiotherapy for esophageal cancer. Nutr Cancer. 2014;66(1):1–5.
66. Howes N, Atkinson C, Thomas S, Lewis SJ. Immunonutrition for patients undergoing surgery for head and neck cancer. Cochrane Database Syst Rev. 2018;8:CD010954.
67. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11–48.
68. Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet. 1998;352(9130):772–6.
69. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, 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.). Crit Care Med. 2016;44(2):390–438.
70. 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.
71. Gu WJ, Deng T, Gong YZ, Jing R, Liu JC. The effects of probiotics in early enteral nutrition on the outcomes of trauma: a meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr. 2013;37(3):310–7.
72. Falcao de Arruda IS, de Aguilar-Nascimento JE. Benefits of early enteral nutrition with glutamine and probiotics in brain injury patients. Clin Sci (Lond). 2004;106(3):287–92.
73. Hasadsri L, Wang BH, Lee JV, Erdman JW, Llano DA, Barbey AK, et al. Omega-3 fatty acids as a putative treatment for traumatic brain injury. J Neurotrauma. 2013;30(11):897–906.
74. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, et al. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit Care Med. 2003;31(10):2444–9.
75. Tan HB, Danilla S, Murray A, Serra R, El Dib R, Henderson TOW, et al. Immunonutrition as an adjuvant therapy for burns. Cochrane Database Syst Rev. 2014;(12):CD007174.
76. Heyland DK, Wischmeyer P, Jeschke MG, Wibbenmeyer L, Turgeon AF, Stelfox HT, et al. A RandomizEd trial of ENtERal Glutamine to minimIZE thermal injury (The RE-ENERGIZE Trial): a clinical trial protocol. Scars Burn Heal. 2017;3:2059513117745241.
77. Berger MM, Spertini F, Shenkin A, Wardle C, Wiesner L, Schindler C, et al. Trace element supplementation modulates pulmonary infection rates after major burns: a double-blind, placebo-controlled trial. Am J Clin Nutr. 1998;68(2):365–71.
78. Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscita-

tion fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. Arch Surg. 2000;135(3):326–31.
79. Coudray-Lucas C, Le Bever H, Cynober L, De Bandt JP, Carsin H. Ornithine alpha-ketoglutarate improves wound healing in severe burn patients: a prospective randomized double-blind trial versus isonitrogenous controls. Crit Care Med. 2000;28(6):1772–6.
80. Davis CD. The gut microbiome and its role in obesity. Nutr Today. 2016;51(4):167–74.
81. Hurt RT, Frazier TH, McClave SA, Cave MC. Pharmaconutrition for the obese, critically ill patient. JPEN J Parenter Enteral Nutr. 2011;35(5 Suppl):72S.
82. Bermon S, Castell LM, Calder PC, Bishop NC, Blomstrand E, Mooren FC, et al. Consensus statement immunonutrition and exercise. Exerc Immunol Rev. 2017;23:8–50.
83. Pearce CB, Sadek SA, Walters AM, Goggin PM, Somers SS, Toh SK, et al. A double-blind, randomised, controlled trial to study the effects of an enteral feed supplemented with glutamine, arginine, and omega-3 fatty acid in predicted acute severe pancreatitis. JOP. 2006;7(4):361–71.
84. Lasztity N, Hamvas J, Biro L, Nemeth E, Marosvolgyi T, Decsi T, et al. Effect of enterally administered n-3 polyunsaturated fatty acids in acute pancreatitis–a prospective randomized clinical trial. Clin Nutr. 2005;24(2):198–205.
85. Wang G, Wen J, Xu L, Zhou S, Gong M, Wen P, et al. Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. J Surg Res. 2013;183(2):592–7.
86. 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.
87. Bongaerts GP, Severijnen RS. A reassessment of the PROPATRIA study and its implications for probiotic therapy. Nat Biotechnol. 2016;34(1):55–63.
88. Jafari T, Feizi A, Askari G, Fallah AA. Parenteral immunonutrition in patients with acute pancreatitis: a systematic review and meta-analysis. Clin Nutr. 2015;34(1):35–43.
89. Langer G, Großmann K, Fleischer S, Berg A, Grothues D, Wienke A, et al. Nutritional interventions for liver-transplanted patients. Cochrane Database Syst Rev. 2012;(8):CD007605.
90. Plank LD, Mathur S, Gane EJ, Peng SL, Gillanders LK, McIlroy K, et al. Perioperative immunonutrition in patients undergoing liver transplantation: a randomized double-blind trial. Hepatology. 2015;61(2):639–47.
91. Zhang Y, Chen J, Wu J, Chalson H, Merigan L, Mitchell A. Probiotic use in preventing postoperative infection in liver transplant patients. Hepatobiliary Surg Nutr. 2013;2(3):142–7.
92. Kota H, Chamberlain RS. Immunonutrition is associated with a decreased incidence of graft-versus-host disease in bone marrow transplant recipients: a meta-analysis. JPEN J Parenter Enteral Nutr. 2017;41(8):1286–92.
93. Celiberto LS, Graef FA, Healey GR, Bosman ES, Jacobson K, Sly LM, et al. Inflammatory bowel disease and immunonutrition: novel therapeutic approaches through modulation of diet and the gut microbiome. Immunology. 2018;155(1):36–52.
94. Akobeng AK, Elawad M, Gordon M. Glutamine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;2:CD007348.
95. De Ley M, de Vos R, Hommes DW, Stokkers P. Fish oil for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007;(4):CD005986.
96. Lev-Tzion R, Griffiths AM, Leder O, Turner D. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2014;(2):CD006320.
97. Turner D, Steinhart AH, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007;(3):CD006443.
98. Butterworth AD, Thomas AG, Akobeng AK. Probiotics for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2008;(3):CD006634.
99. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2006;(4):CD004826.
100. Mallon P, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007;(4):CD005573.
101. Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2011;(12):CD007443.
102. Imdad A, Nicholson MR, Tanner-Smith EE, Zackular JP, Gomez-Duarte OG, Beaulieu DB, et al. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst Rev. 2018;11:CD012774.
103. Garg SK, Croft AM, Bager P. Helminth therapy (worms) for induction of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2014;(1):CD009400.
104. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, Parian A, Matarese LE, Bracewell K, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2019;2:CD012839.
105. Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2018;4:CD000542.
106. Mehta NM, Skillman HE, Irving SY, Coss-Bu JA, Vermilyea S, Farrington EA, et al. Guidelines for the provision and assessment of nutrition support

therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. JPEN J Parenter Enteral Nutr. 2017;41(5):706–42.
107. Carcillo JA, Dean JM, Holubkov R, Berger J, Meert KL, Anand KJ, et al. The randomized comparative pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial. Pediatr Crit Care Med. 2012;13(2):165–73.
108. Carcillo JA, Dean JM, Holubkov R, Berger J, Meert KL, Anand KJS, et al. Interaction between 2 nutraceutical treatments and host immune status in the pediatric critical illness stress-induced immune suppression comparative effectiveness trial. JPEN J Parenter Enteral Nutr. 2017;41(8):1325–35.
109. 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. J Parenter Enter Nutr. 2009;33(3):277–316.
110. Patel JJ, Lemieux M, McClave SA, Martindale RG, Hurt RT, Heyland DK. Critical care nutrition support best practices: key differences between Canadian and American Guidelines. Nutr Clin Pract. 2017;32(5):633–44.
111. 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(1):29–43.
112. 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.
113. Yeh DD, Velmahos GC. Disease-specific nutrition therapy: one size does not fit all. Eur J Trauma Emerg Surg. 2013;39(3):215–33.

Special Considerations in Organ Failure

15

Emily Cantrell, Jay Doucet, and Carlos Ortiz-Leyba

Introduction

The presence or development of multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF) has plagued surgical intensive care units (ICUs) for over four decades. This unfavorable course is felt to be the clinical manifestation of an imbalance between an excessive pro-inflammatory state, known as the systemic inflammatory response syndrome (SIRS), and the response of anti-inflammatory mechanisms, known as the compensatory anti-inflammatory response syndrome, leading to an immunoparetic state.

While exact mechanisms continue to be debated and discovered, patients with MODS/MOF consume a tremendous amount of healthcare resources, and long-term morbidity and mortality remain prohibitively high. In this chapter, we aim to depict the evolving concepts and phenotypes of MOF and MODS in regard to its epidemiology, proposed pathophysiology, and clinical manifestations, as well as review the role of nutritional supplementation in its management.

Concept of MODS/MOF

Although the concept of MODS/MOF seems easy to understand and identify, reality is not always so conclusive. Despite the fact that this entity is well-known, its origin has been subjected to many different hypotheses and presumed mechanisms. While more than two dozen types of organ failure have been described, the common framework used to identify MODS/MOF is based on the presence of symptoms, abnormal biochemical and hematologic tests, and evidence of inadequate organ perfusion. Previously, the Surviving Sepsis Campaign guidelines described organ failure as a state in which organ function is acutely altered such that homeostasis cannot be maintained without pharmacologic or mechanical interventions and in its 2012 review [1] described criteria to consider organ dysfunction or failure (Table 15.1). Despite extensive research on the topic, a conceptual dilemma remains: is organ failure a consequence of microcirculatory disturbances leading to imbalances in organ metabolism and oxygen utilization resulting in severe damage and even

E. Cantrell · J. Doucet (✉)
Department of Surgery, University of California San Diego, San Diego, CA, USA
e-mail: jdoucet@ucsd.edu

C. Ortiz-Leyba
Department of Internal Medicine and Critical Care Unit, Hospital Quirón Sagrado Corazón, Sevilla, Spain

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_15

Table 15.1 Definition of organ dysfunctions (Surviving Sepsis Campaign [1])

Organ dysfunction	Variables	Criteria
Pulmonary	Arterial hypoxemia	$PaO_2/FiO_2 < 300$
Renal	Acute oliguria	Output <0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation
		Creatinine increase >0.5 mg/dL or 44.2 μmol/L
Hematological/ coagulation	Coagulation abnormalities	INR >1.5 or aPTT >60 s
		Platelet count <100,000 μL^{-1}
Gastrointestinal	Ileus	Absent bowel sounds
Hepatic	Hyperbilirubinemia	Plasma total bilirubin >4 mg/dL or 70 μmol/L
Tissue perfusion		
	Hyperlactatemia	>1 mmol/L
	Decreased capillary refill or mottling	

PaO_2/FiO_2 partial pressure arterial oxygen/fraction of inspired oxygen, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time

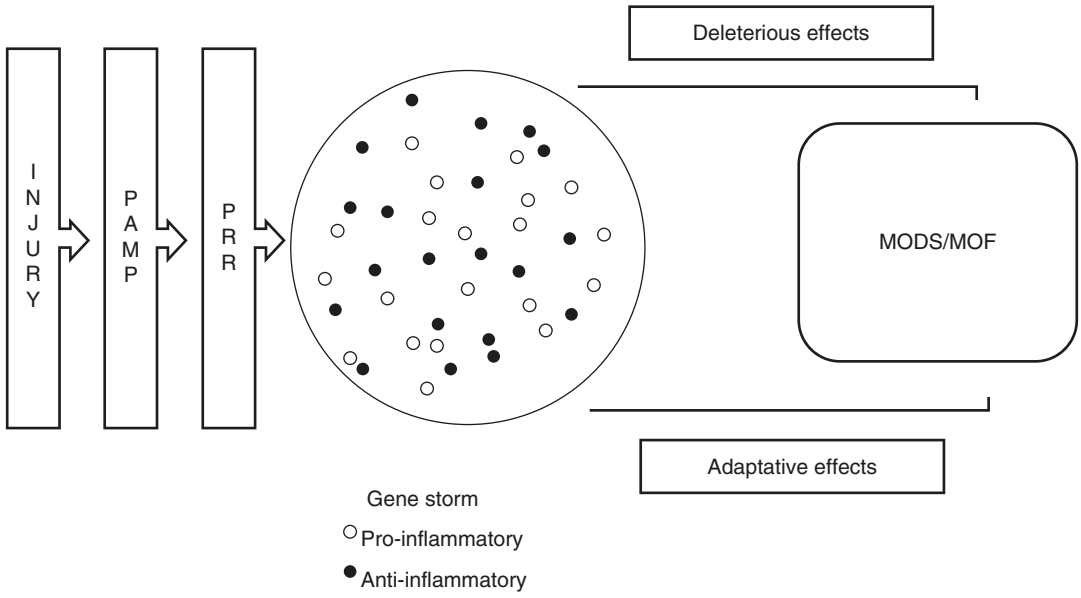

Fig. 15.1 Current organ failure development hypothesis

death of cellular structures as was initial described [2], or is organ failure an adaptive mechanism that allows cells to protect organ function by diminishing their metabolism and allowing a presumable recovery [3] (Fig. 15.1)?

These theories regarding the development of MODS/MOF may be in part the result of the chronology and the clinical profile of this entity. First proposed by Moore et al. [4], a biphasic course was used to describe the presentation of MOF among trauma patients. These authors described an early-onset MOF that appeared on days 0–3 following the initial trauma and a late-onset MOF that presented slightly later, on day 4. In addition, other authors supported the theory that affected organs in early MOF were the lung, heart, and kidney, while the liver, nervous system, and gastrointestinal (GI) tract were involved in late MOF. This resulted in the "two-hit" theory of MOF, where during this period of dysregulation of the early innate immune response, an additional insult or "second hit," such as a

nosocomial infection, would occur leading to recurrent systemic inflammatory response syndrome (SIRS) and subsequent failure of organs, with many believing the GI tract to be the engine behind this second "hit" [5, 6].

Epidemiology of MOF

With advances in technology, critical and trauma care, and initial resuscitation, the epidemiology of MOF has evolved quite significantly since its initial conception (Fig. 15.2). MOF emerged in the 1970s as a result of advances in ICU care that allowed patients to survive single organ failure [7], with the most commonly described events resulting in MOF being trauma and sepsis [8–12]. One of the earliest descriptions of MOF came as a result of the epidemic of penetrating trauma by the so-called Knife and Gun Clubs in the United States which brought with it a high incidence of intra-abdominal infections. This led to the conclusion that MOF was the result of uncontrolled infection. Therefore, research in the 1980s focused on the prevention and treatment of intra-abdominal infections such as the use of perioperative antibiotics, improved surgical techniques and source control, dedicated trauma staff, earlier diagnosis with improved imaging techniques (computerized tomography), ideas of goal-oriented resuscitation, and use of early enteral nutrition.

By the mid-1980s, studies from Europe began reporting a high incidence of MOF after blunt trauma but without any identifiable source of infection. The term "sepsis syndrome" was popularized to describe these patients who appeared septic but had no identifiable source of infection [13]. It was recognized that both infectious and noninfectious insults could result in a similar destructive systemic inflammatory response that if unabated could result in MOF and death [13–15]. Multiple potential pathologic mechanisms were proposed, but bacterial gut translocation gained the most popularity and provided a potential explanation for how early enteral nutrition (EEN) provided beneficial effects [16–20]. As this new variant of MOF was being recognized and better understood, the term "sepsis syndrome" was replaced by the "systemic inflammatory response syndrome "(SIRS) and "compensatory anti-inflammatory response syndrome" (CARS) paradigm.

Research by Moore et al. [21] proposed that MOF was a bimodal phenomenon in which the initial severe insult could cause early

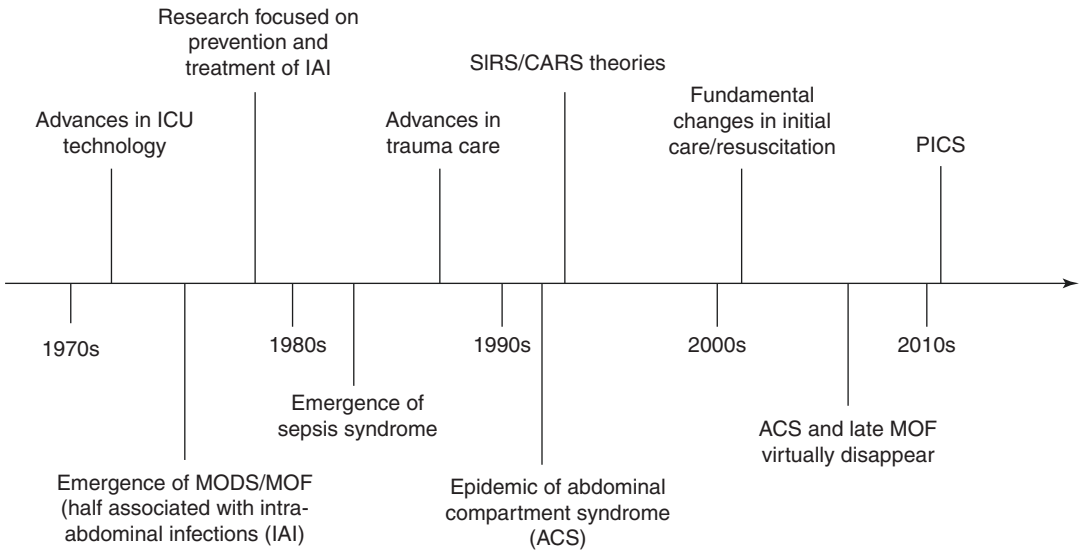

Fig. 15.2 Evolution of MODS/MOF leading to the phenotype of PICS

MOF. This, however, was followed by a relatively quiescent period until late infections began to occur, precipitating a second peak in MOF. Based on immunologic insights in the 1990s, it was postulated that the initial insult precipitated pro-inflammatory SIRS, and if severe enough, early MOF ensued [21, 22]. In an attempt to equilibrate following the SIRS-induced pro-inflammatory state, the body induced CARS, which set the stage for immunosuppression, late infections, and late MOF (Fig. 15.3).

In the 2000s, additional advancements in the initial care of trauma and septic patients were developed which aimed to moderate and quickly correct abnormalities associated with the initial insult. From a trauma standpoint, this included the use of massive transfusion protocols, rapid hemorrhage control, and focused goal-oriented ICU resuscitation. In terms of sepsis, the "Surviving Sepsis Campaign" [23] brought more widespread use of sepsis screening and more consistent implementation of evidence-based care. As a result, this second peak of late MOF deaths has significantly decreased.

With more patients now surviving these early and late insults, a phenomenon of chronically critically ill patients was identified. This population of chronically critically ill ICU patients subsequently became the phenotype referred to as persistent inflammation, immunosuppression, and catabolism syndrome (PICS). Described by Gentile et al. [24], these patients were observed to lose tremendous amounts of lean body mass despite optimal nutrition, suffer recurrent nosocomial infections, and develop decubitus ulcers. While surviving their hospital course, these patients are significantly debilitated and discharged to long-term care facilities where they often fail to rehabilitate and experience dismal long-term outcomes.

Incidence of MOF reportedly ranges between 15% and 61%. Potential reasons for this variation in reported incidence include differences in patient populations, scoring systems and definitions used to identify MOF, and the clinical period in which these observations were made. Per recent studies, trauma patients appear to have an incidence of MOF ranging from 15% to 25% [12, 25] in contrast to burn patients where the

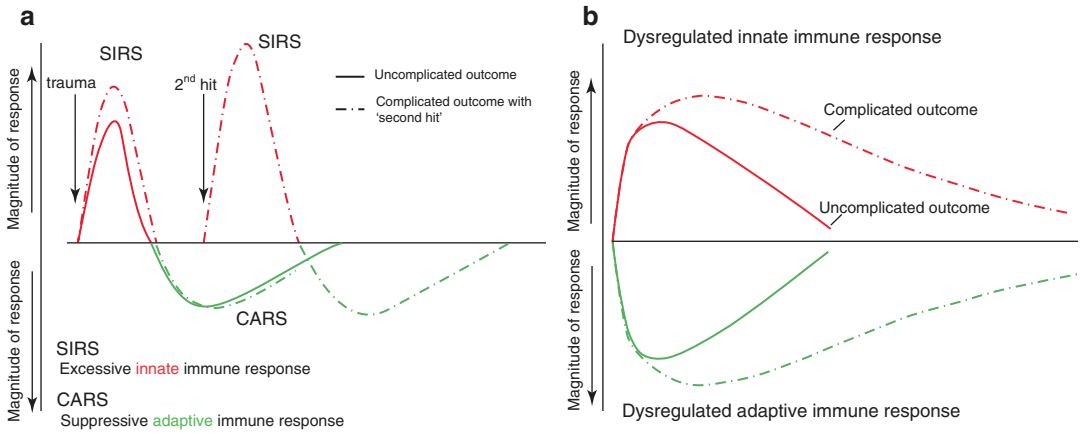

Fig. 15.3 Evolution of the SIRS-CARS model. (**a**) The traditionally accepted SIRS-CARS phenomenon holds that severe sepsis and injury are a consequence of an overabundant and dysregulated early innate immune response from the overproduction of pro-inflammatory mediators and cytokines, leading to endothelial injury, tissue damage, inadequate perfusion, and MOF, ultimately leading to death. In patients who survive this early SIRS event, a compensatory anti-inflammatory response syndrome (CARS) including suppression of adaptive immunity results. Additional insults such as nosocomial infection can case a late "second hit" that may lead to recurrent SIRS. (**b**) Recently, the Glue Grant showed that based on leukocyte genomic expression patterns, there is a simultaneous induction of innate (both pro- and anti-inflammatory genes) and suppression of adaptive immunity genes, and there is minimal genomic or clinical evidence for a "second hit" phenomenon. (From [73]; with permission)

incidence was found to be up to 40% [26]. An observational, multicenter study performed in 79 ICUs across Spain and Latin America on 7615 trauma, medical, surgical, and cardiac ICU patients over a 2-month period noted a MOF incidence of 17.6% [27].

Outcomes

It is well-known that the development of MODS/MOF in critically ill trauma and surgical patients is associated with significantly poorer outcomes. Among trauma patients, mortality is up to six- to eightfold higher in patients who develop MOF versus those who do not [12, 28]. In addition, mortality rates appear to be closely related to the number or organ systems that fail. For example, a patient with four or more affected organ systems has a predicted mortality rate of 100%. Morbidity also closely parallels mortality with patients who develop MODS/MOF having increased days of mechanical ventilation, longer ICU and hospital length of stays, and a higher rate of nosocomial infections [29, 30].

Of those who do survive, patients that develop MODS/MOF exhibit greater mortality over time, even after discharge from acute hospital stay. In a cohort study of 545 medical-surgical ICU patients with MODS followed for 1 year, overall mortality was found to be 52.9%. Of those that died, 29.5% of deaths occurred in the ICU and 14.8% occurred in the hospital ward. Three hundred twenty-seven patients survived to discharge, and of the 266 patients that were able to be contacted at the 1-year study follow-up period, 14.3% of patients had died. Variables that were noted to be associated with delayed mortality included decreased functional conditioning and need for readmission to the hospital [31]. In a multicenter trial from Scotland, 872 patients with MODS/MOF from 10 ICUs were evaluated and found to have a 5-year mortality of 58.2%, with 34.4% occurring within 28 days. Cardiovascular, respiratory, and hepatic failure during the patient's hospital stay were found to be independent factors associated with 5-year mortality [32].

Scoring Systems

Over the years, multiple scoring systems have been developed to stratify the severity of organ dysfunction and predict outcomes. The four commonly accepted and applied scoring systems are the Denver postinjury multiple organ failure score, the Marshall score, the logistic organ dysfunction system (LODS), and the sequential organ failure assessment (SOFA) score [33, 34]. A comparison between the various organ dysfunction scoring systems can be seen in Table 15.2.

The Denver score considers four organs and four grades, while the LODS, Marshall, and SOFA scores take into account six organ systems and five grades. Moreover, the definition of each grade and the weight of each dysfunction vary between each scoring system. One parameter found to be useful in these scores is the value delta, which means the maximum difference between the initial value and the highest score obtained during the patient's stay. Thus, it is common to use *delta* SOFA or *delta* MODS.

The Marshall score was validated on surgical ICU patients and has been found to be predictive of mortality using both the raw score and a delta MODS [11]. These findings were confirmed in a prospective observational cohort study on 1200 mechanically ventilated patients performed in Canada [35]. The SOFA score has been validated in medical-surgical ICU patients and multiple patient populations (sepsis, cardiovascular, trauma, burns) [36]. Although not designed for prognostication, studies have shown that an increasing SOFA score is associated with worse outcomes with a SOFA score of greater than 15 correlating with a mortality rate of 100% [37].

The LODS score was developed through multiple logistic regression analysis on 13,152 ICU patients in 12 countries, allowing for the determination of the degree of organ dysfunction as well as the prediction of mortality. In a French multicenter prospective study on 1685 ICU patients, daily LODS and SOFA scores were compared during the first 7 days of a patient's ICU stay. Both scores were found to display good accuracy for prognosis and prediction of mortality [33]. In

Table 15.2 Main differences among organ dysfunction scores

	Denver [5]	Marshall [11]	SOFA [185]	LODS [186]
Grades	0–3	0–4	1–4	Not applicable
Points	0–12	0–24	0–24	0–22
Pulmonary	PaO_2/FiO_2	PaO_2/FiO_2	PaO_2/FiO_2	PaO_2/FiO_2
Renal	Creatinine	Creatinine	Creatinine/urine output	Blood urea nitrogen/creatinine/urine output
Hepatic	Bilirubin	Bilirubin	Bilirubin	Bilirubin/prothrombin time
Cardiac/cardiovascular	Inotrope dose	PHR	MAP/vasopressor/inotrope doses	Heart rate/SAP
Coagulation/hematology	No	Platelets	Platelets	Leucocytes/platelets
CNS	No	GCS	GCS	GCS

PaO_2/FiO_2 partial pressure arterial oxygen/fraction of inspired oxygen, *PHR* pressure adjusted rate (heart rate × central venous pressure/mean arterial pressure), *MAP* mean arterial pressure, *SAP* systolic arterial pressure, *CNS* central nervous system, *GCS* Glasgow Coma Scale

a validation of the Denver and Marshall scores, Sauaia et al. concluded that both scoring systems were useful tools but that the Denver score showed a greater specificity for mortality and ventilator-free days (higher than 70%). However, the sensitivity and specificity for days of mechanical ventilation and ICU length of stay were less than 70% [38].

In a comparison between LODS and SOFA scores, Peres-Bota et al. concluded that both were accurate predictors of outcome. Nevertheless, in patients with shock or cardiovascular dysfunction, the SOFA score was a better predictor of outcome [39]. This difference has also been noted in patients with severe traumatic brain injury. In a prospective cohort study, the SOFA scoring system was able to better discriminate both mortality and neurologic outcome [40].

Given that MODS/MOF scoring systems were all developed using different modalities on various patient populations, it seems evident that their strength lies in their ability to stratify organ dysfunction in general and their weakness in the loss of accuracy when applied to specific patient populations [41]. This has subsequently led to the development of disease-specific scoring systems. Disease-specific scoring systems include the Glasgow Coma Scale (GCS) for the evaluation of central nervous system dysfunction; risk, injury, failure, loss, and end-stage renal disease (RIFLE) [42] and acute kidney injury network (AKIN) [43] classification of renal involvement; Child-Pugh score for liver failure [44, 45]; and lung injury score (LIS) for patients with acute respiratory distress syndrome (ARDS) [46].

Pathophysiology

General Mechanisms

Dysfunction and/or failure of organs and systems is following multiple different types of injury. Despite this, a detailed and definite knowledge about the pathophysiology remains incomplete, even the bimodal model proposed by Moore et al. [4]. General mechanisms that uncouple the presence of MODS/MOF after any of these entities, however, are quite well-known. Whether the inciting insult is a septic or non-septic event, both trigger a common inflammatory response through activator molecules coming from microorganisms or their products, damaged tissues, denatured proteins from dying cells, or foreign bodies.

These activators, known as pathogen-associated molecular patterns (PAMPs), accomplish their activity either directly or indirectly activating cytokines and other inflammatory mediators, generating biologic and metabolic effects that result in the clinical syndrome of MODS or MOF. PAMPs may be divided into microbial and non-microbial origins. The most well-known microbiologic PAMPs are lipopolysaccharide (LPS), lipoteichoic acid, peptidoglycan, and phenol-soluble modulin. Non-microbiologic PAMPs include various allergens, toxic compounds, and lipoproteins.

Immunologic identification of damaged tissues is mediated by intracellular proteins or by other mediators from damaged cells called alarmins. For some researchers, alarmins and PAMPs combined create an entity called damage-associated molecular patterns (DAMPs). For others, however, DAMPs are synonymous with alarmins. Characteristics of alarmins include release from necrotic cells (not apoptotic) or release from living immune cells by means of endoplasmic reticulum or Golgi apparatus. The ability to recruit and activate other immune cells where receptors are expressed and the capacity to restore lost homeostasis to injured tissues are also characteristics of DAMPs.

DAMPs are recognized by immune cell receptors identified as pattern recognition receptors (PRRs) resulting in the activation of innate immunity and a generalized inflammatory response. Several receptors have been described as PRRs including triggering receptor expressed on myeloid cells (TREM 1), receptor for advanced glycation end products (RAGE), macrophage scavenger receptor (MSR), K+ channels, CD11/CD18 receptors, CD55, CXCR4 chemokine receptor, CD180, and heat shock protein 70/90 receptor (Hsp70/Hsp90), but perhaps the best known PRRs are Toll-like receptors (TLR)

and nucleotide-binding oligomerization domain (NOD)-like receptors (NLR). PRRs trigger differences in transcription factors, with the best known transcription factor being NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). These transcription factors control the transcription of nuclear DNA, resulting in altered regulation of genes responsible for both innate and adaptive immune responses.

Activation of host response to injury is independent of the type of stimulus. Adaptive immunity occurs concurrently, once B-cell receptors are activated. Activation and ultimate cellular recruitment are performed by cytokines and some of the alarmins. Cytokine production tends to be brief and time-limited in response to a stimulus. Cytokines can be divided in two big groups, pro-inflammatory (e.g., TNF-a, IL-1b, IL-6, IL-12, IL-17, INF-c) and anti-inflammatory (e.g., IL-1ra, IL-4, IL-6, IL-10, IP10, IL-13, TGF-b, sTNFR p55, p75, sIL-6R), though some of them (e.g., IL-6) can share both characteristics according to the inflammatory milieu. In addition to the large constellation of cytokines involved in the inflammatory response, different alarmins have been recognized as active clinical agents [47], including S100 proteins, calcium pyrophosphate dihydrate (CPPD), Spliceosome-Associated Protein 130 (SAP130), uric acid and monosodium urate crystals, DNA, mitochondrial DNA, RNA, ATP, hyaluronan, biglycan, heparin sulfate, formylpeptides, and cholesterol crystals. Among alarmins, it is also worth highlighting heat shock proteins (HSP), High Mobility Group Box1 (HMGB1), and Macrophage Migration Inhibitory Factor (MIF).

Some members of the HSP family, HSP60 and HSP70, can be detected in serum. As signal molecules, they have a global pro-inflammatory activity, but may also attenuate ischemia-reperfusion injury (oxidative injury) and protect endothelial cells from neutrophil-mediated necrosis.

HMGB1 is a nuclear protein that binds DNA, modulates transcription and chromatin remodeling, and facilitates the binding of transcription factors and nucleosomes. It is produced by injured, dying, or stressed cells, as well as by macrophages and other immune cells. It is involved in the stabilization of nucleosomes and facilitates gene transcription through the modulation of the activity of steroid hormone receptors. MHBGN1 also induces maturation of dendritic cells and has activity as chemokine, since its effects are also exerted in the endothelium. It binds to TLR4, increasing the release of pro-inflammatory mediators, and interacts with RAGE (receptor for advanced glycation end products) receptors. It mediates fever and anorexia and is considered a late mediator of sepsis (8–32 h). High concentrations have been associated with clinical deterioration. HMGB1 could be also considered a trigger in the stimuli which activate innate immunity [48]. In experimental studies, blocking HMGB1 with polyclonal antibodies protects from lethal endotoxemia and from acute lung injury. Because of this, HMBG1-blocking agents may be considered as a potential therapeutic target.

MIF protein is constitutively expressed in large quantities by epithelial cells of the lung and kidney, immune cells (macrophages, eosinophils), and endocrine cells (pituitary). It is released following exposure to inflammatory cytokines or bacterial products and modulates the immune response through TLR4, allowing quick response of macrophages [49]. In situations of severe sepsis and septic shock, high levels of MIF have been detected, activating a pro-inflammatory response and increasing the secretion of cytokines by the upregulation of TLR4 expression. MIF represents a recognized biomarker and potential molecular target in acute lung injury (ALI), as it is detectable in the alveolar airspaces of patients with sepsis-induced ARDS [50, 51].

MODS/MOF presentation is also related to imbalance in humoral responses with the complement system clearly involved in this process [52]. Complement may be activated in three different pathways: the classic, the mannose-binding lectin, and the alternative pathways. Despite the pathway, all converge on the crossroads of C3 to continue the cascade activation. This process releases large amounts of anaphylatoxin C5a, a central molecule in the inflammatory response. C5a exerts its effects through interactions with the C5AR and C5a-like receptor 2 (C5L2) receptors, which are upregulated during sepsis. The synergistic action of C5a and its receptors contributes,

at an early state, to the inflammatory activity that turns into the expression of tissue factor and triggers the release of MIF and HMGB1.

On the other hand, C5a also facilitates an immunosuppressive reaction through an induction of neutrophil dysfunction and apoptosis of thymocytes and medullary adrenal cells. In an animal model of sepsis, the blockade of C5a improved outcome and avoided MOF [53]. Additionally, in a baboon model of sepsis, the use of the C5a inhibitor compstatin decreased the coagulopathic response by downregulating tissue factor and PAI-1; reduced fibrinogen, fibrin-degradation products, and APTT; and preserved endothelial anticoagulant properties [54]. These findings might have implications on future complement-blocking approaches in the clinical treatment of MODS/MOF.

Neural Regulation

The active participation of the autonomic nervous system (ANS) in the control of inflammatory response opens new fields and perspectives for the understanding of MODS/MOF physiopathology. Stimulation of the adrenergic system leads to an amplification in pro-inflammatory behavior, particularly during the first steps of injury and organ dysfunction, whereas the activation of cholinergic system prompts an anti-inflammatory trend. Catecholamines released in the adrenal glands and neurons of the sympathetic system act through α- and β-adrenergic receptors expressed on different types of cells, while the anti-inflammatory effects of cholinergic pathways are mediated through α7 nicotinic (ACh) receptors (α7nAChRs) [55]. Vagal nerve stimulation subsequently releases acetylcholine that inhibits pro-inflammatory molecules such as HMGB1 and TNF. In an animal model of sepsis, activation of the α-7 receptors with nicotine has shown an improvement of inflammation and increased survival [56].

Microvascular Milieu

The molecular storm triggered by host response to the injury occurs in the microvascular environment. Normal endothelium performs two essential roles. First, it regulates blood vessel tone, and, second, it actively participates in leucocyte recruitment, directing them to sites where the cellular damage and inflammation occur. This process is mediated through the expression of adhesion molecules (ICAM, VCAM, ELAM) that are able to bind to leucocyte integrins CD11/CD18 and initiate leukocyte diapedesis and migration through the endothelial wall. This process results in high levels of nitric oxide (NO) through monocyte inducible NO synthase (iNOS), converting L-arginine to L-citrulline. NO acts as a free radical and is a modulator of vascular tone, causing vasodilatation, increased vascular permeability, and organ dysfunction. Free radical formation is a result of inhibition of mitochondrial function, leading to a decrease in TPA synthesis and an increase of reactive oxygen species (ROS), generating peroxynitrite. The action of ROS on cells contributes to important changes in the release of lipid substrates such as series 2 prostaglandins (PG2) and series 4 leukotrienes (LT4) with additional pro-inflammatory and pro-aggregate activities.

Alterations in the coagulation and fibrinolytic cascades also occur at the level of the endothelium. Procoagulant activity is upregulated and mediated by thromboxane A2, plasminogen activator inhibitor (PAI), platelet-activating factor (PAF), and von Willebrand factor. In addition, there is an associated downregulation of anticoagulant activity factors, including thrombomodulin, protein C receptor, and tissue plasminogen activator (tPA).

Metabolic changes at the level of the endothelium, combined with hypoxia, lead to intravascular platelet aggregations and microvascular thrombosis, manifesting clinically as fever, chills, tachycardia, tachypnea, agitation, and a subsequent organ dysfunction if homeostasis cannot be recovered [57]. Shapiro et al. established the association between organ failure and endothelial cell damage in septic patients by measuring levels of vascular endothelial growth factor (VEGF), a stimulator of permeability, and its receptor sFLT. They concluded that sFLT levels correlated with measured initial SOFA and SOFA at 24 h and that VEGF and sFLT levels also correlated

with inflammatory cascade activation [58]. In a second study performed by the same investigators in patients with sepsis, the role of the microcirculation in the development of MODS/MOF was further supported by measuring a broad panel of endothelial markers including sVCAM-1, sICAM-1, sE-selectin, PAI, VEGF, and sFLT-1, finding an association between endothelial activation and subsequent organ dysfunction and mortality. sFlt-1 was the marker with the strongest association with SOFA score [59].

Animal models also demonstrate a relationship between high levels of angiopoietin-2 (Angpt-2), an endothelial protein released upon inflammatory stimulation, and SOFA measurements [60]. Sakr et al. measured microcirculatory perfusion on 46 patients with septic shock and noted that decreased microcirculatory flow was associated with the development of multiorgan failure and death [61]. Using similar methods, Trzeciak et al. showed that an increase of microcirculatory flow during resuscitation was associated with reduced organ failure [62]. Accordingly, derangements in microcirculation seem to play an important role as the first hit in the development of MODS/MOF, while late MODS/MOF may be more associated with mitochondrial failure [63].

Mitochondrial Role

Mitochondrial function has emerged as one of the cornerstones in the development of MODS/MOF. Release of pro-inflammatory cytokines and other mediators together results in the production of great amounts of NO and ROS creating a maldistribution of macrovascular and microvascular blood flow which, in turn, affects the mitochondrial function and energy production. If the inciting stimulus continues, mitochondrial energy is severely compromised, a situation which may be reversed by regeneration of new mitochondria if the patient enters a recovery state [64].

The classic interpretation of decreased mitochondrial function is that as cells die, organs fail due to a lack of energy. However, an alternative hypothesis has been postulated based on the observation that cell necrosis is not a key feature of the response to sepsis [65]. It is proposed that the decline in mitochondrial function is a protective response, with cells entering a hibernation-like state and MODS/MOF a manifestation of this "physiologic shutdown." This process could be reversed with the generation of new functional mitochondria and a recovery of energy, subsequent metabolic restoration, and clinical improvement. This regeneration, called biogenesis, seems to be triggered by NO production and mitochondrial DNA oxidative damage [66]. On the other hand, if sepsis persists, hibernation stops being an adaptive and potentially protective role and shifts to a pathologic and harmful situation.

Others have also supported this hypothesis. In a murine model of peritonitis, Haden et al. found an increase in the mitochondrial biogenesis with restoration of oxidative metabolism during recovery [67]. In another study based on skeletal muscle biopsies in 28 septic ICU patients, Brealey et al. reported an association between NO overproduction, antioxidant depletion, mitochondrial dysfunction, and decreased ATP concentrations related to organ failure and outcome [68].

Carré et al. studied biogenesis responses in muscle biopsies on 16 critically ill patients with MOF, at the time of admission to ICU versus 10 patients submitted to elective hip surgery as control group. Their study showed that muscle mitochondrial capacity was decreased soon after ICU admission, especially among non-survivors. However, in the group of ICU survivors, early mitochondrial biogenesis and antioxidant defense responses were found. These authors conclude that an overexuberant response to sepsis could increase susceptibility to mitochondrial damage and cellular energetic dysfunction and would subsequently prevent the recovery of normal function [69].

In spite of these studies, criticism has arisen due to heterogeneity of the body of evidence. Differences in methodology of the various studies on mitochondrial dysfunction have prompted criticism of the proposed theories and interpretation of the conclusions. A consensus definition for "mitochondrial dysfunction" seems to be missing [70]. Even in human studies, only the musculoskeletal and circulatory systems have been studied, while MOF affects numerous other organ

systems. Additional studies utilizing new tools and testing are needed to further assess mitochondrial function and its role in MODS/MOF.

Genomics

Recent genomic studies have contributed to a new understanding to physiopathology and timing of MOF. The generally accepted biphasic "two-hit" model, fueled by GI tract dysfunction, nosocomial infections, or new surgery, is now being revisited due to new insights related to the expression of pro- and anti-inflammatory genes.

A study by Xiao et al., examined a cohort of 167 adult severe blunt trauma patients who presented in shock and required transfusion of blood products. Leukocyte transcriptome was measured at several time points over 28 days. The authors noted that the expression of more than 80% of leucocyte transcriptome was significantly altered in a way that was described as "genomic storm." Changes occurred rapidly (4–12 h) after insult and continued for days and weeks. This "genomic storm" included both inflammatory and anti-inflammatory gene upregulation and was independent of inciting stimulus (trauma, burns, low dose of endotoxin). Moreover, the gene profile showed similar behavior despite patient outcome (complicated and uncomplicated recovery). These authors propose a new paradigm for the inflammatory response where changes in the expression of systemic inflammatory genes, and anti-inflammatory and adaptive genes, occur early and concurrently, not sequentially [71]. Interestingly, complicated recovery is not related to a different leucocyte transcriptome pattern, but a prolongation in this gene expression profile [72]. This paradigm reexamines the classical diagram of two curves explaining SIRS, CARS, MOF, and outcome and substitutes it by a new model. Partially based on this concept, Gentile et al. coined the entity "persistent inflammation, immunosuppression, and catabolism syndrome" (PICS), encompassing those ICU patients who linger with manageable organ dysfunctions but usually do not meet established criteria for late MOF (Fig. 15.4). Their clinical course is often

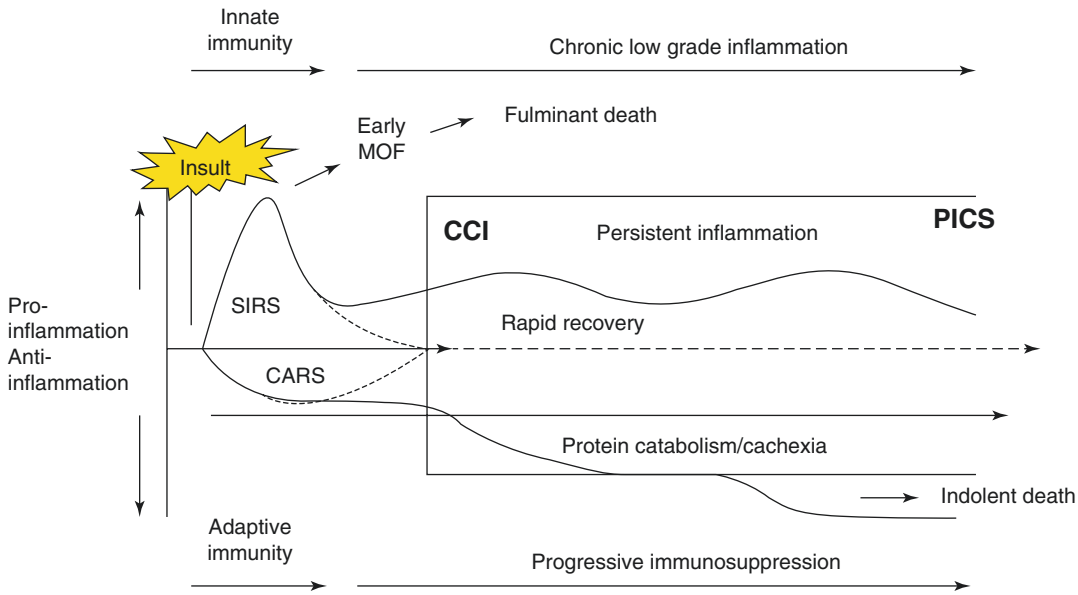

Fig. 15.4 The PICS diagram. Clinical pathway of how PICS develops. Initially there is an inciting incident that triggers SIRS/CARS with respective increases in the innate and adaptive immunity. If the SIRS response is too robust, it has been noticed that these are the patients that are most vulnerable to early MOF and fulminant death. Once the patient persists to CCI, it has been seen that these patients may have chronic low-grade inflammation with persistent immunosuppression. These are the hallmarks of PICS and if unaltered ultimately lead to an indolent death

marked by ongoing protein catabolism with poor nutritional status, poor wound healing, immunosuppression, and recurrent infections [24].

Clinical Presentation

Lung

The lung is one of the most frequently affected organs in the course of MODS/MOF. Beginning with Ashbaugh et al. in 1967, pulmonary dysfunction has been widely studied over the last several decades [73]. With estimated incidence of 34 per 100,000 in the United States [74] and 5–7 per 100,000 in Europe [75–77], the 28-day mortality of acute respiratory distress syndrome (ARDS) continues to be between 20% and 40% and the 1-year mortality an additional 15–20%, based on control group survival in recent randomized control trials [78–80]. The LUNGSAFE study showed that the syndrome remains common and has a mortality of approximately 40%, emphasizing the global burden of ARDS [81].

Currently, using the Berlin definition, ARDS is classified as mild ($200 < PaO_2/FiO_2 \leq 300$ with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cmH_2O); moderate ($100 < PaO_2/FiO_2 \leq 200$ with PEEP ≥ 5 cmH_2O); and severe ($PaO_2/FiO_2 \leq 100$ with PEEP ≥ 5 cmH_2O) [46].

Physiologically, the inflammatory response and resultant increase in lung vascular permeability promote an alveolar invasion of activated neutrophils, red blood cells, and fibrin-rich fluid, resulting in damage to alveolar epithelium and a denuded alveolar basement membrane with loss of type I cells [82]. This drives the formation of hyaline membranes, inactivation of surfactant, and finally collapse of the alveoli [83].

Clinically, ARDS is manifested as a rapid onset of respiratory failure due to arterial hypoxemia that is refractory to treatment with supplemental oxygen. Radiological findings include bilateral infiltrates described as patchy or asymmetric, with or without pleural effusions, consolidation, and atelectasis. As ARDS progresses, an increased alveolar dead space and a decrease in pulmonary compliance result.

Kidney

The kidney is one of the most commonly affected organs in MODS/MOF. The prevalence of acute kidney injury/failure is approximately 60% in patients with MODS/MOF and carries an associated mortality rate between 26% and 64% [42, 84].

Acute renal failure (ARF) was previously defined following RIFLE criteria [85]. More recently, however, a newer definition of AKI has been issued to address the entire spectrum of acute renal failure [86, 87]. Diagnostic criteria for AKI are a reduction in kidney function within 48 h, currently defined as an absolute increase in serum creatinine of greater than or equal to 0.3 mg/dL (≥26.4 μmol/L), an increase in serum creatinine of greater than 50% (1.5-fold from baseline), or documented oliguria of less than 0.5 ml/kg per hour for more than 6 h. There is also a three-grade staging system based on quantitative changes in serum creatinine and urine output (based on RIFLE criteria).

While the true pathophysiology of AKI is unknown, factors such as hypovolemia, inflammatory response, neuronal mechanisms, coagulopathies, and renal arterial vasoconstriction have all been implicated. Sepsis, major surgery (especially open cardiac surgery), and acute decompensated heart failure are also common triggers of acute kidney injury [88].

Since AKI is often a result of renal hypoperfusion, rapid resuscitation is the best first step in the treatment of AKI. Ideally, one or more biomarkers would exist to aid in the early identification of AKI. Current biomarkers under study include urinary neutrophil gelatinase-associated lipocalin (uNGAL), urinary hepatocyte growth factor (uHGF), urinary cystatin C (uCystatin C), kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), monocyte chemotactic peptide (MCP-1), IL-18, liver-type fatty acid-binding protein (L-FABP), and Netrin-1. According to early results, these markers can identify patients with a renal dysfunction prior to the development of a high creatinine level and may increase the possibility for recovery [89, 90]. Additionally, it has been suggested that various biomarkers could reflect different etiologies

of AKI. Cystatin C can predict changes in glomerular filtration rate, whereas neutrophil gelatinase-associated lipocalin is related to tubular stress or injury. At present, however, more research is necessary to better understand these biomarkers before adopting them into clinical practice [91].

Cardiovascular System

The cardiovascular system can be affected via myocardial dysfunction, refractory peripheral vasodilatation, or a combination of the two. Septic injury often results in cardiovascular derangement, often with cardiac autonomic dysfunction, clinically manifested as rhythm disturbances. Cardiac myocytes may be also directly damaged by PAMP such as endotoxin and by NO and its substrate peroxynitrite which induce mitochondrial impairment and a diminished cardiac contractility [92]. This septic cardiomyopathy is characterized by a global cardiac enlargement with biventricular contractility impairment and a striking reduction in left ventricular (LV) ejection fraction and stroke work index [93]. A good biomarker for diagnosis and for assessment of the degree of ventricular dysfunction is troponins.

Vascular dysfunction is characterized by microvascular and endothelial impairment, decreased vasoconstrictor tone, and a diminished responsiveness to vasopressor agents resulting in resistant hypotension [94]. Involved mechanisms seem to be the same as in cardiac dysfunction, with a preponderant role for NO and its metabolites. However, adrenal insufficiency, anomalous catecholamine signaling, damaged potassium channels, and even hyperglycemia are all factors that also could be implicated [95].

Nervous System

Neurological dysfunction is common in MODS/MOF. Disturbances in mental status, confusion, delirium, and even coma are very frequent in severe sepsis and septic shock. Sepsis-associated encephalopathy (SAE) occurs in up to 87% of septic patients. The pathophysiology is still not completely understood and likely multifactorial [96]. Proposed etiologies include effects of microorganism toxins, cytokines and other inflammatory mediators crossing the blood-brain barrier, oxidative stress, or decrease of cerebral blood flow. Electroencephalogram (EEG) is a sensitive test for the diagnosis of SAE when the patient is sedated and mechanically ventilated. Additionally, biomarkers, such as S100B protein, may also prove useful in identifying SAE; however, more research is needed to fully determine their role. While SAE is potentially reversible, its presence is a poor prognostic indicator [97].

Another form of neural dysfunction in MODS/MOF is an axonal polyneuropathy named critical illness polyneuropathy (CIP). CIP often results in generalized weakness and difficulty weaning from mechanical ventilation. As in the case of SAE, its origin and pathophysiology remain relatively unknown and likely multifactorial. Hyperosmolality, parenteral nutrition, non-depolarizing neuromuscular blockers, and neurologic failure are all associated with its development. CIP is significantly associated with an increase in the mortality, duration of mechanical ventilation, and the lengths of intensive care unit and hospital stays [98, 99].

Gastrointestinal Tract

The gastrointestinal tract (GIT) is often affected in MODS/MOF. While the effects of MODS/MOF on intestinal absorption are not fully understood, it is felt to be the result of compromised blood flow, structure damage, inappropriate cell function, alteration of metabolic activity, and impairment of the gastrointestinal barrier itself [100].

Intestinal absorption of amino acids is regulated by three mechanisms: quantity of intraluminal substrate, capacity of the transport systems, and ability of the enterocyte to metabolize the substrates. In both animal and human studies, the intestinal absorption and transport of amino acids were decreased with respect to control groups in septic subjects [101, 102]. The transport of substrates through the intestinal wall is also inhibited by the decrease of mesenteric blood flow. This leads to an increase in anaerobic metabolism which results in

decreased ATP stores, subsequently leading to reduced active transport of intraluminal substrates. This dysfunction results in limited availability of intracellular substrates for the maintenance of metabolic functions and the enterocyte barrier [103].

One interesting hypothesis regarding gut dysfunction is to consider GI failure (GIF) as a motor for the development of secondary MOF since the GI tract lumen is loaded with bacteria and an increase in gut permeability would allow a massive translocation of bacterial products (Fig. 15.5). This hypothesis, raised by Marshall et al., considered gut as an "undrained abscess," and this idea of bacterial translocation was subsequently supported by several experimental studies [5, 104]. Although inflammatory GI tract damage, bacterial translocation, and development of subsequent failure of other organs become a frequent clinically found association, causality has not been proven. It is possible that the increase of the GI tract permeability and translocation are epiphenomena that occur alongside other organ dysfunctions and are not motor for the development of MODs/MOF. In a recent study, aiming to develop a GIF score for 28-day mortality prediction of ventilated patients, authors concluded GIF is often a secondary cause and not the primary cause of organ failure [105]. This conclusion points to another important issue in GIF: the need for a definition and the development of a scoring system to stratify and, if possible, predict GI tract dysfunction. The search for accurate markers has not yet yielded satisfactory results. While plasma citrulline, an amino acid mainly synthe-

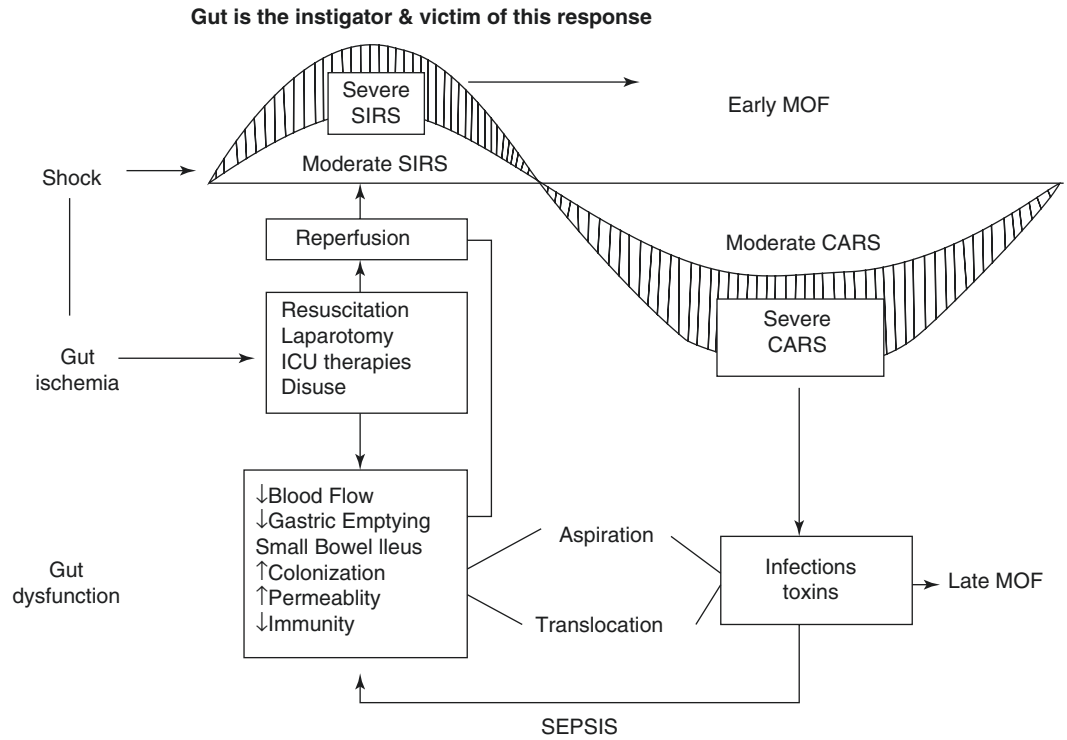

Fig. 15.5 Schematic diagram of the gut response to insult and how it influences SIRS/CARS, early vs. late MOF. Initially the insult from shock produces inflammatory cytokines inciting SIRS. If this response is too robust, early MOF may result. If damage control operation, resuscitation, or various ICU therapies control gut ischemia, then a potential ischemia-reperfusion injury may ensue further driving SIRS or promoting sepsis through the entities that drive gut dysfunction, decreased blood flow, gastric emptying/ileus, immunity, increased permeability, and colonization. Finally, once the inciting insult is dealt with, one of two clinical pathways can increase mortality: (**a**) late MOF driven by a second hit/sepsis or (**b**) CARS dictated by the patient's response to SIRS

sized from glutamine by enterocytes, has been studied as a possible marker for small bowel function, its clinical utility in diagnosis and management of GI dysfunction remains to be verified [106].

Currently, two types of GI dysfunction are seen in MOF, intra-abdominal hypertension (IAH) defined by a sustained increase in intra-abdominal pressure equal to or above 12 mmHg as measured by bladder pressures and the presence enteral feeding (EF) intolerance [107]. Reintam et al. elaborated a GIF score based upon the occurrence of feeding intolerance and IAH, ranging from level 0 (normal gastrointestinal function) to level 4 (abdominal compartment syndrome) based on a prospective, single-center study on 264 mechanically ventilated patients [108]. They concluded that the mean GIF score during the first 3 days had a prognostic value for ICU mortality. Additionally, the ESICM Working Group on Abdominal Problems published a report on terminology, definitions, and management of GI function in the ICU setting [109]. In this consensus, acute gastrointestinal injury (AGI) was scored with four grades of severity: grade I = increased risk of developing GI dysfunction or failure (a self-limiting condition); AGI grade II = GI dysfunction (a condition that requires interventions); AGI grade III = GI failure (GI function cannot be restored with interventions); and AGI grade IV = dramatically manifesting GI failure (a condition that is immediately life-threatening). They also defined primary AGI as associated with primary disease or direct injury to organs of the GI system and secondary AGI when developed as the consequence of a host response in critical illness without primary pathology in the GI system. Feeding intolerance (FI) syndrome was defined as a failure to tolerate at least 20 kcal/kg BW/day via enteral route within 72 h of feeding attempt or if enteral feeding had to be stopped for whatever clinical reason.

Liver

Liver dysfunction in MODs/MOF occurs less frequently than other organ dysfunction. This is somewhat surprising in that crucial metabolic and immunological pathways occur in the liver. Moreover, it also produces and releases high amounts of inflammatory substrates such as cytokines, bioactive lipids, and acute-phase proteins [110].

Early hepatic dysfunction occurs within hours after injury and is induced by hepatosplanchnic hypoperfusion that results in acute increases in transaminases, lactate dehydrogenase, and bilirubin. This early dysfunction is often reversible with adequate resuscitation. Late dysfunction is caused by inflammatory molecules and/or sterile DAMP and characterized by structural and functional injury [111]. Large populations of Kupffer cells and natural killer (NK) cells found in the liver are able to induce high rates of expression of endothelial adhesion molecules [112]. Increased production of inflammatory cytokines in the hepatosplanchnic area occurs despite decreased hepatic blood flow [113]. Dysfunction in the GI tract is also an alleged mechanism of liver dysfunction. Contributing agents for this gut-liver axis would be intestinally induced cytokines [114].

Hematological System

Imbalances in procoagulant and anti-fibrinolytic states that occur in MODs/MOF may lead to the development of disseminated intravascular coagulation (DIC), resulting in increased mortality due to microvascular thrombosis and resultant end-organ ischemia. While DIC is the most severe form of hematologic failure, it occurs much less frequently than isolated thrombocytopenia or abnormal clotting times. The presence of DIC usually prognosticates poor patient outcome depending on the studied population [115].

Metabolic Disturbances

Metabolic disturbances in MODS/MOF are highly dependent on timing, the inflammatory status, and organs affected. Metabolic derangements are characterized by a hypermetabolic state [116]. Common manifestations of this hypermetabolic response include hyperglycemia, increased protein catabolism, lactic acidosis, increased lipolysis, and hypertriglyceridemia. Perhaps the most common manifestation is

hyperglycemia which requires careful management and has been found to be associated with increased mortality and morbidity [117]. While seen less frequently, hypoglycemia is often associated with hepatic failure and a poor prognostic indicator.

Protein catabolism is fueled by the needs for gluconeogenesis, substrates for wound repair, acute-phase reactant production, and substrates for enterocytes and immune cells. Urinary urea nitrogen excretion is greatly augmented in the first days following injury, especially in burns and trauma where catabolic daily losses higher than 25 g are not uncommon.

Increased pro-inflammatory cytokines, mainly TNF, block some enzymes such as lipoprotein-lipase and contribute to a decrease of free fatty acids and a hypertriglyceridemia in a direct proportion to the severity of injury. Resting energy expenditure (REE) is strikingly elevated at the initial phases of MODS/MOF, but as dysfunction progresses, REE requirements decline. In the same manner, albumin and hepatic protein synthesis are downregulated [118, 119].

Treatment

General Management

Management of MODS/MOF can be broken down into three arms: preventing its development, adequate resuscitation to avoid progression if present, and selective organ support.

For prevention, adequate fluid resuscitation and oxygen support to optimize oxygen delivery to tissues are mandatory. At the same time, any potential or real source of injury or infection must be addressed in a rapid fashion. According to Surviving Sepsis Campaign guidelines [1, 120], interventions should be undertaken as soon as possible and within the first few hours after diagnosis, if feasible, including surgical debridement for necrotizing soft tissue infection, any emergency surgical procedure, burn wound excision, removal of suspected intravascular access devices, etc. If severe sepsis is present, appropriate empiric antibiotic treatment needs to be administered within the first hour of the recognition. A restricted transfusion policy for blood should be adopted among critically ill non-bleeding patients with moderate anemia as no clear benefits have been demonstrated [121].

Glucose control is also imperative since hyperglycemia has been associated with MODS/MOF through a mechanism of mitochondrial damage [122].

Once organ dysfunction is present, adequate resuscitation to preserve microcirculation and cellular metabolism is necessary. Careful hemodynamic monitoring, thoughtful use of vasopressors and fluids, and an approach minimizing the initial metabolic derailment are cornerstones in the management in this phase. The use of algorithms and criteria for early identification in organ disorder may also be useful [123, 124].

Treatment of individual organ support is important and is primarily provided in the form of hematologic, pulmonary, renal, and cardiovascular support. Hematologic failure can be restored with blood product administration. Recommendations about mechanical ventilation in the setting of ARDS have been issued regarding tidal volume, plateau pressure, PEEP, recruitment maneuvers, and prone positioning [120, 125]. Renal replacement therapy can be performed by either continuous renal replacement therapies or conventional hemodialysis with continuous renal replacement therapy being preferred in hemodynamically unstable patients. From a cardiovascular standpoint, following appropriate fluid resuscitation, vasopressors may be used to support blood pressure with norepinephrine being recommended as the first-line agent in most circumstances [120, 126]. In select patients with isolated refractory cardiac failure, devices such as intra-aortic balloon pump (IABP) and left ventricular assist devices may be considered. In cases of severe refractory cardiopulmonary failure, extracorporeal membrane oxygenation (ECMO) may be considered as a potential rescue therapy [126].

Nutritional Interventions and Their Impact on MODS/MOF Pathogenesis

Beginning in the 1980s, several studies took place that helped define how critically ill patients are fed today. In multiple comparisons between enteral and parenteral nutrition in critically ill patients, the enteral route consistently proves to be the preferred route. In several studies, trauma patients were randomized to receive early enteral nutrition (EEN) versus total parenteral nutrition (TPN). Patients receiving EEN displayed evidence of improved adaptive immunity and decreased rates of nosocomial infections [127, 128].

Also around this time, new TPN formulas designed to fit the presumed metabolic demands of critically ill patients became more readily available. In another study involving trauma patients, administration of EEN was compared with early TPN, with both regimens containing equal amounts of fat and amino acids and a calorie to nitrogen ratio of 150:1 [129]. Of note, jejunal feeding was tolerated without difficulty in 86% of the EEN patients. Postoperative infections developed in only 17% of EEN patients compared with 37% in the early TPN group. When sepsis was the only morbidity considered between the two groups, the difference was 3% in the EEN group versus 20% in the early TPN group.

By the early 1990s, there was convincing clinical evidence that EEN reduced nosocomial infections after major torso trauma [128, 129]. However, widespread acceptance of EEN was hindered by the inability to explain how EEN worked. To this day, researchers have been unable to fully explain in totality the beneficial effects of EEN.

Currently, it is proposed that both traumatic and septic shock are inciting events of the development of MOF. Both injure the gut and, with resuscitation, cause a reperfusion injury that releases pro-inflammatory mediators that result in SIRS. This also initiates a local inflammatory response that can lead to a variety of gut dysfunctions including impaired mucosal blood flow, paresis of the stomach and bowel, gastric alkalinization, duodenogastric reflux, increased permeability, epithelial apoptosis, and impaired local gut immunity [130]. Early crystalloid resuscitation can amplify inflammation, cause edema, and promote ileus, while early laparotomy with bowel manipulation can lead to gut inflammation, mucosal injury, and ileus. Standard ICU interventions can also exacerbate gut dysfunction. Vasopressors decrease mucosal perfusion, stress gastritis prophylaxis leads to gastric alkalinization, opiates contribute to ileus, antibiotics promote overgrowth of certain bacteria, and TPN results in gut disuse, all of which contribute to decreased local gut immunity, disuse atrophy, and worsening of systemic CARS.

In a short period of time, the normally sterile upper GI tract becomes colonized with potential pathogens, and the gut becomes a reservoir for bacteria and associated toxins. Bacteria and toxins escape the gut via aspiration or translocation resulting in late nosocomial infections and MOF. The resulting sepsis circles back to the gut causing further dysfunction. Thus, in this mechanism, the gut is both the instigator and victim in MODS/MOF. This conceptual framework explains how EEN is able to interrupt the vicious cycle of events to prevent late nosocomial infections and MOF. In several models, enteral nutrition has been shown to reverse mucosal hypoperfusion, attenuate the gut permeability defect, and lessen the severity of CARS seen with critical illness [16, 18, 20–22, 131].

Avoidance of Early Parenteral Nutrition

Achieving adequate caloric needs with EEN can be challenging in critically ill patients, as many of them present with concomitant comorbidities that make EEN prohibitive. As demonstrated by Heyland et al., up to 40% of ICU patients receive no nutrition, and the remaining 60% of patients only received, on average, 60% of their caloric goals [132]. Parenteral nutrition (PN) has shown benefit in providing nutrition to these patients where EEN has to be delayed or is inadequate. PN, however, is not without consequence. PN has

been shown to cause hyperglycemia, hepatocellular injury, and immunosuppression [133–136].

When to initiate PN has long been a point of controversy, debated between societies and groups for many years. To answer this question, Casaer et al. performed a large multicenter PRCT comparing early initiation of supplemental PN (within 2 days of not achieving target nutrition) with late initiation of PN (after 7 days of not achieving target nutrition) in adult ICU patients [137]. Patients receiving late initiation of PN had increased ICU and hospital survival rates without evidence of decreased functional status, decreased infection rates, and lower rates of cholestasis. There was also noted to be a modest cost savings with later initiation of PN.

While enteral nutrition is the preferred and recommended route for nutritional supplementation in critically ill patients, the American Society for Parenteral and Enteral Nutrition (ASPEN) does provide guidelines for the use of PN in patients where enteral routes are not feasible. Currently, it is recommended that patients who are severely malnourished or with high nutritional risk be considered for PN as soon as possible following admission to ICU when enteral nutrition is not possible. In patients who are considered low to moderate nutritional risk, however, PN should not be initiated prior to 7 days following admission. Use of supplemental PN should be considered after 7–10 days in all patients who are unable to meet greater than 60% of energy and protein requirements by the enteral route alone [134].

Early Enteral Nutrition

Compared with early PN, EEN has long been recognized as beneficial in critically ill patients [134, 138, 139]. While its underlying mechanism has resulted in considerable debate, EEN appears to promote vital gut functions including mucosal perfusion, intestinal transit, and mucosal permeability [130]. The gut has been recognized as an important immunologic organ, and the severity of systemic immunosuppression can be lessened by feeding the gut. Enteral nutrition supports the function of the mucosal-associated lymphoid tissue (MALT) that produces up to 70% of the body's secretory immunoglobulin A. Naïve T and B lymphocytes target and enter gut-associated lymphoid tissue where they become sensitized and stimulated by antigens present in the gut lumen. As a result, they become more responsive to potential pathogens in the external environment. Simulated lymphocytes subsequently migrate through mesenteric lymph nodes into the thoracic duct and vascular tree for distribution to extraintestinal sites of MALT. These lymphocytes provide protection with subsequent inoculation which aids in preventing late infections.

Tight Glucose Control

Glycemic control in critically ill patients has been studied extensively with efforts made to improve control of glucose levels, understand insulin interactions with varying delivery routes, and avoid extreme hyper- or hypoglycemia. Differences have been noted between intravenous and oral glucose administration leading to the belief that endogenous insulin secretion depends on both the concentration of glucose load and the route it is given [140]. Scow et al. showed in rats that 60% of oral glucose is taken up by the liver and the rest by the systemic circulation suggesting that both blood glucose levels and gut function have a role in insulin response to nutrition [141].

In a review of six randomized control trials, patients with severe acute pancreatitis showed a statistically significant risk reduction in hypoglycemia and insulin requirements in non-diabetic acute pancreatitis using enteral nutrition vs. PN. Patients receiving enteral nutrition had decreased rates of large swings in blood glucose levels, hypoglycemic events, and insulin requirements when compared to patients receiving parenteral nutrition [142].

In another study, Van den Berghe et al., subsequently, showed that parenterally fed patients required increased insulin doses to achieve normoglycemia, indicating higher blood glucose levels [117]. This idea was further supported by a

meta-analysis by Moore et al., where incidence of hyperglycemia and insulin blood levels were increased in patients receiving TPN [129]. As a result, it is generally felt that enteral nutrition is superior to parenteral nutrition from a glycemic safety profile.

More recently, the NICE-SUGAR trial elucidated that tight glucose control may not be beneficial to all ICU patients. In this study, patients receiving tight glucose control had higher rates of hypoglycemic events compared with patients in the conventional glucose control group. When 90-day mortality was compared between the two groups, the tight glycemic control group was also found to have higher mortality rates. In subgroup analysis, however, two patient groups that seemed to do better with tight glucose control were found to be trauma patients and patients receiving corticosteroids [143].

Immune-Enhancing Enteral Formulas

Current guidelines for the use of immune-modulating enteral formulas are available in postoperative surgical patients after major surgery, trauma patients, large (>30% total body surface area) burn patients, cancer patients, and critically ill patients requiring mechanical ventilation. The various supplements responsible for immune modulation include arginine, omega-3 fatty acids, glutamine, selenium, fish oil, vitamin C, and vitamin E. Outcomes using these immune-modulating enteral formulas have been shown to be associated with reductions in infection, length of mechanical ventilation, and hospital length of stay. The data, however, does not show any reduction in mortality [144–149].

According to Sanderson et al., immune-modulating enteral formulas are felt to directly reduce inflammation by lowering the expression of pro-inflammatory cytokines such as interleukin (IL)-6. In this paper, four lines of evidence were proposed as evidence that these enteral formulas directly lessened inflammation: (1) enteral nutrition directly affects the inflamed intestine; (2) changes in inflammatory markers precede repletion of nutritional status; (3) molecular pathways exist linking changes in luminal contents to the expression of class MHC genes in intestinal epithelium in animal studies; and (4) enteral formulas have a direct effect on cytokine expression by intestinal epithelial cells [150].

In a study performed by Moore et al., 98 trauma patients sustaining major torso trauma were compared on demographics and injury severity score and were randomized to early enteral nutrition with an "immune-enhancing" formula or a standard stress enteral formula. After 7 days of feeding, both groups experienced similar increases in serum total protein, albumin, and transferrin concentrations. Patients randomized to receive the "immune-enhancing" formula, however, experienced significantly greater increases in total lymphocytes, T lymphocytes, and T-helper cell counts, fewer intra-abdominal abscesses, and decreased rates of MOF concluding that "immune-enhancing" enteral diets offer clinical benefits in stressed surgical patients [149].

Further supporting the benefits of immune-modulating enteral nutrition, Galban et al. concluded that not only do immune-enhancing enteral feeds reduce bacteremia and secondary nosocomial infections in septic patients, but also they reduce mortality. These formulas were fortified with arginine, mRNA, and omega-3 fatty acids from fish oil [151].

Arginine

Immune-enhancing enteral diets fortified with arginine have convincingly been shown to be beneficial in surgical patients undergoing major operation and in trauma patients at high risk for MODS/MOF [152, 153]. However, the use of arginine in sepsis remains controversial. Arginine is a semi-essential amino acid that promotes lymphocyte and fibroblast proliferation. It serves as an intracellular substrate for nitric oxide production in macrophages to improve bactericidal activity. It is also a secretagogue that increases levels of somatostatin, prolactin, growth hormone, insulin, and glucagon.

The controversy of arginine in sepsis centers around the fact that arginine is a competitive substrate for arginase 1 and inducible nitric oxide synthase. During severe sepsis/septic shock, there is upregulation of inducible nitric oxide synthase, and available arginine is converted to citrulline and nitric oxide. Arginine levels are subsequently depleted, which suppresses lymphocyte proliferation, resulting in immunosuppression. The concern is that arginine supplementation during severe sepsis/septic shock would result in increased nitric oxide production, causing pathologic vasodilation, worsening the patient's shock. While this scenario is physiologically possible, it is clinically unproven and not relevant as arginine is rarely provided at high doses during resuscitation of hemodynamically unstable with severe sepsis/septic shock.

Several studies have convincingly demonstrated upregulation of arginase 1 in myeloid-derived suppressor cells (MDSCs) after trauma as well as in chronic sepsis [154–157]. When arginase 1 is upregulated, arginine is shunted to the production of ornithine, which is subsequently converted to polyamines and prolines. These substrates are used in wound healing. Arginine supplementation in this setting would increase arginine levels and restore lymphocyte proliferation, while converted arginine would increase polyamines and prolines, promoting wound healing. Given that MDSC upregulation is a prominent feature of the PICS phenotype, arginine supplementation seems like a promising intervention; however, further study is needed.

Glutamine

Glutamine has long been well regarded in the nutritional support of injury, not only because it is an essential amino acid but also because its use has been associated with good outcomes in critical illness. Low plasma glutamine concentration is also an independent predictor of poor outcomes. In a multicenter RCT, Wernerman et al. evaluated intravenous glutamine administration and effects on SOFA scores and mortality [158]. This study demonstrated that administration of glutamine was associated with lower mortality, however, not statistically significant when studied by intention to treat. Glutamine administration also did not alter serial SOFA scores. In another randomized, controlled, and double-blind study, glutamine supplementation did not reduce the appearance of new infections, 6-month mortality, length of stay, and SOFA score nor the use of antibiotics [159].

Other studies, however, demonstrated that glutamine repletion was associated with a reduced rate of infectious complications and a better glycemic control profile than that seen in control groups. However, no changes in SOFA, ICU and hospital length of stay, or mortality were appreciated [160].

In a multicenter RCT, 2-by-2 factorial trial was performed on patients with MOF requiring mechanical ventilation who received nutrition supplemented with glutamine, antioxidants, both, or placebo (REDOXS) with the primary outcome being 28-day mortality [161]. Results were striking in that there was a trend toward increased mortality at 28 days among patients in the study group versus control group (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% confidence interval [CI], 1.00–1.64; $P = 0.05$). Also, hospital mortality and mortality at 6 months were significantly higher among those who received glutamine. There was no difference in rates of organ failure or infectious complications between the study group and control group.

This study sparked great controversy among the scientific community. Criticism is mainly directed at the potential toxicity of the amount in glutamine support (60% of total dietary protein) and in a presumed bias in the allocation of patients according to the number of failing organs at baseline. According to REDOXS study, recommendations about glutamine support are maintained in EN in burn and trauma patients but a caution in patients with shock and MOF, given the possibility of increasing mortality.

Lipids

Omega-6 polyunsaturated fatty acids (Ω-6 PUFA) are essential and required in the inflam-

matory response. In a recent study on patients with sepsis compared to healthy controls, arachidonic acid (AA) concentrations were more reduced among septic patients [162]. Gene expression studies have also confirmed a reduction of the induction of the expression of messenger RNA of cyclooxygenase 2 (COX-2). As a result, authors concluded that reduction in the release of AA and its metabolites, 11- HETE, PGE2, and TXB2, was associated with worse outcome.

Monounsaturated fatty acids (Ω-9 MUFA) and oleic acid metabolites are generally considered as less active than Ω-6 PUFA in the setting of injury and organ failure. In a study of 100 critically ill, mostly surgical patients receiving PN, patients were randomly assigned to receive emulsions of soybean oil (Ω-6) or olive oil-based fat emulsion (Ω-9) [163]. Between groups, no significant differences were found in mortality, length of stay, rates of infectious and noninfectious complications, glycemic control, oxidative stress markers, immune function, and inflammatory markers. These results confirm a previous, observational, and prospective study examining a smaller number of critically ill patients receiving PN, where, again, no differences between the control group (soybean oil) and the study group (olive oil-based fat emulsion), with regard to infection rate, variations on the protein levels of acute phase, clinical variables (stay, mortality), and leukocytosis, were identified [164]. In fact, the study group had a trend toward greater leukocytes, challenging the assumptions that Ω-9 have either a presumed anti-inflammatory or neutral effect.

Polyunsaturated fatty acids (Ω-3 PUFA) have been studied in patients in MOF with ALI or ARDS. Rice et al. performed a randomized, double-blind, and multicenter placebo-controlled OMEGA study on patients with respiratory failure to determine if the supplementation of the diet with n-3 PUFA, γ-linolenic acid, and antioxidants would increase mechanical ventilation-free days [165]. The study was stopped for futility, and the authors concluded that supplementation did not improve the clinical outcomes of patients with ALI and may be harmful.

Another randomized, multicenter study examined the effects of an enteral diet enriched with eicosapentaenoic acid, γ-linolenic acid, and antioxidants on the incidence of organ dysfunction and nosocomial infections in patients with respiratory failure, against a control group with standard enteral nutrition [166]. Results showed that there were no differences in PaO_2/FiO_2 ratio, mechanical ventilation days, or nosocomial infection rate.

Future Options

After decades of searching a magic bullet to block the inflammatory process resulting in MODs/MOF, plenty of conflicting results have been generated. As a result, research is being directed to new approaches and new targets.

Inhibition of C5a in MODS/MOF of septic origin is promising, with preliminary results in rheumatoid diseases [167]. Mesenchymal stem cells may also have an application due to the large number of studies supporting an immunosuppressive function of these cells through production of activated molecules that enhance repair [168–170]. Regulation of neural pathways is another promising strategy. Angiotensin-converting enzyme inhibitors (ACEI) are known to ameliorate depressed autonomic function (heart rate variability [HRV]) and improve endothelial function; in an retrospective study on 178 MODS patients, ACEI treatment was associated with lower short- and longer-term mortality compared with patients without ACEI [171]. On the side of mitochondrial therapies, different therapies have been proposed targeting membrane stabilization, mitochondrial ROS scavenger, mitochondrial antioxidants, and substrate and/or cofactor provision, with promising results in different experimental studies [172].

The horizon for MODS/MOF therapy could be altered by advances in gene therapy, tissue regeneration, and molecular reprogramming, also known as "health engineering," where a joint approach of critical care, systems sciences, molecular engineering, computational biology, and applied mathematics would work for improving prognosis issues [173, 174].

Current Epidemic of PICS and the Nutritional Implications

Based on the evolving clinical epidemiology of MODS/MOF and new immunologic observations, the previously accepted SIRS/CARS conceptual framework has now evolved to include the PICS paradigm (Fig. 15.4) [24]. As discussed previously, trauma or sepsis insults result in simultaneous induction of SIRS and CARS. If SIRS is allowed to get out of control, it can precipitate an early MODS/MOF scenario with a fulminate death trajectory. However, with advancements in medicine and ICU care, the MODS/MOF is being better managed, and more patients are surviving. While some patients go on to a full recovery, some patients are entering into a chronic critically ill state known as PICS with a clinical course characterized by manageable organ dysfunction, recurrent inflammatory insults (i.e., repeat operations or recurrent nosocomial infections), a persistent acute-phase response with dramatic loss of lean body mass despite adequate nutritional support, poor wound healing, and pressure-induced chronic wounds. This phenotype has largely replaced late MOF as the cause of prolonged ICU stays and usually results in a slow indolent death.

This persistent low-grade inflammatory and catabolic state produces a "cachexia" phenotype for which current ICU interventions are not effective at reversing. Currently, there is no existing literature for nutritional support in PICS. Some recommendations have been made by extrapolating data from other disease states with chronic or persistent inflammation such as aging sarcopenia, cancer cachexia, and major burns.

Two strategies used to combat aging sarcopenia and indirectly PICS are anabolic nutrition and resistance exercise. However, when exercise becomes challenging in the bedridden ICU patient, the primary goal becomes nutritional support with a targeted daily protein intake of 0.8–1.5 g/kg/d and dietary-derived amino acids to close or prevent muscle protein catabolism [175–178]. In conjunction with the Society on Sarcopenia, Cachexia and Wasting Disorders, Morley et al. outlined several strategies for providing nutritional supplementation in the aging populations that also likely apply to patients at risk for PICS. Strategies included a combined approach of exercise when possible and increasing supplemental leucine and creatine [179].

It is well-known that a persistent catabolic state occurs following major burns [180]. In hopes of combating this muscle breakdown and protein loss sustained after major burns, anabolic supplementation has become a major area of focus for this patient population. Several anabolic strategies have been studied including the use of growth hormone, intensive insulin therapy, oxandrolone, propranolol, and inpatient active exercise programs. Growth hormone has been shown to be a potent anabolic agent and salutary modulator of post-traumatic responses at 12-month follow-up [181]. Strict glucose control (80–160 mg/dL) in pediatric patients sustaining >30% TBSA burns resulted in increased bone mineralization and muscle strength in this patient population [182]. In addition, studies have shown that oxandrolone substantially decreased resting energy expenditure, increased insulin-like growth factor-1 secretion, and, in combination with exercise, increased lean body mass and muscle strength considerably, while propranolol administration resulted in a reduction of burn-induced proteolysis with an increase in muscle anabolism [183, 184]. Currently, these strategies are being explored in the PICS population (Table 15.3).

Table 15.3 Conditioning factors in the administration of nutritional support in organ dysfunction

Limitations	Consequences
Phase of inflammatory response	Immunoregulators/immunostimulants
Available commercial formulations	Lack of studies with isolated nutrients
Prominence in organ dysfunction	Tailored pharmaconutrition according to clinical situation

Conclusion

The presence of MODS/MOF in the outcome of critically ill patients continues to be a major challenge for clinicians. Its presence is clearly associated with worse prognosis and outcomes as well as increasing hospital costs.

The epidemiology of MODS/MOF continues to evolve, with the underlying mechanistic paradigm of SIRS/CARS once again shifting to now include PICS. As our population continues to age, the number of critically ill patients in the ICU expressing the PICS phenotype is likely to increase prompting the need for further research and more effective approaches to nutritional interventions. While EEN continues to be a valid concept in the care of critically ill patients, nutrition in the later clinical course becomes increasingly more complex, and there needs to be more weight placed on the role of "anabolic nutrition," use of supplemental agents, and use of immune-modulating enteral formulas.

References

1. 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.
2. Eiseman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet. 1977;144(3):323–6.
3. Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet. 2004;364(9433):545–8.
4. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40(4):501–10; discussion 10–2.
5. Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract. The "undrained abscess" of multiple organ failure. Ann Surg. 1993;218(2):111–9.
6. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med. 2012;40(4):1129–35.
7. Moore FA, Moore EE. Evolving concepts in the pathogenesis of postinjury multiple organ failure. Surg Clin North Am. 1995;75(2):257–77.
8. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. NCHS Data Brief. 2011;62:1–8.
9. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012;40(3):754–61.
10. Brattstrom O, Granath F, Rossi P, Oldner A. Early predictors of morbidity and mortality in trauma patients treated in the intensive care unit. Acta Anaesthesiol Scand. 2010;54(8):1007–17.
11. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, et al. Epidemiology of trauma deaths: a reassessment. J Trauma. 1995;38(2):185–93.
12. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. J Trauma Acute Care Surg. 2013;74(3):774–9.
13. Balk RA, Bone RC. The septic syndrome. Definition and clinical implications. Crit Care Clin. 1989;5(1):1–8.
14. American College of Chest Physicians, & Society of Critical Care Medicine Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20(6):864–74.
15. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Med. 2003;29(4):530–8.
16. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. Am J Surg. 2002;183(4):390–8.
17. 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.
18. 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.
19. Peng YZ, Yuan ZQ, Xiao GX. Effects of early enteral feeding on the prevention of enterogenic infection in severely burned patients. Burns. 2001;27(2):145–9.
20. Dobbins WO 3rd. Gut immunophysiology: a gastroenterologist's view with emphasis on pathophysiology. Am J Phys. 1982;242(1):G1–8.
21. 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.
22. Alverdy JC, Laughlin RS, Wu L. Influence of the critically ill state on host-pathogen interactions within the intestine: gut-derived sepsis redefined. Crit Care Med. 2003;31(2):598–607.
23. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis cam-

paign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.
24. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
25. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Arch Surg. 2005;140(5):432–8; discussion 8–40.
26. Kallinen O, Maisniemi K, Bohling T, Tukiainen E, Koljonen V. Multiple organ failure as a cause of death in patients with severe burns. J Burn Care Res. 2012;33(2):206–11.
27. Cabre L, Mancebo J, Solsona JF, Saura P, Gich I, Blanch L, et al. Multicenter study of the multiple organ dysfunction syndrome in intensive care units: the usefulness of Sequential Organ Failure Assessment scores in decision making. Intensive Care Med. 2005;31(7):927–33.
28. Ulvik A, Kvale R, Wentzel-Larsen T, Flaatten H. Multiple organ failure after trauma affects even long-term survival and functional status. Crit Care. 2007;11(5):R95.
29. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. Ann Surg. 1985;202(6):685–93.
30. Zimmerman JE, Knaus WA, Sun X, Wagner DP. Severity stratification and outcome prediction for multisystem organ failure and dysfunction. World J Surg. 1996;20(4):401–5.
31. Hortiguela-Martin VA, Sanchez-Casado M, Rodriguez-Villar S, Quintana-Diaz M, Marco-Schulke C, Gomez-Tello V, et al. Post-Intensive Care Unit mortality and related prognostic factors in a cohort of critically ill patients with multi-organ dysfunction. Med Clin (Barc). 2013;140(11):479–86.
32. Lone NI, Walsh TS. Impact of intensive care unit organ failures on mortality during the five years after a critical illness. Am J Respir Crit Care Med. 2012;186(7):640–7.
33. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, et al. The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA. 1996;276(10):802–10.
34. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.
35. Cook R, Cook D, Tilley J, Lee K, Marshall J, Canadian Critical Care Trials Group. Multiple organ dysfunction: baseline and serial component scores. Crit Care Med. 2001;29(11):2046–50.
36. Lorente JA, Vallejo A, Galeiras R, Tomicic V, Zamora J, Cerda E, et al. Organ dysfunction as estimated by the sequential organ failure assessment score is related to outcome in critically ill burn patients. Shock. 2009;31(2):125–31.
37. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med. 1998;26(11):1793–800.
38. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438–47.
39. Bota DP, Melot C, Ferreira FL, Ba VN, Vincent JL. The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction. Intensive Care Med. 2002;28(11):1619–24.
40. Zygun D, Berthiaume L, Laupland K, Kortbeek J, Doig C. SOFA is superior to MOD score for the determination of non-neurologic organ dysfunction in patients with severe traumatic brain injury: a cohort study. Crit Care. 2006;10(4):R115.
41. Vincent JL, Moreno R. Clinical review: scoring systems in the critically ill. Crit Care. 2010;14(2):207.
42. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10(3):R73.
43. Molitoris BA, Levin A, Warnock DG, Joannidis M, Mehta RL, Kellum JA, et al. Improving outcomes of acute kidney injury: report of an initiative. Nat Clin Pract Nephrol. 2007;3(8):439–42.
44. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1–85.
45. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646–9.
46. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the berlin definition. JAMA. 2012;307(23):2526–33.
47. Chen GY, Nunez G. Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol. 2010;10(12):826–37.
48. Andersson U, Tracey KJ. HMGB1 is a therapeutic target for sterile inflammation and infection. Annu Rev Immunol. 2011;29:139–62.
49. Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. Nat Rev Immunol. 2003;3(10):791–800.
50. Gao L, Flores C, Fan-Ma S, Miller EJ, Moitra J, Moreno L, et al. Macrophage migration inhibitory factor in acute lung injury: expression, biomarker, and associations. Transl Res. 2007;150(1):18–29.

51. Donnelly SC, Bucala R, Metz CN, Grant IS, Robertson CR, Haslett C. Macrophage migration inhibitory factor and acute lung injury. Chest. 1999;116(1 Suppl):111S.
52. Rittirsch D, Redl H, Huber-Lang M. Role of complement in multiorgan failure. Clin Dev Immunol. 2012;2012:962927.
53. Rittirsch D, Flierl MA, Nadeau BA, Day DE, Huber-Lang M, Mackay CR, et al. Functional roles for C5a receptors in sepsis. Nat Med. 2008;14(5):551–7.
54. Silasi-Mansat R, Zhu H, Popescu NI, Peer G, Sfyroera G, Magotti P, et al. Complement inhibition decreases the procoagulant response and confers organ protection in a baboon model of Escherichia coli sepsis. Blood. 2010;116(6):1002–10.
55. Rosas-Ballina M, Tracey KJ. The neurology of the immune system: neural reflexes regulate immunity. Neuron. 2009;64(1):28–32.
56. Tracey KJ. Reflex control of immunity. Nat Rev Immunol. 2009;9(6):418–28.
57. Doerschug KC, Delsing AS, Schmidt GA, Haynes WG. Impairments in microvascular reactivity are related to organ failure in human sepsis. Am J Physiol Heart Circ Physiol. 2007;293(2):H1065–71.
58. Shapiro NI, Yano K, Okada H, Fischer C, Howell M, Spokes KC, et al. A prospective, observational study of soluble FLT-1 and vascular endothelial growth factor in sepsis. Shock. 2008;29(4):452–7.
59. Shapiro NI, Schuetz P, Yano K, Sorasaki M, Parikh SM, Jones AE, et al. The association of endothelial cell signaling, severity of illness, and organ dysfunction in sepsis. Crit Care. 2010;14(5):R182.
60. David S, Mukherjee A, Ghosh CC, Yano M, Khankin EV, Wenger JB, et al. Angiopoietin-2 may contribute to multiple organ dysfunction and death in sepsis*. Crit Care Med. 2012;40(11):3034–41.
61. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med. 2004;32(9):1825–31.
62. Trzeciak S, McCoy JV, Phillip Dellinger R, Arnold RC, Rizzuto M, Abate NL, et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med. 2008;34(12):2210–7.
63. Trzeciak S, Cinel I, Phillip Dellinger R, Shapiro NI, Arnold RC, Parrillo JE, et al. Resuscitating the microcirculation in sepsis: the central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. Acad Emerg Med. 2008;15(5):399–413.
64. Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. Crit Care Med. 2007;35(9 Suppl):S441–8.
65. Abraham E, Singer M. Mechanisms of sepsis-induced organ dysfunction. Crit Care Med. 2007;35(10):2408–16.
66. Harrois A, Huet O, Duranteau J. Alterations of mitochondrial function in sepsis and critical illness. Curr Opin Anaesthesiol. 2009;22(2):143–9.
67. Haden DW, Suliman HB, Carraway MS, Welty-Wolf KE, Ali AS, Shitara H, et al. Mitochondrial biogenesis restores oxidative metabolism during Staphylococcus aureus sepsis. Am J Respir Crit Care Med. 2007;176(8):768–77.
68. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219–23.
69. Carre JE, Orban JC, Re L, Felsmann K, Iffert W, Bauer M, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med. 2010;182(6):745–51.
70. Jeger V, Djafarzadeh S, Jakob SM, Takala J. Mitochondrial function in sepsis. Eur J Clin Invest. 2013;43(5):532–42.
71. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, et al. A genomic storm in critically injured humans. J Exp Med. 2011;208(13):2581–90.
72. Leavy O. Inflammation: trauma kicks up a storm. Nat Rev Immunol. 2011;12(1):3.
73. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
74. Rubenfeld GD, 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(16):1685–93.
75. Linko R, Okkonen M, Pettila V, Perttila J, Parviainen I, Ruokonen E, et al. Acute respiratory failure in intensive care units. FINNALI: a prospective cohort study. Intensive Care Med. 2009;35(8):1352–61.
76. Villar J, Blanco J, Anon JM, Santos-Bouza A, Blanch L, Ambros A, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med. 2011;37(12):1932–41.
77. Sigurdsson MI, Sigvaldason K, Gunnarsson TS, Moller A, Sigurdsson GH. Acute respiratory distress syndrome: nationwide changes in incidence, treatment and mortality over 23 years. Acta Anaesthesiol Scand. 2013;57(1):37–45.
78. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med. 2013;368(9):795–805.
79. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med. 2013;368(9):806–13.
80. Wang CY, Calfee CS, Paul DW, Janz DR, May AK, Zhuo H, et al. One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. Intensive Care Med. 2014;40(3):388–96.
81. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(8):788–800.

82. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1334–49.
83. Tsushima K, King LS, Aggarwal NR, De Gorordo A, D'Alessio FR, Kubo K. Acute lung injury review. Intern Med. 2009;48(9):621–30.
84. Bagshaw SM, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G, et al. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med. 2009;35(5):871–81.
85. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative Workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12.
86. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
87. Huber W, Schneider J, Lahmer T, Kuchle C, Jungwirth B, Schmid RM, et al. Validation of RIFLE, AKIN, and a modified AKIN definition ("backward classification") of acute kidney injury in a general ICU: analysis of a 1-year period. Medicine (Baltimore). 2018;97(38):e12465.
88. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380(9843):756–66.
89. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, Group NM-aI. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54(6):1012–24.
90. Srisawat N, Wen X, Lee M, Kong L, Elder M, Carter M, et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol. 2011;6(8):1815–23.
91. Obermuller N, Geiger H, Weipert C, Urbschat A. Current developments in early diagnosis of acute kidney injury. Int Urol Nephrol. 2014;46(1):1–7.
92. Werdan K, Schmidt H, Ebelt H, Zorn-Pauly K, Koidl B, Hoke RS, et al. Impaired regulation of cardiac function in sepsis, SIRS, and MODS. Can J Physiol Pharmacol. 2009;87(4):266–74.
93. Hunter JD, Doddi M. Sepsis and the heart. Br J Anaesth. 2010;104(1):3–11.
94. Matsuda N, Hattori Y. Vascular biology in sepsis: pathophysiological and therapeutic significance of vascular dysfunction. J Smooth Muscle Res. 2007;43(4):117–37.
95. Levy B, Collin S, Sennoun N, Ducrocq N, Kimmoun A, Asfar P, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. Intensive Care Med. 2010;36(12):2019–29.
96. Lamar CD, Hurley RA, Taber KH. Sepsis-associated encephalopathy: review of the neuropsychiatric manifestations and cognitive outcome. J Neuropsychiatry Clin Neurosci. 2011;23(3):237–41.
97. Consales G, De Gaudio AR. Sepsis associated encephalopathy. Minerva Anestesiol. 2005;71(1–2):39–52.
98. Garnacho-Montero J, Amaya-Villar R, Garcia-Garmendia JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. Crit Care Med. 2005;33(2):349–54.
99. Garnacho-Montero J, Madrazo-Osuna J, Garcia-Garmendia JL, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar A, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med. 2001;27(8):1288–96.
100. Ortiz Leyba C, Lopez Martinez J, Blesa Malpica AL. Nutritional support in sepsis. Nutr Hosp. 2005;20(Suppl 2):51–3.
101. Gardiner K, Barbul A. Intestinal amino acid absorption during sepsis. JPEN J Parenter Enteral Nutr. 1993;17(3):277–83.
102. Salloum RM, Copeland EM, Souba WW. Brush border transport of glutamine and other substrates during sepsis and endotoxemia. Ann Surg. 1991;213(5):401–9; discussion 9–10.
103. Rombeau JL, Takala J. Gut dysfunction in critical illness. Clin Nutr. 1997;16(2):57–60.
104. Louis K, Netea MG, Carrer DP, Kotsaki A, Mylona V, Pistiki A, et al. Bacterial translocation in an experimental model of multiple organ dysfunctions. J Surg Res. 2013;183(2):686–94.
105. Reintam Blaser A, Poeze M, Malbrain ML, Bjorck M, Oudemans-van Straaten HM, Starkopf J, et al. 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.
106. Piton G, Manzon C, Cypriani B, Carbonnel F, Capellier G. Acute intestinal failure in critically ill patients: is plasma citrulline the right marker? Intensive Care Med. 2011;37(6):911–7.
107. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. Intensive Care Med. 2006;32(11):1722–32.
108. Reintam A, Parm P, Kitus R, Starkopf J, Kern H. Gastrointestinal failure score in critically ill patients: a prospective observational study. Crit Care. 2008;12(4):R90.
109. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012; 38(3):384–94.
110. Dhainaut JF, Marin N, Mignon A, Vinsonneau C. Hepatic response to sepsis: interaction between

coagulation and inflammatory processes. Crit Care Med. 2001;29(7 Suppl):S42–7.
111. Spapen H. Liver perfusion in sepsis, septic shock, and multiorgan failure. Anat Rec (Hoboken). 2008;291(6):714–20.
112. Olanders K, Sun Z, Borjesson A, Dib M, Andersson E, Lasson A, et al. The effect of intestinal ischemia and reperfusion injury on ICAM-1 expression, endothelial barrier function, neutrophil tissue influx, and protease inhibitor levels in rats. Shock. 2002;18(1):86–92.
113. Poeze M, Ramsay G, Buurman WA, Greve JW, Dentener M, Takala J. Increased hepatosplanchnic inflammation precedes the development of organ dysfunction after elective high-risk surgery. Shock. 2002;17(6):451–8.
114. Soeters PB, Luyer MD, Greve JW, Buurman WA. The significance of bowel permeability. Curr Opin Clin Nutr Metab Care. 2007;10(5):632–8.
115. Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, Kurosawa S, Stepien D, Valentine C, et al. Sepsis: multiple abnormalities, heterogeneous responses, and evolving understanding. Physiol Rev. 2013;93(3):1247–88.
116. Cerra FB. Hypermetabolism, organ failure, and metabolic support. Surgery. 1987;101(1):1–14.
117. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
118. Frankenfield DC, Omert LA, Badellino MM, Wiles CE 3rd, Bagley SM, Goodarzi S, et al. Correlation between measured energy expenditure and clinically obtained variables in trauma and sepsis patients. JPEN J Parenter Enteral Nutr. 1994;18(5):398–403.
119. Dickerson RN. Optimal caloric intake for critically ill patients: first, do no harm. Nutr Clin Pract. 2011;26(1):48–54.
120. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45(3):486–552.
121. Leal-Noval SR, Munoz-Gomez M, Jimenez-Sanchez M, Cayuela A, Leal-Romero M, Puppo-Moreno A, et al. Red blood cell transfusion in non-bleeding critically ill patients with moderate anemia: is there a benefit? Intensive Care Med. 2013;39(3):445–53.
122. Gunst J, Derese I, Aertgeerts A, Ververs EJ, Wauters A, Van den Berghe G, et al. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. Crit Care Med. 2013;41(1):182–94.
123. Moore LJ, Turner KL, Todd SR, McKinley B, Moore FA. Computerized clinical decision support improves mortality in intra abdominal surgical sepsis. Am J Surg. 2010;200(6):839–43; discussion 43–4.
124. Levitt JE, Calfee CS, Goldstein BA, Vojnik R, Matthay MA. Early acute lung injury: criteria for identifying lung injury prior to the need for positive pressure ventilation*. Crit Care Med. 2013;41(8):1929–37.
125. Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS with prone positioning. Chest. 2017;151(1):215–24.
126. Squiers JJ, Lima B, DiMaio JM. Contemporary extracorporeal membrane oxygenation therapy in adults: fundamental principles and systematic review of the evidence. J Thorac Cardiovasc Surg. 2016;152(1):20–32.
127. 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 22–3.
128. 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.
129. 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.
130. Hassoun HT, Kone BC, Mercer DW, Moody FG, Weisbrodt NW, Moore FA. Post-injury multiple organ failure: the role of the gut. Shock. 2001;15(1):1–10.
131. Moore FA, Moore EE, Poggetti R, McAnena OJ, Peterson VM, Abernathy CM, et al. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. J Trauma. 1991;31(5):629–36; discussion 36–8.
132. 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(1):74–83.
133. Marik PE, Pinsky M. Death by parenteral nutrition. Intensive Care Med. 2003;29(6):867–9.
134. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, 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. 2016;40(2):159–211.
135. Sandstrom R, Drott C, Hyltander A, Arfvidsson B, Schersten T, Wickstrom I, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. Ann Surg. 1993;217(2):185–95.
136. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr. 2007;85(5):1171–84.
137. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late par-

enteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17.
138. Moore FA, Moore EE. The evolving rationale for early enteral nutrition based on paradigms of multiple organ failure: a personal journey. Nutr Clin Pract. 2009;24(3):297–304.
139. Rosenthal MD, Vanzant EL, Martindale RG, Moore FA. Evolving paradigms in the nutritional support of critically ill surgical patients. Curr Probl Surg. 2015;52(4):147–82.
140. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic sujbjects. J Clin Invest. 1967;46(12):1954–62.
141. Scow RO, Cornfield J. Quantitative relations between the oral and intravenous glucose tolerance curves. Am J Phys. 1954;179(3):435–8.
142. Petrov MS, Zagainov VE. Influence of enteral versus parenteral nutrition on blood glucose control in acute pancreatitis: a systematic review. Clin Nutr. 2007;26(5):514–23.
143. The NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
144. Consensus recommendations from the US summitt on immune-enhancing enteral therapy. JPEN J Parenter Enteral Nutr. 2001;25(2 Suppl):S61–3.
145. Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. Ann Surg. 1999;229(4):467–77.
146. 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.
147. Montejo JC, Zarazaga A, Lopez-Martinez J, Urrutia G, Roque M, Blesa AL, et al. Immunonutrition in the intensive care unit. A systematic review and consensus statement. Clin Nutr. 2003;22(3):221–33.
148. Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med. 1995;23(3):436–49.
149. Moore FA, Moore EE, Kudsk KA, Brown RO, Bower RH, Koruda MJ, et al. Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. J Trauma. 1994;37(4):607–15.
150. Sanderson IR, Croft NM. The anti-inflammatory effects of enteral nutrition. JPEN J Parenter Enteral Nutr. 2005;29(4 Suppl):S134–8; discussion S8–40, S84–8.
151. Galban C, Montejo JC, Mesejo A, Marco P, Celaya S, Sanchez-Segura JM, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med. 2000;28(3):643–8.
152. 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(3):385–99, 99 e1.
153. Moore FA. Effects of immune-enhancing diets on infectious morbidity and multiple organ failure. JPEN J Parenter Enteral Nutr. 2001;25(2 Suppl):S36–42; discussion S-3.
154. Mathias B, Delmas AL, Ozrazgat-Baslanti T, Vanzant EL, Szpila BE, Mohr AM, et al. Human myeloid-derived suppressor cells are associated with chronic immune suppression after severe sepsis/septic shock. Ann Surg. 2017;265(4):827–34.
155. Zhu X, Pribis JP, Rodriguez PC, Morris SM Jr, Vodovotz Y, Billiar TR, et al. The central role of arginine catabolism in T-cell dysfunction and increased susceptibility to infection after physical injury. Ann Surg. 2014;259(1):171–8.
156. Darcy CJ, Minigo G, Piera KA, Davis JS, McNeil YR, Chen Y, et al. Neutrophils with myeloid derived suppressor function deplete arginine and constrain T cell function in septic shock patients. Crit Care. 2014;18(4):R163.
157. Gey A, Tadie JM, Caumont-Prim A, Hauw-Berlemont C, Cynober L, Fagon JY, et al. Granulocytic myeloid-derived suppressor cells inversely correlate with plasma arginine and overall survival in critically ill patients. Clin Exp Immunol. 2015;180(2):280–8.
158. 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.
159. 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.
160. Grau T, Bonet A, Minambres E, Pineiro L, Irles JA, Robles A, et al. The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. Crit Care Med. 2011;39(6):1263–8.
161. 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.
162. Bruegel M, Ludwig U, Kleinhempel A, Petros S, Kortz L, Ceglarek U, et al. Sepsis-associated changes of the arachidonic acid metabolism and their diagnostic potential in septic patients. Crit Care Med. 2012;40(5):1478–86.
163. 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.
164. Mateu-de Antonio J, Grau S, Luque S, Marin-Casino M, Albert I, Ribes E. Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. Br J Nutr. 2008;99(4):846–54.
165. Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA. 2011;306(14):1574–81.
166. Grau-Carmona T, Moran-Garcia V, Garcia-de-Lorenzo A, Heras-de-la-Calle G, Quesada-Bellver B, Lopez-Martinez J, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. Clin Nutr. 2011;30(5):578–84.
167. Wagner E, Frank MM. Therapeutic potential of complement modulation. Nat Rev Drug Discov. 2010;9(1):43–56.
168. Ghannam S, Bouffi C, Djouad F, Jorgensen C, Noel D. Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. Stem Cell Res Ther. 2010;1(1):2.
169. Groeneveld KM, Leenen LP, Koenderman L, Kesecioglu J. Immunotherapy after trauma: timing is essential. Curr Opin Anaesthesiol. 2011;24(2):219–23.
170. Gotts JE, Matthay MA. Mesenchymal stem cells and acute lung injury. Crit Care Clin. 2011;27(3):719–33.
171. Schmidt H, Hoyer D, Rauchhaus M, Prondzinsky R, Hennen R, Schlitt A, et al. ACE-inhibitor therapy and survival among patients with multiorgan dysfunction syndrome (MODS) of cardiac and non-cardiac origin. Int J Cardiol. 2010;140(3):296–303.
172. Dare AJ, Phillips AR, Hickey AJ, Mittal A, Loveday B, Thompson N, et al. A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. Free Radic Biol Med. 2009;47(11):1517–25.
173. Teoh H, Quan A, Creighton AK, Annie Bang KW, Singh KK, Shukla PC, et al. BRCA1 gene therapy reduces systemic inflammatory response and multiple organ failure and improves survival in experimental sepsis. Gene Ther. 2013;20(1):51–61.
174. Cobb JP. MORE for multiple organ dysfunction syndrome: Multiple Organ REanimation, REgeneration, and REprogramming. Crit Care Med. 2010;38(11):2242–6.
175. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med. 1994;330(25):1769–75.
176. Sheffield-Moore M, Paddon-Jones D, Sanford AP, Rosenblatt JI, Matlock AG, Cree MG, et al. Mixed muscle and hepatic derived plasma protein metabolism is differentially regulated in older and younger men following resistance exercise. Am J Physiol Endocrinol Metab. 2005;288(5):E922–9.
177. Paddon-Jones D, Sheffield-Moore M, Urban RJ, Sanford AP, Aarsland A, Wolfe RR, et al. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. J Clin Endocrinol Metab. 2004;89(9):4351–8.
178. Paddon-Jones D, Short KR, Campbell WW, Volpi E, Wolfe RR. Role of dietary protein in the sarcopenia of aging. Am J Clin Nutr. 2008;87(5):1562S–6S.
179. Morley JE, Argiles JM, Evans WJ, Bhasin S, Cella D, Deutz NE, et al. Nutritional recommendations for the management of sarcopenia. J Am Med Dir Assoc. 2010;11(6):391–6.
180. Hart DW, Wolf SE, Chinkes DL, Gore DC, Mlcak RP, Beauford RB, et al. Determinants of skeletal muscle catabolism after severe burn. Ann Surg. 2000;232(4):455–65.
181. Hart DW, Herndon DN, Klein G, Lee SB, Celis M, Mohan S, et al. Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. Ann Surg. 2001;233(6):827–34.
182. Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman OE, Norbury WB, et al. Pathophysiologic response to severe burn injury. Ann Surg. 2008;248(3):387–401.
183. Porro LJ, Herndon DN, Rodriguez NA, Jennings K, Klein GL, Mlcak RP, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg. 2012;214(4):489–502; discussion 4.
184. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. N Engl J Med. 2001;345(17):1223–9.
185. Vincent JL, De Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med. 1998;26(11):1793–800.
186. Lorente JA, Vallejo A, Galeiras R, Tómicic V, Zamora J, Cerdá E, et al. Organ dysfunction as estimated by the sequential organ failure assessment score is related to outcome in critically ill burn patients. Shock. 2009;31(2):125–31.

Endocrine Perturbations in Critical Illness

16

Elizabeth H. Holt

Disorders of Glucose Control

Diabetes Management in the Intensive Care Unit

Background

Acute illness results in an increase in circulating concentrations of stress hormones, including adrenaline and cortisol, which impair insulin action, thereby leading to hyperglycemia [1]. Extensive evidence from observational studies reveals a strong correlation between hyperglycemia during critical care and patient outcomes, including mortality [2]. Even when controlling for other markers of severity of illness, the degree of blood glucose elevation appears to be independently associated with adverse events. Importantly, the relationship between glucose and mortality appears to be more tightly linked in patients without a prior history of diabetes—i.e., in those with newly identified hyperglycemia [3]. It remains debated, however, as to whether hyperglycemia during critical illness is a marker for or a mediator of patient outcomes.

Evidence

Clinical trials of tight glycemic control using intensive insulin therapy in the critical care setting, including the surgical intensive care unit (ICU), have had conflicting results. Older studies employing historical controls suggested that moderate control of blood glucose (to the 150–199 mg/dL range) using intravenous (IV) insulin infusion in the cardiothoracic ICU reduced deep sternal wound infection rates in patients undergoing cardiac surgery [4]. In the landmark randomized clinical trial by van den Berghe and Belgian colleagues involving 1548 surgical ICU patients, reducing blood glucose levels to 80–110 mg/dL with an intensive IV infusion protocol (mean blood glucose 103 mg/dL) was associated with a 42% relative reduction in ICU mortality and a 34% relative reduction in hospital mortality, when compared to conventional care (mean blood glucose 153 mg/dL) [5]. These data, however, have not been confirmed by other groups. In fact, in the NICE-SUGAR study, a multicenter randomized clinical trial involving 6104 critically ill medical and surgical patients, intensive glucose management using a similar protocol and target (mean blood glucose 118 mg/dL) resulted in a puzzling 14% *increase* in mortality as compared to conventional therapy (mean blood glucose 145 mg/dL) [6]. Follow-up analyses have linked increased mortality in NICE-SUGAR to the development of severe hypoglycemia (blood glucose <40 mg/dL), occurring in 6.8%

E. H. Holt (✉)
Section of Endocrinology and Metabolism, Yale Medical School, New Haven, CT, USA
e-mail: elizabeth.holt@yale.edu

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_16

of patients in the intensive group and 0.5% in the conventional group. However a cause and effect relationship remains unproven. Other investigators have found that iatrogenic hypoglycemia in the hospital does not carry with it the same negative implications as *spontaneous* hypoglycemia (i.e., that due to malnutrition, sepsis, liver failure) [7]. Accordingly, it may be those patients who are at risk for developing low blood glucose with or without insulin therapy may simply be sicker and higher-risk individuals.

A meta-analysis has shown no overall benefit from intensive insulin therapy in the ICU, although a possible benefit in surgical ICUs was raised [8]. It should be pointed out, however, that this finding was mainly driven by the van den Berghe surgical ICU cohort.

Two more recent studies in ICU patients have shown that not all hyperglycemic ICU patients are the same: those without diabetes or with well-controlled diabetes have a mortality benefit from having tight glycemic control. However, patients whose outpatient glycemic control has been suboptimal do not benefit much from tight glycemic control in the ICU [9, 10].

Guidelines

Based on these data, the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) and, in their 2009, consensus statement encouraged good but not necessarily overly stringent blood glucose control in all critical care settings. Insulin infusion was deemed the most appropriate and flexible form of therapy in this setting, to be used when the blood glucose exceeds 180 mg/dL, with a glucose target of 140–180 mg/dL [11]. The Society of Critical Care Medicine (SCCM) in their 2012 guidelines statement recommends a similar range (<150 mg/dL) [12], although the SCCM's own Surviving Sepsis Campaign's 2012 *International Guidelines for Management of Severe Sepsis and Septic Shock* endorses a somewhat more conservative blood glucose target of ≤180 mg/dL [13]. SCCM also advises the use of IV insulin in the critical care setting.

Insulin Infusions

When IV insulin is administered, validated infusion protocols should be used, either "paper" algorithms or computerized devices, the latter simplifying implementation for nursing staff. The ideal protocol should reduce blood glucose gradually (within several hours) and safely into the target range. In most protocols, hourly blood glucose determinations are necessary for safe implementation, with frequent infusion dosing adjustments. Infusion rates are typically ranged between 1 and 5 U of insulin per hour but can exceed this in highly insulin-resistant individuals. Continuous parenteral feeding and, particularly, total parenteral nutrition (TPN) can also markedly increase insulin requirements. The best protocols adjust the rate based on the blood glucose, rate of changes, and prevailing insulin infusion rates. At our institution, the ICU insulin infusion protocol targets 120–160 mg/dL and has been associated with a median blood glucose of 150 mg/dL (IQR 127–180 mg/dL), achieved after a median of 7 h, with an exceedingly low severe hypoglycemia rate of 1/5000 blood glucose determinations [14]. This rivals the background rate of hypoglycemia in the control/conventional therapy arms of most clinical trials of intensive glucose management.

Plasma venous or arterial blood glucose samples are ideal but only if rapid result turnaround is ensured, such as with point-of-care analyzers. Most institutions, however, continue to use bedside, capillary blood glucose meters in this setting. These are adapted versions of home-use meters, and it should be acknowledged that the accuracy of these devices is only ±15–20% vs. plasma glucose samples. In critically ill patients, with anemia, acidosis, and peripheral vasoconstriction, even wider discrepancies can be observed. There is some interest in the potential use of continuous glucose monitoring (CGM) in the ICU [15]. These devices measure interstitial glucose concentrations from subcutaneous tissues and provide readings every 5 min. They appear to be reasonably accurate in the hospital, but it is not clear if they are reproducible and reliable enough to be used for adjusting insulin

infusions, particularly in the low-normal glycemic range. More studies will be necessary before we can consider the use of CGM in the critically ill.

Subcutaneous Insulin Regimens

Upon transfer from the surgical ICU, if substantial insulin requirements persist (i.e., >1 U/h) or in patients on insulin prior to admission (especially in type 1 diabetics), smooth transitioning to a subcutaneous regimen is important to prevent post-infusion hyperglycemia. Several transition protocols are available, most using initial doses estimated from the terminal hours of the insulin infusion [16]. For example, if a patient has required 2 U/h over the 6 h prior to transition, an estimated need of 48 U can be estimated for the day. Some protocols then take this entire amount (whereas others use 80% of this amount), dividing by 2. Thus, 50% of the daily requirement is administered as a dose of basal insulin (e.g., 24 U QD of insulin glargine or detemir, or 12 U BID of NPH). The balance is administered as a rapid-acting insulin analogue, further divided into three pre-meal doses of, e.g., 8 U TID AC of insulin lispro, aspart, or glulisine. If the patient is not yet eating, the mealtime dose is held, and correction insulin is instead administered over 4–6 h (regular insulin or a rapid analogue) to correct for hyperglycemia. If substantial short- or rapid-acting insulin coverage is required, a portion of this (classically, 50%) can be incorporated into the next day's basal insulin dose.

Previously, in the non-ICU setting, most organizations (AACE-ADA, Society of Hospital Medicine, the Endocrine Society) [11, 17, 18] recommended that blood glucose be maintained below 140. However more recent recommendations from the ADA have relaxed this target to between 140 and 180 mg/dL [19] and stated that more stringent goals (glucose 110–140 mg/dL) can be considered for individual patients. Focusing on safety and the avoidance of hypoglycemia is important, particularly in the less supervised setting of a general surgical ward. The frequent changes in a patient's nutritional status must be considered on a daily or even more frequent basis such that insulin doses are nimbly adjusted to anticipate the patients' requirements. In addition, the patient's trajectory of illness (and, therefore, stress response) and other medications that might impact metabolic control (e.g., glucocorticoids) must be considered as well. Using endocrine consultants or hospital diabetes management teams has been demonstrated to improve glycemic control and clinical outcomes.

As the patient's nutritional status improves and calorie intake normalizes outside of the ICU, the so-called *basal-bolus* insulin strategy is endorsed as the most physiologic, especially in type 1 diabetes, and the more severely insulin-deficient patients with type 2 diabetes [17]. Here, a *basal* insulin (glargine, detemir, NPH) once or twice per day suppresses hepatic glucose production, controlling glucose levels overnight and in between meals. It is given in conjunction with a pre-meal *bolus* of rapid-acting insulin analogue to blunt postprandial glycemic excursions, in an attempt to recapitulate normal insulin secretory dynamics. Furthermore, the mealtime dose is ideally adjusted (i.e., increased) for preprandial hyperglycemia with correction doses of the same type or rapid-acting insulin (e.g., +2 additional units added to the planned nutritional dose, when the pre-meal blood glucose ≥150 mg/dL, +4 U for ≥200 mg/dL). The optimal ratio between basal and the sum of the bolus components is classically 1:1.

Such a complex glucose control strategy will necessitate careful coordination between medical assistants who are charged with obtaining and reporting blood glucose readings, dietary staff who provide the meals, nurses who administer the insulin, and the surgeon or other physician who orders and adjusts the insulin doses. In patients who are made NPO, in preparation of surgery or other procedures, or in whom nutritional intake is in doubt, mealtime boluses will obviously need to be omitted. As noted previously, basal insulin alone (reduced by 20% for a safety margin, unless the patient has remained hyperglycemic), along with "coverage" involving correction rapid analogue every 4–6 h or regular human insulin every 6 h, should be sufficient to control glycemia. When calorie intake improves, fixed mealtime boluses can be resumed.

Transitioning the Patient to Discharge

Upon discharge, the patient's at home glucose control requirements will need to be determined. Those on insulin prior to hospitalization will require resumption of that strategy if it was resulting in acceptable blood glucose control (i.e., HbA1c in or near the targeted range of <7%) [17]. If not, a more intensified strategy will be required (higher dose, more injections, different insulin formulations, etc.). In those who were previously treated with oral agents (or injectable GLP-1 receptor agonists), those drugs can also be resumed upon discharge, as long as the patient has not developed a prevailing contraindication (e.g., renal insufficiency in someone previously treated with metformin) and if the preadmission control was acceptable. If not, an adjustment in the regimen or the use of insulin at home will be necessary. Such changes are usually optimally made using medical consultants or after conversation with the patient's primary care physician or endocrinologist.

In those individuals with newly identified hyperglycemia, not all will require antihyperglycemic therapy upon discharge. This decision should be based on the patients' blood glucose levels toward the end of the hospitalization, the in-hospital treatment required, and measurement of HbA1c, which will reflect blood glucose levels in the 2–3 months prior to admission. In those with normal or near-normal HbA1c levels, so long as blood glucose is not significantly elevated (>180–200 mg/dL), discharge off antihyperglycemic therapy is acceptable, but early outpatient follow-up is necessary so that the patients' glycemic status can be reassessed. Importantly, the patients' capacities for self-care need to be incorporated into the decision to treat with insulin, which can be a dangerous medication when used inappropriately or without proper patient and family education.

Diabetic Emergencies

Epidemiology

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two major acute complications of diabetes mellitus (DM). The rate of hospital admissions for DKA has been rising, and in 2009 it reached 4.6 per 10,000 population, which is about a 44% increase since 1988 [20]. From 2009 to 2014, the rate of DKA hospitalizations rose a total of 54.9%, from 19.5 to 30.2 hospitalizations per 1000 people with diabetes. Each year between 2009 and 2014, there was a more than 6% rise in DKA hospitalizations annually in all age groups, with highest rates among people <45 years old [21]. Fortunately, the death rate due to all hyperglycemic crises has been declining since the 1990s, with an age-adjusted death rate of 7.5 per 1000,000 population in 2009, which is less than half the rate in 1980 [22], and concurrently, in-hospital case fatality rates among persons with DKA consistently decreased from 2000 to 2014 at an annual average rate of 6.8% (from 1.1% to 0.4% [63.6% decline overall]) [21]. Due to the magnitude of these conditions, it is vital to understand how to diagnose and treat these conditions appropriately.

Definitions of DKA and HHS

DKA is present when the following criteria are met: plasma glucose >250 mg/dL, arterial pH ≤7.30, serum bicarbonate ≤18 mEq/L, positive urinary and serum ketones, and an anion gap <10 mEq/L [23]. The degree of acidemia, measured by arterial pH, determines if it is categorized as mild (pH 7.25–7.30, bicarbonate 15–18), moderate (pH 7.00–7.24, bicarbonate 10 to <15), or severe DKA (pH <7.00, bicarbonate <10) [23]. That being said, it has been suggested that these categories should apply only to patients with a simple metabolic acidosis [24–26]. Clinicians should be mindful of the possible presence of mixed acid-base disorders as well, which can be seen in 43–50% of DKA cases [24–26]. HHS is present when the following criteria are met: plasma glucose >600 mg/dL, an arterial pH >7.30, serum bicarbonate >18 mEq/L, and an effective osmolality of >320 mOsm/kg [23, 27]. Small urinary and serum ketones may be seen in HHS, while they are always seen in DKA [23]. In addition, it is important to note that about 33% of patients may have characteristics of both disorders, and thus these conditions are not mutually exclusive [28, 29].

Although we typically think of DKA occurring in patients with type 1 DM, there is also an entity known as ketosis-prone type 2 DM [30, 31]. The initial clinical presentation of DKA in these patients is similar to that of patients with type 1 DM, but ketosis-prone type 2 DM patients differ because they may recover β-islet cell function after a few months [30]. In fact, 10 years after their initial presentation with DKA, up to 40% of these patients do not require insulin therapy [30, 31]. Interestingly, in about 50% of unprovoked DKA in ketosis-prone type 2 DM patients, one cannot determine a precipitating factor for the DKA [32]. In this subset of patients who develop unprovoked DKA, a male predominance has been observed [32]. Common characteristics in patients with ketosis-prone type 2 DM include obesity, low prevalence of autoimmune markers, lack of genetic HLA association, and male predominance [30, 32]. It has also been noted that a significant proportion of these patients are African-American or Hispanic although this entity has also been reported in other populations such as Asians, Caucasians, and Native Americans [32].

Pathophysiology

DKA occurs due to relative insulin deficiency along with an increase in counter-regulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone [23, 27]. The hyperglycemia results from increased gluconeogenesis, increased glycogenolysis, and decreased peripheral glucose utilization in the liver, muscle, and adipocytes [27]. Both insulin deficiency and increased cortisol levels lead to increased proteolysis and lipolysis. Proteolysis creates amino acid substrates that fuel gluconeogenesis, and lipolysis creates glycerol, which also fuels gluconeogenesis, and free fatty acids (FFA). These FFA undergo beta-oxidation in the liver to generate ketones (beta-hydroxybutyrate and acetoacetate) and thus result in an anion gap metabolic acidosis [Anion gap = $Na^+ - (Cl + HCO_3)$] [27]. In addition, increased glucagon relative to insulin decreases malonyl CoA, which results in the disinhibition of carnitine palmitoyl acyltransferase I (CPT I), which is known to transport FFA into the mitochondria for oxidation and thus contributes to this ketogenesis [33]. Furthermore, hyperglycemia itself leads to volume depletion with resulting impaired renal function, which decreases the patient's ability to excrete glucose and ketoanions [34]. In concert, these processes result in hyperglycemia and ketoacidosis.

Interestingly, patients with hyperglycemic crisis may also demonstrate inflammation and hypercoagulability as evidenced by increased levels of proinflammatory cytokines, reactive oxygen species, cardiovascular risk factors, coagulation markers, fibrinolysis, and platelet activity [33, 35, 36]. Clinically, these patients may thus also present with thrombosis, myocardial infarction, and disseminated intravascular coagulation [33, 35].

Similar to DKA, the pathophysiology of HHS involves a relative insulin deficiency, but unlike DKA, the amount of endogenous insulin secretion in HHS is usually greater [23]. This amount of insulin prevents lipolysis and thus explains why ketone bodies are not typically seen in HHS [23, 37]. HHS also results in an osmotic diuresis resulting in an even greater free water deficit, which can be greater than 9 L, than is present in DKA, which is usually about 6 L [28]. Patients with HHS develop hyperosmolarity, hypovolemia, and intravascular and extravascular dehydration. This leads to an increase in counter-regulatory hormones, thereby exacerbating the existing hyperglycemia and insulin resistance [27, 33].

Clinical Presentation

The clinical presentation of DKA and HHS includes symptoms of fatigue, weakness, polyuria, polydipsia, weight loss, and even altered mental status if the presentation is severe [23]. Patients with DKA often also have nausea, vomiting, and abdominal pain that parallels the degree of acidemia present [38]. This pain may be severe enough to prompt a work-up for an acute abdomen 50–75% of the time [27, 38]. One distinguishing feature between DKA and HHS is the duration of symptoms prior to presentation. DKA is an acute process that typically develops within 24 h, whereas HHS is a process that develops over several days to weeks [23].

Physical exam findings in both conditions may include tachycardia, hypotension,

dry mucous membranes, and poor skin turgor. Findings present in DKA may also include Kussmaul respirations, breath with a fruity odor due to ketones, nausea, vomiting, and abdominal tenderness to palpation [23, 38]. Altered mental status may be present in both conditions but tends to be more common and more severe in HHS because of the degree of hyperosmolarity [Effective Serum Osmolality = 2 × (measured) Na + [mEq/L] + Glucose (mg/dL)/18] present [28, 39]. Obtundation and coma usually occur when the effective osmolality is greater than 330 mOsm/kg [27]. If the patient's osmolality does not reach this threshold and altered mental status is present, it is essential to broaden the differential diagnosis for the neurologic change [23, 27]. In addition to the above, patients with HHS may have other neurologic changes such as hemiparesis, hemianopia, and seizures [23].

Evaluation

The initial evaluation of the patient presenting in hyperglycemic crisis should include an immediate finger-stick glucose and urinalysis to look for ketones. Initial labs should include a plasma glucose, serum ketones, an arterial blood gas to check the degree of acidemia, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate), BUN, Cr, lactic acid, and osmolality [23]. Based on the patient's clinical picture and the above labs, one can make a diagnosis based on the definitions of DKA and HHS mentioned above.

This evaluation often reveals pseudohyponatremia resulting from the shift of water to the extracellular space. The traditional teaching is that a corrected sodium value should be calculated to account for this shift. To do this, for every 100 mg/dL of glucose greater than 100, 1.6 mEq/L is added to the measured serum sodium level [28]. That being said, in HHS, where the plasma glucose is greater than 400 mg/dL, a factor of 2.4 mEq/L may be more appropriate [40].

Although the patient's serum potassium level may be normal or elevated on presentation, the patient's total body potassium level is usually low [28]. This is a result of relative insulin deficiency, which causes an extracellular shift of potassium [33]. It is for this reason that one must watch for the development of hypokalemia when insulin treatment is started [33].

The patient should be admitted to the ICU if there is worsening level of consciousness, airway compromise, hemodynamic instability, or severe acidemia. Recently, Huang et al. reported the use of the "PHD Score" in order to assess mortality risk in patients presenting with hyperglycemic crises in Taiwan [41]. A validation study on this scoring method showed that in the low-, intermediate-, and high-risk groups, respectively, the mortality rates were 5.8%, 20.5%, and 56%, indicating the tool was quite useful in identifying the sickest patients [42].

In addition to the above, a simultaneous evaluation for a precipitating factor should be done. Since the most common precipitant for hyperglycemic crises is infection, labs should include a complete blood count (CBC) with differential, urinalysis with urine culture, sputum culture, viral nasal swab, and blood cultures, and imaging should include a chest X-ray [23]. Although leukocytosis is usually seen in DKA even in the absence of infection, a white blood cell count of greater than $25 \times 10^3/mm^3$ or bandemia $\geq$10% should raise the concern for the presence of an infection [23, 43].

Other precipitants include accidental or intentional insulin noncompliance, myocardial infarction, cerebrovascular accident, pancreatitis, and medications (e.g., corticosteroids, diuretics, beta-blockers, calcium channel blockers, cimetidine, diazoxide, phenytoin, sympathomimetic agents, pentamidine, typical or atypical antipsychotics) [23, 28, 44]. Of note, pancreatitis cannot be diagnosed based on the values of amylase and lipase alone because these values may be significantly elevated in up to 25% of DKA patients without pancreatitis [45]. Additional risk factors for DKA also include psychological illness, eating disorders, and cocaine use [23, 46]. If the patient presents with recurrent DKA, a urine toxicology panel and an overdose panel should be considered [39, 46]. Endocrine disorders that are associated with hyperglycemia and should be kept in mind include Cushing syndrome, acromegaly,

pheochromocytoma, thyrotoxicosis, and hyperaldosteronism [44].

Management

In DKA and HHS, the aims of therapy are to treat the patient's dehydration, hyperglycemia, and electrolyte abnormalities. It is also important to treat the precipitant of the hyperglycemic crisis, if one is found [23]. The treatment is described in detail below, and it is important to note that the patient's finger stick should be checked hourly, and electrolytes, BUN, and creatinine should be checked every 2–4 h until the patient's hyperglycemic crisis has resolved.

Treatment begins with intravenous fluids (IVF) to restore intravascular, interstitial, and intracellular volume [23]. If hyperosmolarity is present, IVF can also help to correct it and thereby lead to an improved response to insulin therapy [47]. Typically, normal saline is started at a rate of 15–20 mL/kg body weight/h or 1–1.5 L in the first hour [23]. The patient's hemodynamics, volume status, electrolyte status, urine output, and corrected serum sodium value determine the next type of IVF that is given [23]. If the patient remains hypovolemic, normal saline is continued. Half-normal saline (0.45% NaCl) should be used if the corrected serum sodium is normal or elevated [23]. Of note, if cardiac or renal dysfunction is present, one must be watched carefully for signs of volume overload. If the patient develops cardiogenic shock, pressor support is necessary.

Next, insulin therapy should only be started when the patient is hemodynamically stable and the serum potassium level is greater than 3.3 [23, 33]. The reason is that insulin both (1) causes water to move from the extracellular to the intracellular space leading to further hypotension and (2) causes an intracellular shift of potassium leading to worsening hypokalemia [23, 33]. In order to ensure that the patient's serum potassium remains adequate, it should be repleted when it is at the upper limit of normal [23]. Insulin therapy may begin with a 0.1 U/kg body weight bolus followed by an infusion of 0.1 U/kg/h or as an infusion of 0.14 U/kg/h without an initial bolus [23, 48]. The goal is to decrease plasma glucose at a rate of 50–75 mg/dL/h, and the insulin infusion should be titrated to this goal using hourly finger sticks [23]. Of interest, although an insulin infusion is used in many hospitals, it has been demonstrated that for the treatment of mild to moderate DKA, subcutaneous rapid-acting insulin use every 1–2 h is as effective as regular IV insulin therapy [49, 50].

Total body phosphate depletion is also present in patients with DKA but is typically only repleted if the serum phosphate is less than 1 mEq/L or if the patient has comorbidities such as cardiac or respiratory compromise or anemia [23, 51]. The reason is that evidence is lacking that aggressive phosphate repletion improves patient outcomes in DKA and repletion carries the risk of developing hypocalcemia [51, 52].

Bicarbonate therapy is controversial and is typically only used in severely acidemic patients because they are at risk for developing cerebral vasodilatation and coma, decreased myocardial contractility, and gastrointestinal complications [23, 53]. At pH levels between 6.9 and 7.1, studies have not shown any benefit in morbidity or mortality when bicarbonate is used to treat DKA patients [23, 54]. In DKA, the patient's ketoacidosis improves as ketone bodies are metabolized in the citric acid cycle [33]. Since there are no randomized controlled trials in DKA patients with a pH <6.9 and there are serious complications that may occur with severe acidemia, bicarbonate therapy is given in these patients. The typical dose is 100 mmol of bicarbonate in 400 mL H_2O + 20 mEq KCl infused over 2 h. This is repeated every 2 h until the pH is ≥7. In addition, the serum potassium is monitored every 2 h [23]. The potential complications of bicarbonate therapy include worsening hypokalemia, intracellular acidosis, cerebral edema, and paradoxical central nervous system acidosis [23].

When the patient's plasma glucose reaches 200 mg/dL in DKA, dextrose should be added to the IVF, and the insulin infusion rate is decreased to 0.02–0.05 U/kg/h. This is done to achieve a plasma glucose between 150 and 200 mg/dL and avoid hypoglycemia, while further insulin therapy is required to close the anion gap and prevent more lipolysis and ketoacid production [23]. Insulin and dextrose therapy are contin-

ued in this manner until the DKA has resolved, which is defined by achieving a plasma glucose of <200 mg/dL and two of the following: serum bicarbonate ≥15 mEq/L, venous pH >7.3, and/or anion gap ≤12 mEq/L. In HHS, dextrose is added, and the insulin infusion rate decreased when the plasma glucose reaches 300 mg/dL. In HHS, this is continued with a goal plasma glucose of 200–300 mg/dL until the patient's HHS has resolved, which is defined by the normalization of osmolality and mental status [23].

When both conditions have met criteria for resolution, transition from IV to subcutaneous insulin may start with 1–2 h of overlap in order to prevent relapse of hyperglycemia or ketoacidosis. If the patient was already on insulin prior to this crisis, then the patient's home doses may be used if the patient's glycemic control was adequate prior to admission. If this is a new diagnosis of diabetes, then dosing may begin at 0.5–0.8 U/kg/day. A basal-bolus-correction (BBC) regimen may be used where 50% of the total daily dose is given as a basal insulin (e.g., glargine or detemir), the remainder is divided into three equal doses given as rapid-acting insulin (e.g., aspart, glulisine, or lispro) at mealtimes, and a correction scale of rapid-acting insulin is also used [23]. Recently, it has been demonstrated that in patients with type 2 DM, the use of a "basal-plus correction" regimen, which uses a long-acting insulin (e.g., glargine) and a correction scale of rapid-acting insulin at mealtimes, achieves similar glycemic control as the BBC regimen [55].

Complications

Complications that may occur in DKA and HHS include hypoglycemia, hypokalemia, hyperchloremic metabolic acidosis, and cerebral edema [23, 56]. Cerebral edema is more common in pediatric patients but quite rare in adults with DKA. Possible contributors to its development may include increased cerebral blood flow, inflammatory mediators, cerebral ischemia, hypoxia, and a quick decrease in osmolality in the setting of IVF repletion [23, 56]. A patient with cerebral edema may have a headache, worsening level of consciousness, papilledema, bradycardia, hypertension, seizures, or respiratory compromise and even respiratory arrest. If this occurs, it is vital to treat with mannitol and mechanical ventilation [56].

Adrenal Disorders

Adrenal Insufficiency

Background

Any critical illness is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis, stemming from the release of corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary [57]. This, in turn, activates the adrenal cortex to augment its production of glucocorticoids, mainly cortisol. Recent evidence also suggests that decreased cortisol metabolism in critical illness may also increase circulating cortisol concentrations in critical illness [58]. Irrespective of cause, the hypercortisolemia that results has myriad effects on metabolic processes (mainly insulin counter-regulatory effects), vascular responsiveness to catecholamines, and modulation of the immune response. In the surgical ICU, occasional patients are admitted with preexisting adrenal insufficiency, either due to primary or secondary adrenal disease. In addition, dysfunction in the HPA axis should be considered in patients who exhibit suspicious features of adrenal failure, particularly hypotension without known cause or when hypotension becomes refractory to usual therapies.

Adrenal insufficiency is distinguished into primary and secondary causes. In *primary adrenal failure*, both adrenal glands are themselves dysfunctional, resulting in deficiency in both glucocorticoids (i.e., cortisol), mineralocorticoids (i.e., aldosterone), and adrenal androgens (i.e., DHEA, androstenedione), the first two being critical for survival. When deficient, and unless these hormones are replaced, patients rapidly develop hypotension, electrolyte imbalance (hyperkalemia, hyponatremia, metabolic acidosis), and hypoglycemia. Over time, due to the effects of increased pituitary ACTH secretion, the skin hyperpigments. This condition may result from

autoimmune adrenalitis, bilateral adrenalectomy, the use of adrenolytic medications, or glandular destruction from infectious or infiltrative diseases or, rarely, bulky tumor metastases. In contrast those with *secondary* (*or central*) *adrenal insufficiency* (from hypothalamic or pituitary dysfunction) experience loss of glucocorticoids and androgens only, with preserved mineralocorticoid secretion, the latter of which is under the predominate control or the renin-angiotensin system. Accordingly, the maintenance of vascular volume (through the effects of aldosterone) remains unimpaired. Hypotension still occurs (due to cortisol's effects on enhancing catecholamine action) but is usually not as severe as occurs in patients with primary adrenal failure. Hyperkalemia is absent, although hyponatremia, which is of multifactorial origin in adrenal insufficiency, still occurs. Individuals with this form of adrenal failure often have had a prior history of pituitary tumor, cranial irradiation, or longer-term suppression of the HPA axis from chronic high- or moderate-dose glucocorticoid therapy.

Symptoms of acute adrenal insufficiency ("adrenal crisis"), in addition to vascular collapse, hypoglycemia, and electrolyte disorders, also include profound fatigue, nausea, vomiting, abdominal pain, myalgias, low-grade fever, and mental status changes. Adrenal crisis may share some features of an acute abdomen, although, typically, signs of peritoneal irritation, lactic acidosis, and marked leukocytosis are lacking. Adrenal insufficiency should be suspected in any critically ill patient who presents with one or more of these features, particularly the persistent hemodynamic instability persisting after adequate fluid resuscitation. Of course, in the critically ill, such signs and symptoms are common and may be difficult to attribute solely to hypoadrenalism. Accordingly, the clinic laboratory plays a critical role in diagnosis and must be used as an important part of the comprehensive clinical assessment of the patient.

Assessing Adrenal Function in the ICU

Laboratory investigation of adrenal function in the critically ill patient is controversial. In most circumstances in the ICU, obtaining a single measurement of serum or plasma cortisol concentration should suffice to rule out a diagnosis of adrenal insufficiency. The stress from critical illness will maximize adrenal steroid output, and a random cortisol level should usually suffice as, essentially, a dynamic test to assess the integrity of the entire HPA axis. It should be noted, however, that "normal values" for the cortisol response to acute illness have not been fully defined, although most experts agree that an ambient level above 20–25 mg/dL indicates adequate adrenal response. This is, however, to some degree dependent on the severity and acuity of illness. Most authorities also agree that cortisol levels below 10 μg/dL raise the likelihood of at least partial adrenal insufficiency in this setting; the lower the level, the more secure one may be in this assessment. Making interpretation of measured cortisol levels more challenging is that this measurement of *total* cortisol concentration (which includes cortisol bound to cortisol-binding globulin [CBG]) may not reflect the adequacy of circulating free (i.e., unbound) cortisol, particularly in those with malnutrition and protein deficiency where CBG is low, and thus the total cortisol is low, but the active, free cortisol may be normal.

When in doubt, the adrenal response to 250 μg of IV bolus of cosyntropin, a synthetic ACTH analogue, should be performed, with a 30 min cortisol value of ≥18–20 μg/dL widely viewed as an acceptable response, although some authors prefer to see an increase of at least 9 μg/dL. It should also be noted that the response to cosyntropin merely assesses the *adrenal* response to a pharmacological stimulus but may fail to detect secondary adrenal insufficiency, particularly if its onset has been acute. Of course, the "gold standard" test of the integrity of the entire HPA axis remains the insulin tolerance test to precipitate hypoglycemia. This is obviously both impractical and potentially dangerous in the critically ill and is not advised.

Guidelines for evaluation and management of primary adrenal insufficiency from the Endocrine Society emphasize that patients presenting with findings concerning adrenal insufficiency should be treated empirically with steroids until their

condition allows for dynamic testing to be performed. When possible the cosyntropin stimulation test should be performed as above, with cortisol values <18 ug/dL consistent with adrenal insufficiency [59].

A related topic pertains to the diagnosis and management of *relative* or *functional* adrenal insufficiency, which has seen evolving definitions, diagnostic strategies, and opinions over the past decade. This condition is defined as subnormal adrenal steroid production in the absence of any anatomic or structural defects of the HPA axis and implies "exhaustion" of the secretory adrenocortical reserve in the context of near-maximal stimulation. Proposed contributing factors include the suppression of cortisol and/or ACTH production by circulating inflammatory cytokines, the development of tissue resistance to glucocorticoid action, and resistance of the adrenal cortex to ACTH. Despite years of study, however, there remains lack of agreement on the clinical significance, the biochemical definition, and the very existence of this state [60, 61].

One older, but frequently cited, multicenter, randomized, controlled clinical trial from France involved 300 patients with septic shock unresponsive to fluid resuscitation. The investigators showed a significant reduction in mortality rate (hazard ratio (HR) 0.67, $p = 0.02$) in patients with a post-cosyntropin cortisol augmentation of ≤9 μg/dL who were randomized to a stress steroid regimen of 200 mg of IV hydrocortisone and 50 μg of fludrocortisone per day. However, the larger ($N = 499$) multicenter Corticosteroid Therapy of Septic Shock (CORTICUS) [62] trial in 2008 was not able to confirm any benefit in mortality (HR 1.09, p 0.51) in those subjects randomly assigned to IV hydrocortisone, although quicker reversal of shock was found in the hydrocortisone group (3.3 days vs. 5.8 days in the placebo group, $p < 0.001$). There were, however, more superinfection events, including new septic shock episodes in those randomized to the steroid regimen. Importantly, the pre-randomization response to cosyntropin did not at all predict the response to hydrocortisone. Accordingly, this test is no longer routinely recommended by the SCCM in its Surviving Sepsis Campaign [63]. Moreover, the CCS advises that IV hydrocortisone at a dose no higher than 200 mg/day be given only to adult septic shock patients after blood pressure is documented to be poorly responsive to fluid resuscitation and vasopressor therapy (see Table 16.1).

When the diagnosis of adrenal insufficiency is suspected in a patient whose condition is deteriorating rapidly, treatment with 50–100 mg of hydrocortisone IV every 6–8 h is reasonable until the diagnosis can be confirmed. Of course, such therapy will make the subsequent evaluation of cortisol levels difficult. Any steroid with glucocorticoid activity, including dexamethasone, will interfere with normal adrenal function. Accordingly, measured cortisol concentrations, once steroid therapy has begun, must be interpreted cautiously. That is, cortisol levels will be low when any steroid is given that has suppressive effects on adrenocortical function, and most glucocorticoid medications will additionally interfere with laboratory cortisol assays. Consultation with a laboratory medicine expert and/or an endocrinologist can be very helpful when such questions are raised.

We would underscore that the question of *relative* adrenal insufficiency is an entirely separate clinical consideration from the management of patients with previously diagnosed hypoadrenalism or in patients with an overt, newly identi-

Table 16.1 Society of Critical Care Medicine (SCCM) guidelines for corticosteroid use in patients with septic shock

1. Do not use intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. In case this is not achievable, suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C)
2. Do not use the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B)
3. In treated patients hydrocortisone should be tapered when vasopressors are no longer required (grade 2D)
4. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock (grade 1D)
5. When hydrocortisone is given, use continuous infusion (grade 2D)

Adapted from Refs. [11, 63]

fied diagnosis of hypoadrenalism. Examples of the latter include patients with first presentation of primary (autoimmune adrenalitis, bilateral adrenal hemorrhage, etc.) or secondary adrenal failure (post-transsphenoidal pituitary surgery, pituitary apoplexy, etc.). In these individuals, prompt therapy with stress doses of glucocorticoids is critical for successful patient outcomes (see below).

Management of Established Adrenal Disease in the ICU

Patients with a history of either primary or secondary adrenal insufficiency will require special attention to hormonal needs in the setting of critical illness. Oral glucocorticoids (hydrocortisone, cortisone acetate, prednisone, or methylprednisolone) are instead provided IV, either intermittently or by continuous infusion. The standard of care is to provide the so-called stress doses of steroids, equivalent to 200–300 mg of hydrocortisone per day (usual strategies involved 50–75 mg IV every 6 h or 100 mg IV every 8 h). If fluid overload and sodium retention is a concern, the patient can be treated with a steroid with less mineralocorticoid effects at equivalent doses (see Table 16.2). These include methylprednisolone or dexamethasone, the latter having essentially no sodium retentive properties. The dose is maintained for 1–3 days until the patient experiences improvement in his or her clinical status and then gradually reduced (over several days to 1–2 weeks) to the baseline dose and transitioned to oral dosing, as allowed by the patient's condition [64].

In patients with primary adrenal disease who are critically ill, fludrocortisone is typically held when IV hydrocortisone is given, since the latter has substantial activity at the mineralocorticoid receptor when given at doses exceeding 50–100 mg/day. In addition, the extracellular fluid space is usually being repleted and sustained by IV crystalloid (0.9% NaCl or Ringer's lactate) solutions. The reinstitution of fludrocortisone will be required when IV fluids are reduced to maintenance requirements and when hydrocortisone doses are reduced to below 50–100 mg/day. If glucocorticoids are used that have less mineralocorticoid effect, fludrocortisone may need to be continued, especially when dexamethasone is used. The development of mild hyperkalemia may be used as a sign of inadequate aldosterone-like activity, along with clinical assessment of intravascular volume. Plasma renin activity is a more sensitive marker for mineralocorticoid insufficiency, but this may be difficult to interpret in the critically ill. More importantly, most hospital laboratories do not report results of the plasma renin activity rapidly enough to be of practical use in the inpatient setting [65, 66].

Pheochromocytoma

Preoperative Preparation

Proper preoperative preparation of the pheochromocytoma patient is of utmost importance as surgery on an unprepared patient may lead to hypertension, stroke, and death. In addition, other triggers for worsening hypertension in the pheochromocytoma patient should be avoided. These include beta-blockers (when given in the absence of alpha-blockers), metoclopramide, and glucagon. The rationale behind the preparation of the pheochromocytoma patient is to control

Table 16.2 Relative potencies of steroid hormones

	Glucocorticoid potency	Mineralocorticoid potency
Hydrocortisone	1	1
Cortisone acetate	0.8	0.8
Prednisone	4	0.8
Methyl-prednisolone	5	0.5
Dexamethasone	30	0
Fludrocortisone	15	150
Aldosterone	0	400+

Adapted from Ref. [59]

hypertension safely and to expand intravascular volume. In addition, agents given preoperatively prepare the vasculature for high levels of catecholamines that may be released at the time of surgery as the adrenal gland is manipulated. The mainstays of preparation include alpha-blockade, beta-blockade, and in some cases metyrosine.

- *Alpha-blockade*: Traditionally this was done with the nonselective alpha-blocker phenoxybenzamine. Today, selective alpha-blockers such as prazosin [67] or doxazosin are used more commonly. Treatment should start a few weeks preoperatively, so that the patient has at least 2 weeks of blood pressure at target (120/70) prior to surgery. Doxazosin may be initiated at 1 mg QHS and titrated up over several days to 2 weeks as symptoms and blood pressure will allow. The goal is a mildly orthostatic patient. During the time of dose titration, it is important to expand intravascular volume by encouraging oral salt and water intake in order to make up for the vasodilatory properties of the alpha-blockade. In the hospital setting, intravascular volume expansion can also be accomplished with infusion of saline. It should be noted that labetalol is not a substitute for combined alpha- and beta-blockade in patients with pheochromocytoma, as it has insufficient alpha-blocking properties relative to its beta-blocking properties.
- *Beta-blockade*: Patients who are already on alpha-blockers and are tachycardic may be treated with beta-blockers as well. Beta-blockade should be started at a low dose and titrated to give a heart rate in the normal range. Beta-blockade should not be started prior to alpha-blockade in pheochromocytoma patients. The blockade of peripheral beta-receptors which mediate vasodilation, in the presence of unopposed alpha-mediated vasoconstriction, can lead to more severe elevation in blood pressure. Labetalol is often used due to its additional alpha-blocking activity. A heart rate of 70 is the target.
- *Metyrosine*: In individuals who cannot tolerate alpha- and beta-blockade, or where tumor burden is considerable, metyrosine therapy should be considered [68]. Metyrosine is an inhibitor of the tyrosine hydroxylase enzyme. It therefore inhibits production of catecholamines from tyrosine, resulting in a lowering of catecholamine levels systemically. It may be started at 250 mg PO BID and titrated up as tolerated a few days before surgery in addition to alpha- and beta-blockade, to lower catecholamines preoperatively and minimize catecholamine release during the surgical exploration. Side effects of metyrosine include crystalluria (at high doses), so adequate fluid intake must be ensured. In addition metyrosine may cause extrapyramidal side effects and sedation. Recent studies where pheochromocytoma patients were randomized to alpha-blockade with or without metyrosine have not shown an overall benefit of metyrosine on outcomes [69], but have shown a decreased risk of cardiovascular-specific complications with the addition of metyrosine [70].
- *Volume expansion*: As noted above, volume expansion is an important part of the preparation with alpha-blockade. In addition, volume expansion should be emphasized the night before surgery so that the patient's intravascular volume is adequate to withstand the drop in catecholamines that will occur after the adrenal vasculature is ligated.
- Management of hypertensive crisis, both in the operating room and prior to surgery, can be accomplished with IV nitroglycerin or nicardipine; sodium nitroprusside would be a second choice. Esmolol may be of use if the patient is tachycardic.

Postoperative Management

- It is not uncommon for patients to develop hypotension after surgery for pheochromocytoma. This is due to a combination of the acute decline in catecholamine levels, as well as residual effects of blood pressure-lowering agents administered preoperatively. This can be managed with fluid resuscitation; rarely pressors are needed as well. Home blood pressure medications other than beta-blockers are held in the immediate postoperative period.

- Hypotension may be managed with IV fluids and, if needed, low-dose phenylephrine.
- Hypertension is managed with IV labetalol; if heart rate is low, the use of IV nicardipine or amlodipine is recommended.
- It should be noted that individuals with pheochromocytoma and diabetes often experience an improvement in their insulin sensitivity postoperatively. Therefore, reintroduction of oral diabetes medications and insulin should be done cautiously as it is best to err on the side of inadequate therapy rather than causing hypoglycemia.

Cushing Syndrome

Patients with Cushing syndrome are occasionally encountered in the surgical ICU, typically after an infectious complication requiring surgery. In this circumstance, prompt control of hypercortisolism, to enhance previously suppressed immune function and deranged wound healing, is of critical importance. The standard method to permanently control elevated plasma cortisol concentrations in patients with Cushing syndrome is to address the underlying cause. Cushing syndrome is classically divided into ACTH-dependent and ACTH-independent etiologies. Patients with ACTH-dependent disease usually harbor an ACTH-secreting pituitary adenoma. When possible, transsphenoidal resection of the tumor, usually a microadenoma, is advisable. The other ACTH-dependent cause is an ectopic hormone secretion syndrome, classically from a pulmonary neoplasm, either a small cell carcinoma or a bronchial carcinoid. Outside of the lungs, other ectopic ACTH-producing tumors include a variety of neuroendocrine tumors, including thymic carcinoids, medullary carcinoma of the thyroid, and pancreatic islet cell tumors. Very often in ectopic ACTH syndrome, the disease is metastatic at diagnosis and cannot be cured surgically. ACTH-independent causes of Cushing syndrome are primary adrenal diseases, such as adrenal adenomas, carcinomas, and, rarely, either micronodular or macronodular adrenal hyperplasias. Surgical resection is key to cure these conditions, although adrenocortical carcinoma is an aggressive tumor that is often already quite advanced, potentially incurable, at diagnosis. The diagnostic evaluation of these syndromes is beyond the scope of this chapter. Importantly, however, in the setting of critical illness, irrespective of cause of Cushing syndrome, the patient is not an optimal surgical candidate. Accordingly, medical therapy of hypercortisolism is required.

When urgent control of hypercortisolism is needed, options include adrenolytic therapy. Potential oral medications include ketoconazole, metyrapone, and mitotane [71]. Each has significant side effects which may mitigate their utility in the setting of critical illness. Moreover, for maximal effectiveness, these drugs usually require several weeks of dose titration. Newer options include the oral cortisol (and progesterone) receptor antagonist, mifepristone, and the injectable somatostatin receptor antagonist, pasireotide. The former may be used in any form of Cushing syndrome, whereas the latter is approved only for ACTH-secreting pituitary adenomas. Other neuroendocrine tumors associated with ectopic ACTH syndrome, including carcinoid, may also respond to other somatostatin receptor antagonists, including octreotide and lanreotide. Pasireotide has the disadvantage of being frequently associated with hyperglycemia, which itself is associated with adverse outcomes in the ICU.

One agent that can be considered in the rare case of severe, uncontrolled Cushing syndrome requiring prompt control in a critically ill patient is etomidate [72]. This IV anesthetic agent has been found to have potent anti-adrenal effects. It blocks two enzymes involved in glucocorticoid biosynthesis, 11β-hydroxylase and 17α-hydroxylase. When properly titrated, it can achieve a eucortisolemic state within several hours. Of course, careful assessment of ventilatory status is crucial when using this agent, although subhypnotic doses (0.1 mg/kg/h) have also been successfully employed [73]. When used, the dose should be titrated to achieve a plasma cortisol level in the high-normal range (15–25 mg/dL). Relative hypocortisolism should, of course, be avoided in the critically ill.

The complex, critically ill patient with Cushing syndrome requires a comprehensive, multidisciplinary approach to optimize outcomes. They frequently present with perturbations of electrolytes (particularly hypokalemia), hyperglycemia, hypertension, and fluid overload. Ideally, an endocrinologist should be consulted to assist in patient evaluation and management.

Thyroid Disorders

Hypothyroidism

Epidemiology

The prevalence of hypothyroidism is known to depend on the variables of age, race, sex, and iodine intake. Based on National Health and Nutrition Examination Survey (NHANES) 1999–2002, the prevalence of hypothyroidism (thyroid-stimulating hormone, TSH >4.5 mIU/L; overt hypothyroidism with T4 <4.5 μg/dL; mild hypothyroidism with T4 ≥4.5 μg/dL) in the general US population was 3.7% (0.3% overt and 3.4% mild) [74]. Its prevalence increases with age and was found to be more common in women and non-Hispanic whites (compared to non-Hispanic blacks) [74].

Definition and Clinical Presentation

Hypothyroidism refers to a state where there is a reduced production of thyroid hormone in the body [75, 76]. Overt hypothyroidism is defined biochemically as an elevated serum TSH and a reduced serum-free thyroxine (FT4) concentration [77, 78]. Subclinical hypothyroidism is defined as an elevated TSH with a normal FT4 level [77, 78]. The majority (99%) of hypothyroidism is due to primary hypothyroidism, which is due to permanent loss or destruction of the thyroid gland, and it may be congenital or acquired [75]. Acquired causes include Hashimoto's thyroiditis, iodine deficiency, drugs (e.g., lithium, amiodarone, ipilimumab), infiltrative diseases, surgical resection, external radiation, or radioactive iodine [75]. Central or secondary hypothyroidism occurs when there is a defect in TSH production [75], and these individuals will have low FT4 with inappropriately low or normal TSH.

Clinically, hypothyroidism may affect all organ systems, and its symptoms may include fatigue, weight gain, reduced appetite, cold intolerance, constipation, myalgias, and depression [75]. Common physical exam features include puffy appearance periorbitally, at the dorsa of hands and feet, and in the supraclavicular fossa, coarse skin, typically pale and cool, hair loss, thinning of the lateral eyebrows, brittle nails, hoarse voice, bradycardia, and reflexes with a delayed relaxation phase [75]. Cardiovascular effects include a decreased stroke volume, inotropy, and chronotropy, increased systemic vascular resistance, and pericardial effusion. Pulmonary effects include hypoventilation, carbon dioxide retention, and obstructive sleep apnea [75]. In addition, impaired renal excretion of water and water retention from hydrophilic deposits in tissues result in increased total body water and thus lead to hyponatremia [75]. Overt hypothyroidism is treated with thyroid hormone supplementation, which is typically based on weight-based dosing of 1.7 μg/kg once daily [79]. That being said, lower doses (e.g., 25 μg PO once daily) are used initially for elderly patients or patients with coronary artery disease due to the risk of increasing myocardial oxygen demand [79].

Myxedema coma is a rare but serious complication of severe, long-standing hypothyroidism that is an endocrine emergency. It has a high mortality rate of 20–60%, and for that reason these patients require ICU care [80]. It usually occurs in the winter and in elderly patients. Clinically, it may be characterized by hypothermia, myxedematous appearance, bradycardia, severe hypotension, carbon dioxide retention, and altered mental status that may present as disorientation, confusion, psychosis, or rarely coma [80]. Dilutional hyponatremia may also be present, and thus one must watch for seizures as well. Gastrointestinal complications such as ileus and megacolon may occur as well. Precipitants may include cold exposure, infection, trauma, stroke, surgery, or the use of central nervous system depressants or anesthetics [75, 80, 81]. Of note, infection may

be present without associated fever due to the hypothyroid state.

Treatment of myxedema coma requires intravenous (IV) levothyroxine administration due to unpredictable absorption from the gut. Due to rare occurrence of myxedema coma, controlled studies on its treatment regimens are lacking. Typically, 500 μg of levothyroxine is administered intravenously in a single dose followed by daily doses of 100 μg IV [75]. Alternatively, some recommend a combination of levothyroxine 200–300 μg IV and liothyronine 25 μg IV, each given as a single dose initially, followed by one dose of levothyroxine 100 μg IV 24 h later, and then levothyroxine 50 μg IV daily until the patient regains consciousness [75]. Due to the possibility of concomitant adrenal insufficiency, stress dose hydrocortisone (e.g., 100 mg IV every 8 h) should be given simultaneously to prevent adrenal crisis while the metabolic rate increases [75, 81]. In addition, mechanical ventilation may be required if hypercapnia or hypoxia is present [80]. One should avoid active external warming with heating pads due to the resulting peripheral vasodilatation that can lead to vascular collapse [75]. Instead, internal warming by gastric perfusion may be considered. Hypotension should be treated with fluids and vasopressor agents if necessary [80]. Due to the dilutional hyponatremia, hypotonic fluids should be avoided to prevent worsening hyponatremia. Some patients may require hypertonic saline and glucose to improve severe hyponatremia and hypoglycemia that may be present [75]. For the possibility of infection, empiric broad-spectrum antibiotics should be given until the infectious work-up is complete.

In general, hypothyroid patients requiring surgery may be categorized into one of these three groups: patients with (1) known hypothyroidism that are on thyroid supplementation and are currently euthyroid, (2) mild to moderate hypothyroidism, and (3) severe hypothyroidism (myxedema coma) [81].

In the first group, surgery should not be delayed since they are euthyroid. The physician should just be aware of the diagnosis and the need for levothyroxine supplementation, whose half-life is 6–7 days in a euthyroid patient, and thus it may be held for a day while the patient is NPO for the procedure [79, 82]. Alternatively, levothyroxine may be given intravenously as about 50–75% of the patient's oral dose while the patient is NPO [83].

Regarding the second group, unfortunately, there are no randomized controlled studies looking at outcomes in hypothyroid patients undergoing surgery. The largest are two retrospective case-control studies that have been done looking at surgical outcomes. Weinberg et al. looked at 59 patients with hypothyroidism compared with euthyroid controls and found that there were no differences in surgical outcome, perioperative complications, or length of stay in the hospital [84]. This study suggested that for patients with mild to moderate hypothyroidism, there was no evidence to delay surgery. A study by Ladenson et al. looked at 40 patients with hypothyroidism and found that the hypothyroid patients had more intraoperative hypotension in noncardiac surgery and more heart failure in cardiac surgery [85]. The combined group of hypothyroid patients undergoing any surgery also had more postoperative gastrointestinal (e.g., prolonged constipation and ileus) and neuropsychiatric complications. There were no differences in perioperative arrhythmia, hypothermia, hyponatremia, impaired wound healing, postoperative infection, pulmonary complications, or death [85]. Airway obstruction has been reported in hypothyroid patients in the postoperative period, and thus airway patency should be monitored [86]. Thus, if patients with mild to moderate hypothyroidism need urgent surgery, it may be performed, but the patient should be closely monitored for possible postoperative complications as described above.

A controversial area is whether patients with mild to moderate hypothyroidism who present for cardiac catheterization or cardiac surgery should be treated with thyroid hormone replacement [81, 87]. The reason is that thyroid hormone therapy can increase the myocardial oxygen demand thereby causing ischemia [81]. A prospective study by Drucker et al. looked at ten untreated hypothyroid patients with mild to moderate hypothyroidism and ischemic heart disease who underwent coronary artery bypass surgery

and found that all of these patients tolerated this surgery well without any thyroid hormone supplementation [87]. Thus, it is felt that if patients with mild to moderate hypothyroidism require urgent cardiac revascularization, in many cases this procedure may be performed prior to starting thyroid supplementation [81]. If it is safe to delay the cardiac surgery, then another approach would be to start a low dose of levothyroxine (e.g., 25 μg PO daily), at least to partially correct the hypothyroidism prior to surgery [81]. Most of all, it is important to make a decision based on the individual patient's risks and benefits.

In summary, limited evidence suggests that surgery may be performed in patients with mild to moderate hypothyroidism without delay but that one must be watchful for complications as noted above. In patients with severe hypothyroidism or myxedema, we recommend delaying surgery until their clinical condition has improved. If, however, the surgery is emergent and must be performed in a patient with severe hypothyroidism, treatment with intravenous T3 or T4 and stress dose glucocorticoids as detailed above should be given perioperatively [82].

Thyrotoxicosis

Epidemiology

Based on National Health and Nutrition Examination Survey (NHANES) 1999–2002, the prevalence of hyperthyroidism (thyroid-stimulating hormone, TSH <0.1 mIU/L) in the general US population was 0.5% [74]. Hyperthyroidism is more common in females, nonwhites, and the elderly.

Definitions and Clinical Presentation

Thyrotoxicosis refers to any state of excess thyroid hormone, whereas hyperthyroidism specifically refers specifically to thyrotoxicosis caused by overproduction and release of thyroid hormone [75]. Causes of hyperthyroidism include Graves' disease, toxic multinodular goiter, toxic adenoma, type 1 amiodarone-induced thyrotoxicosis, or rarely metastatic functioning thyroid carcinoma [75]. The most common is Graves' disease, which is a disorder where autoantibodies stimulate the TSH receptors and lead to an increase in thyroid hormone production [75]. Thyrotoxicosis with transient excess thyroid hormone release includes thyroiditis, which may be autoimmune, viral, or drug-induced (e.g., type 2 amiodarone-induced thyrotoxicosis, and thyrotoxicosis caused by lithium, interferon-α, IL-2, GM-CSF, or immunotherapy for cancer) [75, 88].

Clinically, hyperthyroidism may affect all organ systems, and its symptoms may include weight loss, increased appetite, heat intolerance, palpitations, nausea, emesis, hyperdefecation, and irregular or absent menses in women [75, 80]. Insomnia, anxiety, and emotional lability may also be seen. Physical exam findings may often include damp skin, tachycardia, atrial fibrillation, proptosis, exophthalmos, stare, lid lag, goiter, proximal muscle weakness, tremor, and hyperkinesia [75]. In addition to abnormal thyroid function tests, additional lab findings may include elevated alanine aminotransferase (ALT) and alkaline phosphatase (AP) levels, which may be due to decreased splanchnic blood flow, and hypercalcemia, which is due to increased bone resorption relative to bone formation [75].

Thyroid storm is a rare but severe complication of hyperthyroidism that has a mortality rate of 20–50% and is considered an endocrine emergency [89, 90]. It is most commonly seen in Graves' disease. Precipitants may include infection, trauma, surgical emergencies, or planned operations. Other less common precipitants may include radiation thyroiditis, parturition, or DKA [75]. In this condition, the patient cannot tolerate the metabolic stress present. Similar to other patients with thyrotoxicosis, fever, diaphoresis, tachycardia, arrhythmias, and tremor may be present, but these features are typically much greater in magnitude. In addition, these patients may also have emesis, pulmonary edema, high-output congestive heart failure (CHF), hypotension, agitation, delirium, psychosis, and even coma [75]. Thyroid storm is a clinical diagnosis, but there is a scoring system that can aid with its diagnosis. This score takes into account features of the patient's presentation including temperature; central nervous system effects such as

agitation, delirium, psychosis, extreme lethargy, seizure, and coma; gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal pain, and jaundice; cardiovascular complications including tachycardia, CHF, and atrial fibrillation; and the presence of a known precipitant [91].

Due to the severity of thyroid storm, the patient should be placed in the ICU. The goals in the treatment of thyroid storm are to achieve a euthyroid state, treat the intercurrent illness if one is present, and provide supportive care [75]. Propylthiouracil (up to 400 mg every 4–6 h) is the preferred thionamide because it inhibits both thyroid hormone synthesis and thyroidal and peripheral conversion from T4 to the more active hormone, T3 [75]. Saturated solution of potassium iodide (SSKI; 50 mg iodide per drop; 5 drops every 6 h) or Lugol's solution (8 mg iodine per drop; 5–10 drops three times per day) is given to decrease the release of preformed thyroid hormone from the gland [66]. These should be administered at least 1 h after the patient is given thionamide therapy to prevent the use of that iodide as substrate for more thyroid hormone production. Stress dose steroids (hydrocortisone 100 mg IV every 8 h or dexamethasone 8 mg once daily) should be given to inhibit the release of thyroid hormone and decrease peripheral conversion from T4 to T3. Beta-blockers should be used to control the patient's tachycardia unless asthma or cardiac failure is present. Propranolol is most commonly used, as it is a nonselective beta-blocker. Higher than expected doses of beta-blockers may be needed due to increased metabolism of beta-blockers in the hyperthyroid state. Due to the risk of high-output heart failure in these patients, a short-acting beta-blocker such as esmolol or labetalol may be preferred in some cases [75]. If there is a contraindication to using beta-blockade, a calcium channel blocker such as diltiazem is an alternative rate control agent. After an infectious work-up including blood and urine cultures has been sent, empiric broad-spectrum antibiotics may be given. Supportive care includes treating the fever with acetaminophen and ice packs. Salicylates worsen free thyroid hormone levels by displacing T3 and T4 from thyroxine-binding globulin (TBG) and transthyretin and thus are not recommended [92].

In general, hyperthyroid patients requiring nonthyroidal surgery may be categorized into one of the three groups: patients with (1) known hyperthyroidism that are on antithyroid medications and are currently euthyroid, (2) mild to moderate hyperthyroidism, and (3) severe hyperthyroidism (thyroid storm). In the first group of patients, surgery does not need to be delayed. They should take their antithyroid medications on the morning of surgery [81, 93]. For those who have uncontrolled hyperthyroidism that is mild or moderate, surgery should not be performed unless it is urgent or emergent [81]. If surgery must be performed despite the presence of uncontrolled hyperthyroidism, the anesthesiologist must be aware of the patient's condition and anticipate the likely need for antithyroid medications (thionamides such as propylthiouracil or methimazole), beta-blockers, corticosteroids, and iodine (SSKI; Lugol's solution) [81]. In patients with thyroid storm, surgery should be avoided unless it is emergent and therapy has been initiated.

In general, indications for thyroidectomy include thyroid malignancy, refractory thyrotoxicosis from amiodarone, toxic MNG, toxic adenoma, or Graves' disease [94, 95]. In these patients, a euthyroid state should be achieved before the thyroidectomy is performed in order to decrease the risk of complications such as thyroid storm. The appropriate treatment should be given, which may include antithyroid medications, steroids, and beta-blockers for the reasons described above [81, 96].

Nonthyroidal Illness Syndrome

Nonthyroidal illness syndrome (NTIS) is also known as "low T3 syndrome" or "euthyroid sick syndrome." NTIS refers to the thyroid function testing abnormalities that are found in patients with illness unrelated to the thyroid. It may be seen in up to 75% of hospitalized patients. Although the lab abnormalities are variable, it is typically characterized by a low triiodothyronine (T3), elevated reverse T3 (rT3), low or low-normal TSH, and sometimes a low free thyroxine

(FT4) [97]. The degree of these changes is more profound in patients who are critically ill, and lower FT4 levels in ICU patients have been associated with increased mortality [44, 68]. Some believe that these changes in thyroid hormone levels are protective to patients who are ill by decreasing overall metabolism [75, 98].

The majority of circulating T3 is made peripherally in the liver and kidney by 5′-deiodination of T4, and the remainder is secreted by the thyroid [75, 99]. This is performed by D1 and D2 5′-monodeiodinases [75]. T4 may also be converted to rT3, which is hormonally inactive, by the D3 5′-deiodinase. The mechanisms that are believed to lead to the lab findings in NTIS include (1) low T3 level due to inhibition of 5′-monodeiodination, (2) elevated rT3 due to inhibition of 5′-monodeiodinase activity resulting in less rT3 to diiodothyronine (T2) conversion (less clearance), and (3) low T4 level due to decreased T4 binding and transient central hypothyroidism [75, 100–102]. The mechanisms that lead to inhibition of 5′-monodeiodinase activity leading to low T3 include (1) exogenous glucocorticoids or elevated endogenous serum cortisol levels, (2) free fatty acids, (3) cytokines (e.g., IFN-α, TNF, IL-6, NF-kB), and (4) drugs such as amiodarone, propranolol, and propylthiouracil [101, 103–107].

In the recovery phase of illness, patients with NTIS may develop a transient rise in their TSH, but this typically normalizes within 1–2 months [75]. Treatment of patients with NTIS is controversial, but there is no evidence that treatment of NTIS patients with thyroid supplementation is beneficial [108, 109]. Thus, in acutely ill patients, thyroid function tests are not generally recommended unless the patient's clinical presentation is felt to be due to hypothyroidism or thyrotoxicosis.

Calcium Disorders

Serum Calcium in Normal Conditions

Careful regulation of calcium balance in the body is essential because calcium is the main mineral component of the skeleton; calcium plays important roles in neuronal transmission, muscle contraction, and blood clotting; and calcium is a key intracellular signal that controls numerous processes throughout the body.

A typical normal range for serum total calcium concentration is between 8.8 and 10.2 mg/dL. Of this calcium, 50–60% of the calcium is bound to plasma proteins or is complexed with anions such as citrate and phosphate. The remaining ionized or "free" calcium is responsible for its physiologic actions. The concentration of ionized calcium is normally maintained in a very tight range: 4.5–5.3 mg/dL.

The body maintains normal serum calcium by regulating its entry through the intestine, its exit via the kidney, and its storage in bone. These processes are controlled by parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$]. PTH is produced by the parathyroid glands. 1,25-$(OH)_2D_3$ is made by a sequence of events beginning when cholecalciferol (vitamin D_3) is produced by exposure of the skin to UV light; it is also derived from dietary sources or supplements. In the liver, vitamin D_3 is converted to 25-(OH) vitamin D_3, which in turn is hydroxylated in the kidney to produce the active form, 1,25-$(OH)_2D_3$ (calcitriol). The effect of PTH and 1,25-$(OH)_2D_3$ is to keep plasma-ionized calcium concentration under tight control, despite variations in calcium supply.

Fluctuations in plasma-ionized calcium concentration are monitored by parathyroid cells via the cell membrane calcium-sensing receptor (CaSR) [110]. Binding of calcium ions to the extracellular domain of the CaSR activates a series of intracellular signaling events, ultimately controlling PTH secretion. Plasma-ionized calcium levels above normal lead to downregulation of PTH secretion, while low-ionized calcium causes an increase in PTH secretion. PTH activates bone resorption and distal nephron calcium resorption. PTH also increases renal production of calcitriol, which stimulates calcium absorption by the small intestine.

Hypercalcemia

Hypercalcemia is a frequently encountered metabolic abnormality. Presenting signs and symp-

toms may be absent or subtle, except in cases where calcium is significantly elevated or has risen rapidly. The diagnostic work-up of hypercalcemia is straightforward [111]. Identifying the cause of hypercalcemia requires a complete history, physical examination, laboratory tests, and diagnostic imaging studies.

History and Physical Examination

Most patients with mild hypercalcemia (serum calcium level <11.0 mg/dL) do not have symptoms, although they may have mild fatigue, changes in cognition, depressed mood, or constipation. In individuals with serum calcium values between 12 and 14 mg/dL, there may be anorexia, nausea, abdominal pain, constipation, muscle weakness, and depressed mental status. Dehydration may be seen caused by decreased urine concentrating ability due to high urinary calcium levels. At calcium levels above 14 mg/dL, there may be progressive lethargy and coma.

A review of the medical record may help determine the duration of the hypercalcemia and its cause. Prescription medications, food, and dietary supplements should be considered possible causative agents. A family history should be performed to identify evidence of any related endocrinopathies. Patients who have hyperparathyroidism associated with multiple endocrine neoplasia (MEN) may show evidence of the other conditions that make up these syndromes. Patients with sarcoidosis may have fever, lymphadenopathy, rashes, or pulmonary manifestations. Hypercalcemia of malignancy typically develops only when a significant tumor burden is present; thus, most of these patients have an established cancer diagnosis.

On physical exam, evidence for dehydration should be sought. Aside from depressed mental status and signs of dehydration, physical exam findings are generally normal in hypercalcemic patients, particularly if calcium levels are only modestly elevated.

Laboratory Studies

The first step in evaluating hypercalcemia is to rule out spurious hypercalcemia caused by an increase in concentrations of the plasma proteins that bind calcium. This may be seen in HIV infection, chronic hepatitis, and multiple myeloma. The ionized calcium concentration in these situations remains normal. To correct the measured serum calcium for elevations in plasma protein, the serum calcium level should be lowered by 0.8 mg/dL for every 1 g/dL of albumin above the normal range. When performed under optimal conditions, ionized calcium measurement is more accurate than adjusted total serum calcium.

Once hypercalcemia is confirmed, the next step is measurement of the serum PTH concentration [112]. The results of PTH measurement indicate whether hypercalcemia is mediated by PTH and thus help identify the cause of hypercalcemia. The hypercalcemia is considered PTH mediated if serum calcium is high and the PTH level is elevated or inappropriately normal. When PTH levels are low in the face of high serum calcium, the hypercalcemia is said to be non-PTH mediated, or PTH independent.

Serum creatinine should be measured as hypercalcemia may be seen in the setting of renal failure, and renal function may be impaired in the setting of dehydration or nephrocalcinosis. Levels of 25-(OH) vitamin D should be measured to rule out supplemental vitamin D intoxication. High 1,25-$(OH)_2$D levels may be seen in granulomatous disease and some lymphomas. Inorganic phosphorus measurement may be helpful as low serum phosphate is often seen in primary hyperparathyroidism, while high phosphate may occur in vitamin D intoxication.

Other diagnostic studies may be dictated by clinical circumstances. Electrocardiography is recommended for patients with severe hypercalcemia to detect shortening of the QTc interval or atrioventricular block.

Causes of Hypercalcemia

Primary Hyperparathyroidism High serum calcium and PTH concentrations [in the absence of lithium use or familial hypocalciuric hypercalcemia (FHH)] is evidence of primary hyperparathyroidism. PTH levels are usually increased to no more than five times the upper limit of normal. More significant hypercalcemia and PTH elevations should raise suspicion for parathyroid carci-

noma. In 75–80% of patients, a solitary parathyroid adenoma is present, hyperplasia involving multiple parathyroid glands is found in 15–20% of patients, and parathyroid carcinoma is present in less than 1%. On occasion, double adenomas are found [113]. Patients with multiple endocrine neoplasia type I (MEN I) or MEN II typically have parathyroid hyperplasia involving all parathyroid glands [114].

Familial Hypocalciuric Hypercalcemia FHH, also referred to as benign familial hypercalcemia, is a rare genetic condition caused by inactivating mutations in the CaSR. This results in insensitivity of the parathyroid cell to serum calcium, a higher set point for the extracellular ionized calcium concentration and inappropriately normal to mildly elevated PTH levels. Patients with FHH have chronic asymptomatic hypercalcemia associated with relatively low urinary calcium excretion. This is usually a benign condition requiring no treatment.

Tertiary Hyperparathyroidism Diseases that result in a low serum calcium or a high serum phosphate typically will be associated with an elevation in PTH as a compensatory measure. This increase of PTH is termed secondary hyperparathyroidism. Common causes of secondary hyperparathyroidism include vitamin D deficiency, intestinal malabsorption of calcium or vitamin D, renal calcium wasting, severe dietary calcium insufficiency, and hyperphosphatemia from chronic renal insufficiency.

In patients with long-term secondary hyperparathyroidism, hyperplasia or neoplasia of the parathyroid glands may develop. This results in autonomous parathyroid function, with the production of excess PTH at all times, resulting in hypercalcemia. This is most often seen in patients with chronic kidney disease. More than one parathyroid gland is usually affected.

Once the diagnosis of primary hyperparathyroidism is made, additional testing may be necessary to determine whether the condition is severe enough to warrant parathyroidectomy [115]. If MEN II is in the differential diagnosis, medullary thyroid cancer should be excluded, and pheochromocytoma must be ruled out before the patient can safely go to surgery.

Malignancy-Associated Hypercalcemia If the serum calcium is elevated and the PTH is low, the patient has PTH-independent hypercalcemia. Malignancy is the most common cause of PTH-independent hypercalcemia and is usually to blame when an acutely elevated calcium level is discovered. When the PTH is low and the patient is not known to have a malignancy, other diagnostic options should include thyrotoxicosis, vitamin D intoxication, sarcoidosis, immobilization, certain endocrine disorders, and drugs and supplements.

Hypercalcemia of malignancy has two forms: humoral hypercalcemia of malignancy (HHM) and local osteolytic hypercalcemia (LOH). HHM results from production by the tumor of a circulating factor that affects calcium metabolism, either at the level of skeletal calcium release, renal calcium handling, or intestinal calcium absorption. Occasionally it can be caused by the unregulated production of calcitriol (usually by B cell lymphomas) or other mediators that interfere with calcium homeostasis. The best-recognized cause of HHM is parathyroid hormone-related protein (PTHrP) [106]. The PTHrP peptide is homologous with PTH, and they share a common receptor. When PTHrP circulates at supraphysiologic concentrations, it causes similar metabolic effects to PTH, inducing osteoclasts to resorb bone, reducing renal calcium output, and increasing renal phosphate clearance [116].

Tumors that produce HHM by secreting PTHrP are typically squamous carcinomas, adenocarcinoma of the breast or ovary, renal carcinoma, transitional cell carcinoma of the bladder, islet cell tumors of the pancreas, T cell lymphomas, and pheochromocytoma [117]. HHM typically develops in patients with a large tumor burden, so it is uncommon for HHM to be the presenting feature of a cancer. A high serum PTHrP level will confirm the diagnosis of HHM.

LOH occurs when a bony metastasis causes release of calcium through the elaboration of

cytokines or other factors that activate bone resorption by osteoclasts. In LOH there is evidence of bone metastases by symptoms and/or imaging studies. Multiple myeloma, adenocarcinomas of the breast, and certain lymphomas may cause LOH.

PTH-independent hypercalcemia may occur in sarcoidosis, tuberculosis, and other granulomatous diseases, when granulomas release excessive calcitriol. Elevation of serum 25-hydroxyvitamin D indicates excessive vitamin D intake, while elevation of serum 1,25-dihydroxyvitamin D occurs in granulomatous diseases. Endocrine disorders that may occasionally lead to hypercalcemia include severe hyperthyroidism (which activates bone resorption) and Addison's disease (where volume depletion causes hypercalcemia). Immobilization stimulates bone resorption and can result in elevated serum calcium levels, particularly in bedbound hospitalized patients. Thiazide diuretics may cause hypercalcemia due to enhanced retention of calcium by the kidney. In many cases this develops in individuals with underlying mild primary hyperparathyroidism [118].

Treatment of Hypercalcemia

A malignancy is often the cause of acute hypercalcemia. When the serum calcium level is significantly elevated, treatment should include intravenous hydration, along with measures to enhance renal calcium excretion and reduce bone resorption and/or intestinal calcium absorption, depending on which is the cause of calcium excess.

Saline Hydration

Most individuals with acute hypercalcemia have some degree of hypovolemia, which worsens their ability to excrete calcium. Thus, the first intervention should be fluid resuscitation with normal saline. The use of normal saline is important, as arrival of sodium at the distal nephron will enhance urinary calcium excretion. When the intravascular volume is repleted, a loop diuretic such as furosemide may be started to allow additional saline hydration and to enhance calcium excretion. A serum calcium·phosphate product above 70 indicates the patient is at risk for calciphylaxis, so reduction of the serum phosphate level with phosphate binders should be undertaken along with efforts to lower serum calcium.

Bisphosphonate Therapy

If the serum calcium does not return to an acceptable level with intravenous saline and diuresis, then pharmacologic therapy is required [119]. Most causes of severe hypercalcemia involve increased osteoclast-mediated bone resorption, so drugs that inhibit this process are helpful. The drug of choice is a bisphosphonate, such as pamidronate or zoledronic acid, both of which are given intravenously. Pamidronate 60–90 mg is given intravenously over a few hours and is generally well tolerated. Serum calcium levels will typically begin to decline within 24–48 h following the infusion, although the peak effect may take several days. The actions of pamidronate may last several weeks, but retreatment may be undertaken if renal function will allow. Zoledronic acid is given at 4 mg intravenously over at least 15 min [120]. It has a greater potency and a longer duration of action than pamidronate. A repeat dose may be provided after 7 days if renal function allows.

Other Treatments for Hypercalcemia

In cancer patients with hypercalcemia refractory to bisphosphonate therapy, denosumab may be used [121]. Denosumab is a RANK ligand inhibitor that reduces osteoclast-mediated bone resorption, thus lowering serum calcium.

When a more rapid decline in serum calcium is desired, subcutaneous injections of calcitonin can be employed. Calcitonin is administered at a starting dosage of 4 U/kg every 12 h. Tachyphylaxis to the actions of calcitonin usually limits its effects to a few days. In severe or refractory hypercalcemia, hemodialysis against a low-calcium bath may be necessary.

Glucocorticoid therapy has an important role when hypercalcemia results from an increase in intestinal calcium absorption, as occurs in vitamin D intoxication or granulomatous diseases. Glucocorticoids inhibit the renal or granulomatous 1α-hydroxylase activity resulting in a decrease in production of calcitriol, and they also

directly impair intestinal calcium transport. In hypercalcemia due to lymphoma, treatment with steroids may also indirectly reduce hypercalcemia due to their antineoplastic effect.

In malignancy-associated hypercalcemia, chemotherapy, surgery, or radiation therapy targeted at the tumor itself may also reduce the hypercalcemia.

Management of a patient with primary hyperparathyroidism is based upon the degree of hypercalcemia, the severity of symptoms or end-organ effects, and the risk of future complications [122]. Guidelines for surgical intervention in patients with asymptomatic primary hyperparathyroidism were most recently updated at a National Institutes of Health workshop in 2014 [115].

In patients who are very hypercalcemic but cannot or will not have surgery, the calcimimetic agent cinacalcet has been used to control hypercalcemia. Calcimimetic agents such as cinacalcet activate the CaSR and thus diminish PTH production, ultimately leading to reduced serum calcium.

Hypocalcemia

Chronic, mild, or moderate hypocalcemia is often asymptomatic. However, when the serum calcium level falls below 7.5–8 mg/dL (in the setting of normal albumin), individuals may develop symptoms of neuromuscular irritability, including tremor, muscle spasms, and paresthesias.

The cause of hypocalcemia can usually be elucidated after a careful history. Dietary calcium and vitamin D intake, sun exposure, and alcohol intake should be evaluated. Head and neck surgery or irradiation can lead to hypoparathyroidism. Rare conditions, such as autoimmune disease and iron overload disorders, should be considered. Other conditions, such as pancreatitis, rhabdomyolysis, tumor lysis syndrome, or transfusion therapy, are possible causes for hypocalcemia.

On physical exam, Chvostek and Trousseau signs may be elicited. With more severe hypocalcemia, tetany or seizures may appear. Prolongation of the QTc interval may be evident on electrocardiogram, indicating the patient is at risk for cardiac arrhythmias.

Hypocalcemia is often caused by vitamin D deficiency or hypoparathyroidism. Injury or removal of the parathyroid glands during thyroidectomy or other head and neck surgeries can lead to hypoparathyroidism, which is manifested by hypocalcemia and a low serum PTH. Patients who have parathyroidectomy for primary hyperparathyroidism may have transient postoperative hypocalcemia due to deposition of large quantities of calcium into the unmineralized matrix of the skeleton. This is known as "hungry bone syndrome."

Autoimmune destruction of the parathyroid glands may occur in certain conditions [123]. Infiltrative diseases, such as hemochromatosis, may impair parathyroid function, as can external beam irradiation to the neck. Congenital absence of the parathyroid glands is seen in DiGeorge syndrome. Hypomagnesemia may cause hypoparathyroidism because magnesium is needed for both PTH release and PTH action. This is commonly seen in alcoholic patients who are frequently hypomagnesemic and malnourished.

Disorders of vitamin D supply, production, or activation may lead to hypocalcemia. In vitamin D deficiency, serum calcium concentrations are usually not severely affected, due to compensatory increases in PTH and its downstream effects to keep serum calcium normal.

Hypocalcemia can be seen in acute pancreatitis, when fatty acids released through the action of pancreatic enzymes complex with calcium. Hypocalcemia due to the formation of calcium phosphate complexes takes place in severe hyperphosphatemic states, such as renal failure, rhabdomyolysis, and tumor lysis syndrome. In these conditions, formation of calcium phosphate complexes results in a decrease in ionized calcium concentrations. Hypocalcemia may also be seen in patients given multiple red blood cell transfusions with cells to which calcium chelators have been added to prevent clotting.

Treatment of Hypocalcemia

In patients with symptoms of severe hypocalcemia (e.g., those with neuromuscular irritability or QTc prolongation), calcium (as calcium gluconate) should be administered by slow intravenous

infusion to increase the serum calcium level until symptoms resolve. Bolus administration of intravenous calcium will have only a transient effect on serum calcium. An example of a calcium infusion is 10 ampules (total 100 mL) of 10% calcium gluconate in 1 L of D_5W, infused at 50 cc/h. Serum calcium should be monitored frequently and the rate of infusion adjusted to maintain levels at the low end of the normal range. Simultaneously, any deficiency of magnesium and/or vitamin D should be corrected. Hypocalcemia may recur rapidly after discontinuation of the calcium infusion, so oral calcium should be administered prior to tapering the infusion. In patients with milder hypocalcemia, calcium infusion is not necessary, and calcium can be administered orally as calcium carbonate or calcium citrate in doses starting at 1000–1500 mg of elemental calcium daily in divided doses with meals. If appropriate, calcitriol also should be provided.

In chronic hypoparathyroidism, treatment with calcitriol is necessary because renal production of calcitriol will not occur in the absence of PTH. Serum calcium should be kept at the lower end of the normal range, sufficient to relieve symptoms and reverse tetanic signs (e.g., Chvostek sign).

References

1. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27:553–91.
2. Honiden S, Inzucchi SE. Analytic review: glucose controversies in the ICU. J Intensive Care Med. 2011;26:135–50.
3. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. Circulation. 2008;117:1018–27.
4. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg. 1999;67:352–60.
5. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
6. NICE-SUGAR Study Investigators, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hébert PC, Heyland DK, Robinson BG. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–18.
7. Kosiborod M, Inzucchi SE, Goyal A, Krumholz HM, Masoudi FA, Xiao L, Spertus JA. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA. 2009;301:1556–64.
8. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180:821–7.
9. Egi M, Bellomo R, Stachowski E, et al. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med. 2011;39:105–11.
10. Plummer MP, Bellomo R, Cousins CE, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med. 2014;40:973–80.
11. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32:1119–31.
12. Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med. 2012;12:3251–76.
13. Surviving Sepsis Campaign. http://www.survivingsepsis.org/Guidelines/Pages/default.aspx. Accessed 3 Nov 2013.
14. Shetty S, Inzucchi SE, Goldberg PA, Cooper D, Siegel MD, Honiden S. Adapting to the new consensus guidelines for managing hyperglycemia during critical illness: the updated Yale insulin infusion protocol. Endocr Pract. 2012;18:363–70.
15. Finfer S, Wernerman J, Preiser JC, Cass T, Desaive T, Hovorka R, et al. Clinical review: consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013;17:229.
16. Avanzini F, Marelli G, Donzelli W, Busi G, Carbone S, Bellato L, et al. Transition from intravenous to subcutaneous insulin: effectiveness and safety of a standardized protocol and predictors of outcome in patients with acute coronary syndrome. Diabetes Care. 2011;34:1445–50.
17. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:16–38.

18. Maynard G, Wesorick DH, O'Malley C, Inzucchi SE, Society of Hospital Medicine Glycemic Control Task Force. Subcutaneous insulin order sets and protocols: effective design and implementation strategies. J Hosp Med. 2008;3:29–41.
19. American Diabetes Association. Diabetes care in the hospital: standards of medical care in diabetes—2019. Diabetes Care. 2019;42(Supplement 1):S173–81.
20. Centers for Disease Control. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics/dkafirst/fig7.htm. Accessed 18 Aug.
21. Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality — United States, 2000–2014. MMWR Morb Mortal Wkly Rep. 2018;67:362–5. https://doi.org/10.15585/mmwr.mm6712a3externalicon.
22. Centers for Disease Control. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics/mortalitydka/fRateDKAGenAgeAdjusted.htm. Accessed 18 Aug.
23. Kitabchi A, Umpierrez G, Miles J, Fisher J. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335–43.
24. Elisaf MS, Tsatsoulis AA, Katopodis KP, Siamopoulos KC. Acid-base and electrolyte disturbances in patients with diabetic ketoacidosis. Diabetes Res Clin Pract. 1996;34(1):23–7.
25. Yasuda K, Tanahashi H, Hayashi M, Yamakita N. Hyperglycemic crises in adult patients with diabetes: response to Kitabchi et al. Diabetes Care. 2009;32(12):e157; author reply e158.
26. Adrogué HJ, Wilson H, Boyd AE, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med. 1982;307(26):1603–10.
27. Kitabchi A, Nyenwe E. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin N Am. 2006;35(4):725–51, viii.
28. Ennis E, Kreisberg R. Diabetic ketoacidosis and the hyperglycemic hyperosmolar syndrome. In: LeRoith D, Taylor S, Olefsky J, editors. Diabetes mellitus. Philadelphia: Lippincott Williams & Williams; 2004. p. 627.
29. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, Ellis SE, O'Sullivan PS. Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. J Gen Intern Med. 1991;6(6):495–502.
30. Umpierrez G, Smiley D, Kitabchi A. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med. 2006;144(5):350–7.
31. Mauvais-Jarvis F, Sobngwi E, Porcher R, et al. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. Diabetes. 2004;53(3):645–53.
32. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. Endocr Rev. 2008;29(3):292–302.
33. Magee M, Bhatt B. Management of decompensated diabetes. Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Crit Care Clin. 2001;17(1):75–106.
34. Kitabchi A, Umpierrez G, Murphy M, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care. 2001;24(1):131–53.
35. Büyükaşik Y, Ileri N, Haznedaroğlu I, et al. Enhanced subclinical coagulation activation during diabetic ketoacidosis. Diabetes Care. 1998;21(5):868–70.
36. Stentz F, Umpierrez G, Cuervo R, Kitabchi A. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes. 2004;53(8):2079–86.
37. Joslin EP, Kahn CR, Weir GC. Joslins diabetes mellitus. 13th ed. Malvern: Lea & Febiger; 1994.
38. Umpierrez G, Freire A. Abdominal pain in patients with hyperglycemic crises. J Crit Care. 2002;17(1):63–7.
39. Umpierrez G, Kelly J, Navarrete J, Casals M, Kitabchi A. Hyperglycemic crises in urban blacks. Arch Intern Med. 1997;157(6):669–75.
40. Hillier T, Abbott R, Barrett E. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106(4):399–403.
41. Huang CC, Kuo SC, Chien TW, et al. Predicting the hyperglycemic crisis death (PHD) score: a new decision rule for emergency and critical care. Am J Emerg Med. 2013;31(5):830–4.
42. Elangovan A, Cattamanchi S, Farook A, Trichur R. Validation of predicting hyperglycemic crisis death score: a risk stratification tool for appropriate disposition of hyperglycemic crisis patients from the emergency department. J Emerg Trauma Shock. 2018;11(2):104–10.
43. Slovis C, Mork V, Slovis R, Bain R. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. Am J Emerg Med. 1987;5(1):1–5.
44. Trence D, Hirsch I. Hyperglycemic crises in diabetes mellitus type 2. Endocrinol Metab Clin N Am. 2001;30(4):817–31.
45. Yadav D, Nair S, Norkus E, Pitchumoni C. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol. 2000;95(11):3123–8.
46. Nyenwe E, Loganathan R, Blum S, et al. Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. Endocr Pract. 2007;13(1):22–9.
47. Bratusch-Marrain P, DeFronzo R. Impairment of insulin-mediated glucose metabolism by hyperosmolality in man. Diabetes. 1983;32(11):1028–34.
48. Kitabchi A, Murphy M, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care. 2008;31(11):2081–5.

49. Umpierrez G, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med. 2004;117(5):291–6.
50. Umpierrez G, Cuervo R, Karabell A, Latif K, Freire A, Kitabchi A. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care. 2004;27(8):1873–8.
51. Kitabchi A, Umpierrez G, Murphy M, Kreisberg R. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care. 2006;29(12):2739–48.
52. Fisher J, Kitabchi A. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab. 1983;57(1):177–80.
53. Mitchell J, Wildenthal K, Johnson RJ. The effects of acid-base disturbances on cardiovascular and pulmonary function. Kidney Int. 1972;1(5):375–89.
54. Morris L, Murphy M, Kitabchi A. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med. 1986;105(6):836–40.
55. Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care. 2013;36(8):2169–74.
56. Roberts M, Slover R, Chase H. Diabetic ketoacidosis with intracerebral complications. Pediatr Diabetes. 2001;2(3):109–14.
57. Sakharova OV, Inzucchi SE. Endocrine assessments during critical illness [review]. Crit Care Clin. 2007;23:467–90.
58. Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, et al. Reduced cortisol metabolism during critical illness. N Engl J Med. 2013;368:1477–88.
59. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89.
60. Annane D, Briegel J, Sprung CL. Corticosteroid insufficiency in acutely ill patients [letter]. N Engl J Med. 2003;348:2157–9.
61. Hamrahian AH, Fleseriu M, AACE Adrenal Scientific Committee. Evaluation and management of adrenal insufficiency in critically ill patients: disease state review. Endocr Pract. 2017;23(6):716–25.
62. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358:111–24.
63. Rhodes A, Evans L, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med J. 2017;45(3):486–552.
64. Marik PE. Glucocorticoids in sepsis: dissecting facts from fiction. Crit Care. 2011;15:158.
65. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med. 2004;350:1629–38.
66. Steven KH. Adrenal cortical steroids. In: Drug facts and comparisons. 5th ed. St. Louis: Facts and Comparisons, Inc.; 1997. p. 122–8.
67. Havlik RJ, Cahow CE, Kinder BK. Advances in the diagnosis and treatment of pheochromocytoma. Arch Surg. 1988;123(5):626–30.
68. Steinsapir J, Carr AA, Prisant LM, Bransome ED. Metyrosine and pheochromocytoma. Arch Intern Med. 1997;157(8):901–6.
69. Butz JJ, Weingarten TN, Cavalcante AN, Bancos I, Young WF Jr, McKenzie TJ, et al. Perioperative hemodynamics and outcomes of patients on metyrosine undergoing resection of pheochromocytoma or paraganglioma. Int J Surg. 2017;46:1–6.
70. Wachtel H, Kennedy EH, Zaheer S, Bartlett EK, Fishbein L, Roses RE, Fraker DL, et al. Preoperative metyrosine improves cardiovascular outcomes for patients undergoing surgery for pheochromocytoma and paraganglioma. Ann Surg Oncol. 2015;22(Suppl 3):S646–54.
71. Gadelha M, Neto LV. Efficacy of medical treatment in Cushing's disease: a systematic review. Clin Endocrinol. 2014;80:1–12.
72. Carroll TB, Peppard WJ, Herrmann DJ, Javorsky BR, Wang TS, Patel H, et al. Continuous etomidate infusion for the management of severe Cushing syndrome: validation of a standard protocol. J Endocr Soc. 2018;3(1):1–12.
73. Schulte HM, Benker G, Reinwein D, Sippell WG, Allolio B. Infusion of low dose etomidate: correction of hypercortisolemia in patients with Cushing's syndrome and dose-response relationship in normal subjects. J Clin Endocrinol Metab. 1990;70(5):1426–30.
74. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid. 2007;17(12):1211–23.
75. Williams RH, Melmed S. Williams textbook of endocrinology. 12th ed. Philadelphia: Elsevier/Saunders; 2011. http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20090530966.
76. Roberts CG, Ladenson PW. Hypothyroidism. Lancet. 2004;363(9411):793–803.
77. Cooper DS. Clinical practice. Subclinical hypothyroidism. N Engl J Med. 2001;345(4):260–5.
78. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821):1142–54.
79. Product information: SYNTHROID(R) oral tablets lsotAL, North Chicago, IL, 2008. http://www.rxabbvie.com/pdf/synthroid.pdf.
80. Fliers E, Wiersinga WM. Myxedema coma. Rev Endocr Metab Disord. 2003;4(2):137–41.

81. Kohl BA, Schwartz S. How to manage perioperative endocrine insufficiency. Anesthesiol Clin. 2010;28(1):139–55.
82. Schiff RL, Welsh GA. Perioperative evaluation and management of the patient with endocrine dysfunction. Med Clin North Am. 2003;87(1):175–92.
83. Product information: levothyroxine sodium intravenous injection lsiiAP, LLC (per FDA), Schaumburg, IL, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202231s003lbl.pdf.
84. Weinberg AD, Brennan MD, Gorman CA, Marsh HM, O'Fallon WM. Outcome of anesthesia and surgery in hypothyroid patients. Arch Intern Med. 1983;143(5):893–7.
85. Ladenson PW, Levin AA, Ridgway EC, Daniels GH. Complications of surgery in hypothyroid patients. Am J Med. 1984;77(2):261–6.
86. Benfari G, de Vincentiis M. Postoperative airway obstruction: a complication of a previously undiagnosed hypothyroidism. Otolaryngol Head Neck Surg. 2005;132(2):343–4.
87. Drucker DJ, Burrow GN. Cardiovascular surgery in the hypothyroid patient. Arch Intern Med. 1985;145(9):1585–7.
88. Ferrari SM, Fallahi P, Galetta F, Citi E, Benvenga S, Antonelli A. Thyroid disorders induced by checkpoint inhibitors. Rev Endocr Metab Disord. 2018;19(4):325–33.
89. Ashkar FS, Miller R, Gilson AJ. Thyroid function and serum thyroxine in thyroid storm. South Med J. 1972;65(3):372–4.
90. Mazzaferri EL, Skillman TG. Thyroid storm. A review of 22 episodes with special emphasis on the use of guanethidine. Arch Intern Med. 1969;124(6):684–90.
91. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin N Am. 1993;22(2):263–77.
92. Larsen PR. Salicylate-induced increases in free triiodothyronine in human serum. Evidence of inhibition of triiodothyronine binding to thyroxine-binding globulin and thyroxine-binding prealbumin. J Clin Invest. 1972;51(5):1125–34.
93. Spell NO. Stopping and restarting medications in the perioperative period. Med Clin North Am. 2001;85(5):1117–28.
94. Langley RW, Burch HB. Perioperative management of the thyrotoxic patient. Endocrinol Metab Clin N Am. 2003;32(2):519–34.
95. Franzese CB, Fan CY, Stack BC. Surgical management of amiodarone-induced thyrotoxicosis. Otolaryngol Head Neck Surg. 2003;129(5):565–70.
96. Streetman DD, Khanderia U. Diagnosis and treatment of Graves disease. Ann Pharmacother. 2003;37(7–8):1100–9.
97. Adler SM, Wartofsky L. The nonthyroidal illness syndrome. Endocrinol Metab Clin N Am. 2007;36(3):657–72, vi.
98. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA. 1981;245(1):43–5.
99. Utiger RD. Altered thyroid function in nonthyroidal illness and surgery. To treat or not to treat? N Engl J Med. 1995;333(23):1562–3.
100. Chopra IJ. An assessment of daily production and significance of thyroidal secretion of 3, 3′, 5′-triiodothyronine (reverse T3) in man. J Clin Invest. 1976;58(1):32–40.
101. Chopra IJ, Williams DE, Orgiazzi J, Solomon DH. Opposite effects of dexamethasone on serum concentrations of 3,3′,5′-triiodothyronine (reverse T3) and 3,3′5-triiodothyronine (T3). J Clin Endocrinol Metab. 1975;41(5):911–20.
102. Chopra IJ. Clinical review 86: euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab. 1997;82(2):329–34.
103. Chopra IJ, Teco GN, Mead JF, Huang TS, Beredo A, Solomon DH. Relationship between serum free fatty acids and thyroid hormone binding inhibitor in nonthyroid illnesses. J Clin Endocrinol Metab. 1985;60(5):980–4.
104. van der Poll T, Romijn JA, Wiersinga WM, Sauerwein HP. Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man. J Clin Endocrinol Metab. 1990;71(6):1567–72.
105. Stouthard JM, van der Poll T, Endert E, et al. Effects of acute and chronic interleukin-6 administration on thyroid hormone metabolism in humans. J Clin Endocrinol Metab. 1994;79(5):1342–6.
106. Corssmit EP, Heyligenberg R, Endert E, Sauerwein HP, Romijn JA. Acute effects of interferon-alpha administration on thyroid hormone metabolism in healthy men. J Clin Endocrinol Metab. 1995;80(11):3140–4.
107. Nagaya T, Fujieda M, Otsuka G, Yang JP, Okamoto T, Seo H. A potential role of activated NF-kappa B in the pathogenesis of euthyroid sick syndrome. J Clin Invest. 2000;106(3):393–402.
108. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab. 1986;63(1):1–8.
109. Becker RA, Vaughan GM, Ziegler MG, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med. 1982;10(12):870–5.
110. Brown EM. Physiology and pathophysiology of the extracellular calcium-sensing receptor. Am J Med. 1999;106(2):238–53.
111. Marx SJ. Hyperparathyroid and hypoparathyroid disorders. N Engl J Med. 2000;343(25):1863–75.
112. Inzucchi SE. Management of hypercalcemia. Diagnostic workup, therapeutic options for hyperparathyroidism and other common causes. Postgrad Med. 2004;115(5):27–36.

113. Kebebew E, Hwang J, Reiff E, Duh QY, Clark OH. Predictors of single-gland vs multigland parathyroid disease in primary hyperparathyroidism: a simple and accurate scoring model. Arch Surg. 2006;141(8):777–82; discussion 782.
114. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658–71.
115. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–9.
116. Dunbar ME, Wysolmerski JJ. Parathyroid hormone-related protein: a developmental regulatory molecule necessary for mammary gland development. J Mammary Gland Biol Neoplasia. 1999;4(1):21–34.
117. Rankin W, Grill V, Martin TJ. Parathyroid hormone-related protein and hypercalcemia. Cancer. 1997;80(8 Suppl):1564–71.
118. Wermers RA, Kearns AE, Jenkins GD, Melton LJ. Incidence and clinical spectrum of thiazide-associated hypercalcemia. Am J Med. 2007;120(10):911.e919–5.
119. Ziegler R. Hypercalcemic crisis. J Am Soc Nephrol. 2001;12(Suppl 17):S3–9.
120. Novartis. Zometa package insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21223lbl.pdf.
121. Hu MI, Glezerman IG, Leboulleux S, Insogna K, Gucalp R, Misiorowski W, et al. Denosumab for treatment of hypercalcemia of malignancy. J Clin Endocrinol Metab. 2014;99(9):3144–52.
122. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med. 1999;341(17):1249–55.
123. Betterle C, Greggio NA, Volpato M. Clinical review 93: autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab. 1998;83(4):1049–55.

Part IV

Thyroid and Parathyroid Disturbances

The Microbiome, Surgical Stress, and Infection

17

Mitchell Jay Cohen

Introduction

The microbiome represents a very complex system and experimentally emerging biology which drives not only infection but also biologic mechanisms affecting surgical outcomes previously thought to be noninfectious. This chapter provides an introduction to the microbiome for surgeons. Work around the biome and in particular its relationship to surgery are a very rapidly evolving science with seemingly unlimited complexity despite extremely immature and limited data and understanding. Despite this, much is known, and even the early data and its framework can guide our understanding of surgical disease and treatment. In doing so we will provide essential definitions, followed by a discussion of what perturbs the biome, how the biome and perturbations affect infection, what other biologic mechanisms are affected by the biome and its perturbations, and finally a discussion of future clinical and research endeavors on this topic.

M. J. Cohen (✉)
Denver Health Medical Center, Denver, CO, USA

Division of Bioinformatics and Personalized Medicine, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: Mitchell.Cohen@dhha.org

Definitions

The microbiome is a biologic community of all microbial taxa which reside in a specific location or host. In short it is a community of organisms which contribute to the microbial health and function of a host [1–3]. While many will suggest that the microbiome is technically the genome of the microbes which inhabit the host (in this case a human), we will use microbiome interchangeably defined as the genome (how this is surveyed) and/or the actual microbial community. The host for the microbiome can be a large population, a single organism such as a single person or a single location within that organism such as the colon or lung. The organ-specific definition is perhaps the most common conception used in medicine or surgery, e.g., the gut microbiome, the colon microbiome, or the lung microbiome. The defining characteristic of a biome is not however limited to a collection of individual microbes (bacteria, viruses, fungi) or taxa but rather that this collection has evolved temporally and locally to behave synergistically as a community with incumbent function in relation to the host and environment. This then is perhaps the most important descriptor for surgical disease and medicine, namely, that the biome functions as a complex biological unit with a role in health and function of the human it inhabits [4]. From this it makes sense that a perturbation of the biome through an unbalancing from

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_17

changed anatomy, inflammatory or physiologic stress, disease, antibiotics, or injury would result in disease [5].

Surveying the Biome

The microbiome is surveyed through sequencing of the nucleic acids of the taxa in the population. This is most commonly done through 16srRNA sequencing which uses a highly conserved region of ribosomal DNA among all bacterial taxa as binding targets for primers. Sequencing of approximately 200 base pairs then allows for identification of highly variable regions which are unique to each organism. Through identification of the number and frequency of each sequence in a biological sample, the biome can be determined. These are represented in operational taxonomic units or OTUs [6].

While characterization of the microbiome represents a rapidly evolving science, a few terms are important to understand. The diversity within a biome is described in measuring the alpha and beta diversity. Most simply the alpha diversity is a measure of the total number of different taxa in a single sample as well as its inter-sample diversity. This is a count of the total number of different OTUs within the sample. Beta diversity is a measure of the intra sample diversity or more simply the differences between samples. Beta diversity is further described using several different metrics. The most commonly used are UniFrac and Bray-Curtis and the Jaccard distance. The UniFrac accounts for the distances between sequences in a phylogenetic tree. The Bray-Curtis dissimilarity index measures the difference between samples by abundance of individual species. Finally, the Jaccard distance is based on the presence of species without accounting for the abundance (as in the Bray-Curtis dissimilarity index). While a basic understanding of these concepts is essential to being able to interpret the emerging literature on the biome in human health and surgical disease, it is important to remember that bioinformatic and machine learning techniques are continually being developed and reapplied to increasingly large and complex datasets.

Differences and Changes in the Biome

There has been considerable advancement in the ability to survey the biome. Indeed, faster sequencing, shorter reading frames, and improvements in informatics approaches to handling the huge datasets which are generated have allowed a rapidly growing literature over the past 5 years [1, 7]. These advances have in turn allowed faster more economical non-culture-based quantification of microbial populations and have resulted in an enhanced understanding in the relationship between commensal organisms and human health across a number of injury and disease states. Perhaps the best known, most clinically understood and resultant clinical application has centered around *Clostridium difficile* infection. It is widely understood that perturbation of the gut microbiome (generally through antibiotics) results in a narrowed diversity allowing for opportunistic *Clostridium difficile* overgrowth and infection [8]. From this understanding and an increasing clinical incidence and virulence, the promise of rapid diagnostics and therapeutics such as fecal transplants aims to restore balance across taxa which is discussed below. This approach which stems from basic control systems engineering theory suggests that the best way to modulate a deleterious response is through a controller (in this case restoration of the complexity of the biome) rather than reducing or eliminating the signal (through the more traditional use of oral and intravenous antibiotics). A vast literature and clinical protocols which are discussed later in this chapter have been developed and implemented with promising but varying success.

Perturbations of the Biome: Trauma, Burn, and Sterile Inflammation

Many interventions and biological and physiological perturbations can change microbial composition of the host. Sterile inflammation in the form of trauma, shock, or burn injury can directly affect the biome in the gut and lung [5,

9–11]. While acute changes do indeed change the biome, there is a large body of literature that has established slower chronic changes. These changes in microbial composition occur throughout the body and across different systems (lung, sinus, GI track) and are affected by living situation, cohabitation, socioeconomic status, diet, and acute and chronic health. This of course makes the effectors of acute changes difficult as the baseline for an individual, cohort, or population can be difficult to define. Despite this several groups have reported on changes in the biome resulting from exposure to antibiotics, sterile and non-sterile (infectious) inflammation, surgery (both sterile inflammation and anatomic changes), and medications.

Studies of burn injury in both animal and human demonstrate a narrowing of alpha diversity and a propensity toward infectious complications as well as intestinal leak. Within hours of traumatic injury (sterile inflammation) and prior to any direct insult on microbial species from antibiotics, multiple groups have reported changes in phylogenetic composition and taxa relationship in the GI track of severely injured and shock patients [10, 12–14]. In particular trauma and burn injury both result in changes alpha and beta diversity thereby making the gut biome narrower and less diverse and hypothetically more virulent [10]. Polytrauma results in alterations in beta diversity with changes in particular communities including *Lachnospiraceae* and *Mogibacteriaceae* which were increased shortly after injury and *Barnesiellaceae* and *Bacteroidaceae* which were similarly decreased. Other species reduced after sterile trauma include *Bacteroidales*, *Fusobacteriales*, and *Verrucomicrobiales*, while enrichment was seen in *Clostridales* and *Enterococcus* [10].

Effects on the diversity of the biome do not seem to be necessarily located in the injured region. Moderate traumatic brain injury in a controlled cortical impact model in rodents results in changes in alpha and beta diversity in the gut microbiome despite no direct injury to the GI tract. These changes persisted throughout the 7-day course of the model and were directly correlated with the size of the injury. Of note this group reported that the usually beneficial bacteria species were reduced in the injured animals which also showed a compensatory increase in virulent species of *Bacteroidaceae*, *Enterobacteriaceae*, *and Pseudomonadaceae* [14]. Other groups have shown similar results in animal models of stroke and blood-brain barrier breakdown [15, 16]. Even chronic changes can result in susceptibility to poor outcome and perturbed biology after different insults. One group has described an association between both active and passive smoke exposure which results in an altered lung microbiome which makes patients more likely to develop ARDS after blunt injury [17]. While trauma and other sterile inflammation might be expected to be "big" physiologic perturbations to the biome, even straightforward surgical manipulation and preparation which has been considered safe and beneficial surgical practice can deleteriously affect the biome and potentially have problems for outcome. Independent of direct anatomic changes, the stress of surgery can directly affect the biome. Catecholamine release has been shown to directly affect the biome balance including *P. aeruginosa*, *E. coli*, and *Campylobacter jejuni*. Abundance of phyla has other effects outside the gut as well. Gut bacteria have been associated with changes in the acute stress response, and in keeping with this, a US group has studied the microbiome of patients with PTSD and showed that while there was no difference in total alpha or beta diversity between patients with and without PTSD, three phyla *Actinobacteria*, *Lentisphaerae*, and *Verrucomicrobia* were enriched in patients with higher PTSD scores [18]. All of these are consistent with elevated stress and consistent with other studies quantifying maternal stress and a pro-inflammatory milieu.

Bowel Preparation

For decades surgeons have been taught and largely adhered to the ideals of mechanically and chemically preparing the bowel before surgery. This has been largely based on the principal that sterilizing the colon before surgery through anti-

biotics and mechanical cleansing would eliminate bacteria which would contribute to infection and anastomotic breakdown especially in the setting of both direct (to tissues from manipulation) and physiologic (from overall surgical stress). Whether these bowel preps are beneficial and more specifically what is the best prep (mechanical vs. chemical vs. both) has remained a topic of considerable debate and conflicting data, and the practice of whether and how to prep the bowel before surgery has swung along a continual pendulum [4, 19, 20]. That said little attention has been paid until recently about the effects of bowel preparation on the biome and the effect of any changes on the biome on success and complication rates from bowel surgery. This of course has been because it has been impossible, difficult, or extremely expensive to survey the biome and the effect of bowel prep; however, the changing ability to evaluate the microbiome has revealed much about our hardened surgical practices. Several studies have attempted to determine whether mechanical prep, antibiotic prep, and NPO status prior to surgery affect the species composition in the gut. Some older data exists suggesting that mechanical prep does change the gut biome, specifically changing the abundance of *Lactobacillus* (reduced) and *Staphylococcus* and *E. coli* (increased). Unfortunately, most of these have been performed using culture technology. Newer sequencing-based data has allowed survey of the biome after mechanical- and antibiotic-based preparations and as would be expected has shown an imbalance of the biome from the cleansing. Recent data has once again questioned the benefit of bowel prep. Whether it is beneficial or deleterious and what effects the change on the biome has on anastomotic, functional, and overall outcome remains an open scientific question with several groups working to evaluate mechanism and effect.

Anatomic Changes

Along with surgical stress and bowel preparation, anatomic changes as a result of surgery can fundamentally alter the biome. Several surveys of microbial diversity after Roux-en-Y gastric bypass have suggested that the biome altered as a result of this operation [4, 21, 22]. How these changes in the biome result from the change in anatomy and how much of this results from changes in diet and metabolism as a result of weight loss remains an open scientific question. There is increasing data that the anatomic changes themselves affect the biome. Newer understandings in the importance of the biome in digestion and metabolism suggest that the altering effects of weight loss surgery affect the biome in uncharacterized ways. In addition, other data has shown that bowel resections also directly affect the biome.

The Biome and Cancer

Other emerging issues include the relationship of the biome to cancer. Abundant evidence suggests that there exists a bidirectional relationship between chemotherapeutic regimens and the biome. Chemotherapy and radiation for multiple hematologic and solid organ tumors both directly and indirectly affect both beta and alpha diversity [23–25]. Animal models have suggested that restoration of the biome through supplementation of probiotics can modulate these effects. The prevalence of cancer and breast cancer metastasis has been associated with changes in the biome. Whether these correlations are just that or represent functional relationships remains an open experimental question. Unfortunately there has to date been no comprehensive characterization of the multiple taxa and their various relationships with disease states. Despite this, taken together, there are multiple relationships between the microbiome and disease and considerable work being done to better characterize these relationships.

Function

The human biome especially in the gut has multiple described functions which have been and are continually being elucidated. The first

is barrier function and protection against invasion by virulent taxa. The balance from an intact biome helps prevent against more opportunistic taxa from gaining hold and resulting in disease. This occurs from balance and also from a form of barrier function in the GI track and lung. The gut biome participates in metabolism augmenting carbohydrate and fat metabolism which is thought to encourage healthy weight. Indeed, several investigators have shown that an imbalance in the gut biome is correlated with obesity. Consumption of a fat diet results in an increased ratio of *Firmicutes* to *Bacteroidetes* resulting in a changed biome associated with obesity. Perhaps because it is the most studied or perhaps because it is the most important, much understanding centers around *Bacteroides*. From Physical and Biologic of the gut biome have to do with protection both physical (from enhanced barrier function as well as balancing more virulent and taxa.

Effects of Changing the Biome on Outcome

The biome changes based on social and environmental factors as well as the stress of surgery and trauma, antibiotics and changes in postsurgical diet. In addition, the changes in anatomy from GI procedures result in an altered biome [4]. As described in the introduction to this chapter, perhaps the best described is opportunistic infections such as *C. difficile* colitis. It is well described that the changes in the biome cause a shift toward opportunistic taxa resulting in an imbalance and infection. The effects of *Clostridium difficile* colitis are well described including diarrhea, fluid and electrolyte imbalance, impaired absorption and nutrition, toxic megacolon, necrosis, perforation, and even death. For decades, the goal has been to fight the infection with a regimen that targets the *Clostridium difficile* including metronidazole and vancomycin. Others have suggested cleaning the toxin and bacterial load with colonic lavage. Overall these have met with varying results. With additional understanding of the biome, the idea of stool transplants has taken off. Indeed, restoring the biome with healthy taxa of stool from a healthy donor has excellent clinical and scientific plausibility [8, 26–28]. Even the American Association of Blood Banks sees their role as a provider of stool samples (as well as other cellular therapeutics) as their future.

Anastomotic Breakdown

There is emerging evidence that the biome can contribute to the strength and healing of anastomoses after surgery [19, 29, 30]. Several studies have correlated changes in the biome particularly an unbalance in the biome in higher rates of anastomotic disruption after foregut and colon surgery. Several animal studies have provided insight on putative mechanisms for these anastomotic breakdowns. Investigators using both radiation injury and ischemia have suggested that the radiation and ischemia are not sufficient alone, but rather resulting anastomotic breakdown results from infectious changes either exogenous or endogenous. In the ischemia model, the ischemia from surgically devascularized bowel resulted in an overgrowth of *E. faecalis* and in particular a strain of *E. faecalis* with high collagenase activity which was correlated with anastomotic breakdown. Similarly, the radiation model showed that the combination of radiation and inoculation with *Pseudomonas aeruginosa* resulted in anastomotic breakdown at higher rates than sham or radiation only rats [29]. In addition to anastomotic healing, the biome affects intestinal motility, long known to be affected by a complex balance of sympathetic and parasympathetic activation, anatomic structure, hormonal control, and infection. More recently however the ability to survey the biome has suggested that taxa imbalances are associated with other direct changes in GI mobility [31–34].

The Future

The microbiome represents a previously unrecognized complex system which has bidirectional on surgical disease and physiological function and outcome. As the ability to sequence and therefore surveil the microbiome

becomes faster and more economical, its science is rapidly evolving. Much is known about the effects of surgery and disease on the biome and the effects of the biome on surgical disease, healing, and outcome; however, this work is extremely preliminary. Many large characterization efforts as well as reductionist mechanistic studies are underway to understand specific drivers of biome effects on surgical disease, and these findings will no doubt revolutionize our concepts of surgical treatment. To date the data suggests that we should understand the biome as a complex system, and it is no longer acceptable to ignore it or treat it as an infectious threat to be treated through antibiotics and sterilization. It is easy to foresee a day where the biome is quickly sequenced and characterized and manipulated through a variety of means as a primary treatment or adjunct for broad-based surgical treatment of multiple diseases from trauma to obesity to cancer.

Bibliography

1. Alverdy JC. Microbiome medicine: this changes everything. J Am Coll Surg. 2018;226:719–29. https://doi.org/10.1016/j.jamcollsurg.2018.02.004.
2. Integrative HMPRNC. The integrative human microbiome project. Nature. 2019;569:641–8. https://doi.org/10.1038/s41586-019-1238-8.
3. Rup L. The human microbiome project. Indian J Microbiol. 2012;52:315. https://doi.org/10.1007/s12088-012-0304-9.
4. Guyton K, Alverdy JC. The gut microbiota and gastrointestinal surgery. Nat Rev Gastroenterol Hepatol. 2017;14:43–54. https://doi.org/10.1038/nrgastro.2016.139.
5. Alverdy JC, Luo JN. The influence of host stress on the mechanism of infection: lost microbiomes, emergent pathobiomes, and the role of interkingdom signaling. Front Microbiol. 2017;8:322. https://doi.org/10.3389/fmicb.2017.00322.
6. Gevers D, Pop M, Schloss PD, Huttenhower C. Bioinformatics for the human microbiome project. PLoS Comput Biol. 2012;8:e1002779. https://doi.org/10.1371/journal.pcbi.1002779.
7. Brinker P, Fontaine MC, Beukeboom LW, Falcao Salles J. Host, symbionts, and the microbiome: the missing tripartite interaction. Trends Microbiol. 2019;27:480–8. https://doi.org/10.1016/j.tim.2019.02.002.
8. Johanesen PA, et al. Disruption of the gut microbiome: Clostridium difficile infection and the threat of antibiotic resistance. Genes (Basel). 2015;6:1347–60. https://doi.org/10.3390/genes6041347.
9. Asquith M, Rosenbaum JT. The interaction between host genetics and the microbiome in the pathogenesis of spondyloarthropathies. Curr Opin Rheumatol. 2016;28:405–12. https://doi.org/10.1097/BOR.0000000000000299.
10. Howard BM, et al. Characterizing the gut microbiome in trauma: significant changes in microbial diversity occur early after severe injury. Trauma Surg Acute Care Open. 2017;2:e000108. https://doi.org/10.1136/tsaco-2017-000108.
11. Rocha BS, Nunes C, Laranjinha J. Tuning constitutive and pathological inflammation in the gut via the interaction of dietary nitrate and polyphenols with host microbiome. Int J Biochem Cell Biol. 2016;81:393–402. https://doi.org/10.1016/j.biocel.2016.10.021.
12. Nicholson SE, et al. A prospective study in severely injured patients reveals an altered gut microbiome is associated with transfusion volume. J Trauma Acute Care Surg. 2019;86:573–82. https://doi.org/10.1097/TA.0000000000002201.
13. Nicholson SE, et al. Polytrauma independent of therapeutic intervention alters the gastrointestinal microbiome. Am J Surg. 2018;216:699–705. https://doi.org/10.1016/j.amjsurg.2018.07.026.
14. Nicholson SE, et al. Moderate traumatic brain injury alters the gastrointestinal microbiome in a time-dependent manner. Shock. 2019;52:240–8. https://doi.org/10.1097/SHK.0000000000001211.
15. Singh V, et al. Microbiota dysbiosis controls the neuroinflammatory response after stroke. J Neurosci. 2016;36:7428–40. https://doi.org/10.1523/JNEUROSCI.1114-16.2016.
16. Braniste V, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6:263ra158. https://doi.org/10.1126/scitranslmed.3009759.
17. Panzer AR, et al. Lung microbiota is related to smoking status and to development of acute respiratory distress syndrome in critically ill trauma patients. Am J Respir Crit Care Med. 2018;197:621–31. https://doi.org/10.1164/rccm.201702-0441OC.
18. Hemmings SMJ, et al. The microbiome in posttraumatic stress disorder and trauma-exposed controls: an exploratory study. Psychosom Med. 2017;79:936–46. https://doi.org/10.1097/PSY.0000000000000512.
19. Pennington EC, et al. Use of mechanical bowel preparation and oral antibiotics for elective colorectal procedures in children: is current practice evidence-based? J Pediatr Surg. 2014;49:1030–5; discussion 1035. https://doi.org/10.1016/j.jpedsurg.2014.01.048.
20. Ioannidis A, Zoikas A, Wexner SD. Current evidence of combination of oral antibiotics and mechanical bowel preparation in elective colorectal surgery and their impact on anastomotic leak. Surg Innov. 2019:1553350619851672. https://doi.org/10.1177/1553350619851672.
21. Luijten J, Vugts G, Nieuwenhuijzen GAP, Luyer MDP. The importance of the microbiome in bariatric

surgery: a systematic review. Obes Surg. 2019;29:2338–49. https://doi.org/10.1007/s11695-019-03863-y.
22. Lee CJ, et al. Changes in gut microbiome after bariatric surgery versus medical weight loss in a pilot randomized trial. Obes Surg. 2019. https://doi.org/10.1007/s11695-019-03976-4.
23. Alexander JL, Kohoutova D, Powell N. Science in focus: the microbiome and cancer therapy. Clin Oncol (R Coll Radiol). 2019;31:1–4. https://doi.org/10.1016/j.clon.2018.09.004.
24. Bhatt AP, Redinbo MR, Bultman SJ. The role of the microbiome in cancer development and therapy. CA Cancer J Clin. 2017;67:326–44. https://doi.org/10.3322/caac.21398.
25. Helmink BA, Khan MAW, Hermann A, Gopalakrishnan V, Wargo JA. The microbiome, cancer, and cancer therapy. Nat Med. 2019;25:377–88. https://doi.org/10.1038/s41591-019-0377-7.
26. Khanna S, et al. A novel microbiome therapeutic increases gut microbial diversity and prevents recurrent Clostridium difficile infection. J Infect Dis. 2016;214:173–81. https://doi.org/10.1093/infdis/jiv766.
27. Lee YJ, et al. Protective factors in the intestinal microbiome against Clostridium difficile infection in recipients of allogeneic hematopoietic stem cell transplantation. J Infect Dis. 2017;215:1117–23. https://doi.org/10.1093/infdis/jix011.
28. Rubin TA, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. Anaerobe. 2013;19:22–6. https://doi.org/10.1016/j.anaerobe.2012.11.004.
29. Gaines S, Shao C, Hyman N, Alverdy JC. Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery. Br J Surg. 2018;105:e131–41. https://doi.org/10.1002/bjs.10760.
30. Gershuni VM, Friedman ES. The microbiome-host interaction as a potential driver of anastomotic leak. Curr Gastroenterol Rep. 2019;21:4. https://doi.org/10.1007/s11894-019-0668-7.
31. Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection. Br J Surg. 2017;104:e14–23. https://doi.org/10.1002/bjs.10405.
32. Ge X, et al. Potential role of fecal microbiota from patients with slow transit constipation in the regulation of gastrointestinal motility. Sci Rep. 2017;7:441. https://doi.org/10.1038/s41598-017-00612-y.
33. Tajima Y, et al. Comparison of the risk of surgical site infection and feasibility of surgery between sennoside versus polyethylene glycol as a mechanical bowel preparation of elective colon cancer surgery: a randomized controlled trial. Surg Today. 2016;46:735–40. https://doi.org/10.1007/s00595-015-1239-7.
34. Zinocker MK, Lindseth IA. The western diet-microbiome-host interaction and its role in metabolic disease. Nutrients. 2018;10. https://doi.org/10.3390/nu10030365.

18 Special Considerations at the Extremes of Age

Timothy J. Harrison, Robert D. Barraco, Ryan A. Lawless, and Michael D. Pasquale

Introduction

The Current State

According to the Federal Interagency Forum on Aging document *Older Americans 2016: Key Indicators of Well-Being*, the American population continues to get older at an exponential pace [1]. In 2014, 46 million people over the age of 65 lived in the USA, accounting for 15% of the total population. The "baby boomers" (people born between 1946 and 1964) started turning 65 in 2011, and the number of older people will increase dramatically during the 2014–2030 period. The older population in 2030 is projected to be twice as large as their counterparts in 2000, growing from 35 million to 74 million and representing approximately 21% of the total US population. The population of people over 85 could see growth from 6 million in 2014 to nearly 20 million by 2060 [1]. So, it is obvious that we are getting older, but are we truly improving [2]? In the USA, life expectancy is actually down from 78.7 years to 78.6 years, a trend not seen since 1915–1918, a 4-year period that saw the end of World War I and a flu pandemic that killed nearly 700,000 people [3]. A possible reason for this is the opioid epidemic causing a steady increase in overdoses and deaths due to suicide. While the statistics don't show an increase in life expectancy overall, our aging population is still faced with a growing number of chronic health conditions leading to a decline in functionality. In 2013, 44% of people age 65 and over enrolled in Medicare reported limitations in activities of daily living (ADL), instrumental activities of daily living (IADL), or living in a long-term care facility. ADL include bathing, getting dressed, eating, getting in and out of chairs, and using the toilet. IADLs include using the telephone, doing housework, meal preparation, shopping, and managing finances. Many of the chronic conditions reported by our older population may be attributed to a poor-quality diet. The Healthy Eating Index (HEI) was originally developed in 1995 as a tool to evaluate the extent to which Americans are following the dietary recommendations. The HEI-2015 (the latest revision) is composed of 13 components and provides a comprehensive analytic approach to characterizing complex diets which allows researchers to make comparisons between total diet and health outcomes [4]. The HEI uses a scoring system to evaluate a set of foods, with scores ranging from 0 to 100. An ideal overall HEI score of 100

T. J. Harrison · R. D. Barraco (✉) · M. D. Pasquale
Department of Surgery, Lehigh Valley Health Network, Allentown, PA, USA
e-mail: Robert_D.Barraco@lvhn.org

R. A. Lawless
Department of Surgery, Denver Health Medical Center, Denver, CO, USA

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4_18

reflects that the set of foods aligns with key dietary recommendations. The total HEI-2015 score for Americans is 59 out of 100 which indicates that the average diets of Americans do not conform to dietary recommendations [4]. This especially holds true in our elderly population. It is estimated up to 16% of the elderly population living in the community have protein-deficient malnutrition, and this number increases by four- to fivefold when this population is admitted to the hospital. These numbers translate to nearly 51.3 billion dollars per year in health-care costs [1]. To counteract our aging population, providing nutritional support and assisting in activities of daily living must be a priority in our ongoing health reform.

Metabolic Requirements

Physiologic Changes of Aging

Aging decreases the human basal metabolic rate (BMR); however, physiologic aging does not progress at the same rate in each individual. From the ages of 30 to 70, the BMR decreases by 16%. There is a concomitant body composition change toward increased fat and decreased protein content [5, 6]. Lean body mass changes dramatically on average, from 45% of total body weight (TBW) for a 30-year-old to 27% for a 70-year-old. There is a doubling of the total body fat, from 14% of TBW at 30 years of age to 30% of TBW at 70 years of age [7].

Appetite changes with age as well. Among the factors contributing to this change are changes in the senses of taste and smell. These changes are secondary to decreasing number of taste buds, peripheral olfactory atrophy, and decreasing saliva production. Sweet and salt quality change first due to loss of taste buds in those areas, leading to food tasting bitter with an unappetizing odor. Bitter and sour taste buds are lost later [5, 7, 8]. The physiologic regulation of appetite is a complex neural and hormonal network involving the autonomic nervous system, enteric nervous system, and hypothalamic-pituitary-adrenal axis in homeostatic balance. This balance is disrupted with chronic diseases, cancers, inflammatory processes, and polypharmacy resulting in an overall decrease in appetite [9].

Gastrointestinal tract changes affect geriatric nutrition. Age-related changes include esophageal dysmotility from a change in peristalsis, chronic atrophic gastritis, intestinal bacterial overgrowth, and chronic constipation. These factors in addition to laxative abuse, which occurs more commonly in the elderly population, impact the intake and absorption of nutrients [5, 6]. Dyspepsia, a frequent symptom among elderly patients, is most commonly related to peptic ulcer disease, gastroesophageal reflux, or gastric cancer [10]. Lactose intolerance develops in the elderly population as the quantity of lactase, an essential enzyme involved in dairy product digestion, decreases leading to stomach cramping and diarrhea. The result is malnutrition and vitamin/mineral deficiencies in the geriatric population [8]. When combined with age-related reductions in skin integrity and immunocompetence, malnutrition increases the incidence of complications such as wound failure/infection and nosocomial infections. These complications in the critically ill geriatric patient lead to negative outcomes, even death [5, 6].

Changes in the renal system also influence nutritional requirements. Nephrosclerosis increases with age leading to a decline in renal function. Up to 40% of available nephrons are sclerotic by age 85. Patients with diabetes, hypertension, dyslipidemia, and/or atherosclerosis exhibit even higher rates of sclerosis. As a result, the ability to regulate fluid balance and acid-base status deteriorates. This in turn predisposes the elderly to dehydration as the kidney is unable to respond to renal sodium and water losses. Decreased responsiveness to ADH, decreased renin-angiotensin system activity, and diminished thirst are likely causes [8, 10].

Vitamin Deficiencies

The risk for deficiencies in many vitamins and nutrients increases as we age. These deficiencies are caused in part by diminished appetite, the

inability to masticate certain foods (e.g., fresh fruits and vegetables), and the increased incidence of lactose intolerance. This section will discuss the most common vitamin deficiencies in the aging population.

Vitamin D deficiency is one such deficiency. The cause is multifactorial, with decreased consumption of vitamin D-fortified dairy products secondary to an increased incidence of lactose intolerance. In institutionalized patients, limited exposure to direct sunlight disrupts the conversion of vitamin D to its active form. Lastly, as the kidney ages, the ability to convert vitamin D to the active form decreases in addition to the occurrence of nephrosclerosis. Therefore, to prevent deficiency, vitamin D should be supplemented (600 IU daily) in the diet, and efforts should be directed at providing the elderly with more exposure to sunlight [7, 10].

The next most common vitamin deficiency is vitamin B12 or cobalamin. Vitamin B12 is obtained through the digestion of red meat. Deficiency is often related to food costs, dietary caloric restrictions, or difficulty with mastication due to poor dentition. Twenty percent of the geriatric population is deficient in vitamin B12 [10]. Gastric atrophy is a condition caused by decreased gastric acid secretion related to aging and/or the use of acid-reducing medications diminishing intrinsic factor production. Intrinsic factor is essential for the release of vitamin B12 from its carrier protein as well as absorption. Signs of vitamin B12 deficiency include anemia, neuropathy, and dementia [7, 10].

Vitamin K deficiency is not common in healthy adults; however, certain medications may lead to a deficiency such as anticoagulants, antibiotics, and sulfa drugs. Poor vitamin K intake may be related to fractures, osteoporosis, osteoarthritis, and atherosclerosis [11, 12]. Increasing intake of vitamin K is not recommended in those taking warfarin due to it counteracting the anticoagulant effect of the drug. This vitamin should be kept in mind when starting medications in the intensive care or general medical setting (e.g., warfarin) [7]. A few years ago, a new class of oral anticoagulants came out to rival warfarin. The novel oral anticoagulants (NOACs) include dabigatran, a direct thrombin inhibitor, and rivaroxaban and apixaban, which act on factor Xa. These medications have revolutionized oral anticoagulation because they are at least as effective as warfarin, but are more convenient to administer as they are given in fixed doses and do not require routine coagulation monitoring. The downfall of the NOACs is that the reversal agents are expensive and, as result, are not carried on all formularies.

Nutritional Monitoring

A single standard assessment of nutritional status in the elderly population has not been agreed upon. Multiple screening tools assist in the identification of "at-risk" individuals within the population. Identification of the "at-risk" individual, as well as the malnourished patient, is important due to the impact nutrition has on outcomes in the intensive care and hospital setting. Malnourished patients have increased hospital length of stay, higher complication rate, and higher mortality rate overall. A discussion about risk factors, screening tools, and biochemical markers of malnutrition follows.

Diagnosis of Malnutrition

Defining malnutrition has changed slightly over the past few years and continues to remain a challenge. In 2012, the Academy of Nutrition and Diabetics and the American Society for Parenteral and Enteral Nutrition (ASPEN) published criteria for the diagnosis of malnutrition, defining it as "undernutrition." Although for a time, widely accepted by the nutrition community, the ASPEN criteria had its share of inconsistencies. In 2018, a new worldwide consensus definition was published by the Global Leadership Initiative on Malnutrition (GLIM). The purpose of GLIM was to reach a global consensus on the identification and endorsement of criteria for the diagnosis of malnutrition in clinical settings. The GLIM definition is based on five diagnostic criteria, three which are phenotypic (clinical) and two of which

are etiologic (causes). The diagnosis of malnutrition requires at least one phenotypic criterion and one etiologic criterion, while the severity of malnutrition is based solely on phenotypic criterion. Phenotypic criteria are unintended weight loss >5% in less than or equal to 6 months, or >10% in >6 months, low body mass index <20 if <70 years or <22 if greater than or equal to 70 years, and reduced muscle mass according to objective measures and/or physical exam. Etiologic criteria are less than or equal to 50% of the caloric requirement for >1 week, or any reduction for >2 weeks, or chronic gastrointestinal disorders with adverse nutritional impact, and an inflammatory component such as chronic disease, or acute disease/injury with severe systemic inflammation, or socioeconomic/environmental starvation.

The severity of malnutrition is broken down into two stages.

- Stage I: 5–10% unintended weight loss in less than or equal to 6 months, or 10–20% weight loss in >6 months, low BMI <20 if <70 years, or <22 if greater than or equal to 70 years, mild to moderate deficit (validated per assessment methods).
- Stage II: weight loss >10% in less than or equal to 6 months, or >20% in >6 months, low BMI <18.5 if <70 years, or <20 if greater than or equal to 70 years, and reduced muscle mass, severe deficit (validated per assessment method).

The GLIM criteria are less subjective, and more clinically relevant, and they include parameters that are more consistent with traditional concepts of nonsevere and severe malnutrition [13].

Risk Factors for Malnutrition

There are many risk factors related to malnutrition in the elderly population. These factors can be broken down into age-related and age-unrelated [14]. Age-unrelated risk factors include cancer, chronic and severe organ failure, gastrointestinal diseases, alcoholism, chronic infectious and/or inflammatory diseases, as well as all factors likely to cause one or more of the following: a reduction in food intake, an increase in energy requirements, and malabsorption.

Age-related risk factors include psychological, social, and environmental factors such as depression, grieving, financial hardship, and admission to long-term care facilities. Oral, dental, and swallowing disorders also put the elderly at increased risk.

Dementia, other neurologic diseases, and acute issues that result from trauma, such as pain, fractures, and surgery increase the risk of malnutrition as well. These factors lead to decreased oral intake, loss of appetite, and decompensation of stable medical comorbidities.

Screening Tools

Today, there are several screening tools utilized throughout the country. Screening for malnutrition is comprised of several components such as evaluation for risk factors, appetite and caloric intake, comparison of weights, and calculation of body mass index (BMI). When choosing a screening tool for your facility, it is important to consider whether or not the screening tool is validated for the right population. If the screening tool requires calculations, or is lengthy with many parameters, it may be time-consuming and subject to error. As screening is only the first step to identify those that require nutritional assessment, a screening tool needs to achieve a high sensitivity, even if this is at the expense of a high specificity (or false positives). [15]. According to the most recent published ASPEN guidelines, it is suggested that a determination of nutrition risk (i.e., nutritional risk screening [NRS 2002], Nutrition Risk in Critically Ill [NUTRIC] score) be performed on all patients admitted to the ICU for whom volitional intake is expected to be insufficient [16]. A high nutrition risk will then identify those patients most likely to benefit from early enteral nutrition (EN). In 2018, a review of several nutrition screening tools was performed on different patient populations, including in-hospital,

community, residential care, and rehabilitation [17]. The biggest difficulty with validation studies is the criterion against which the tool is compared. In the absence of a true gold standard, the Subjective Global Assessment (SGA) and Mini-Nutritional Assessment-Full Form (MNA-FF) were used. The tools with the greatest evidence of validity were the Malnutrition Universal Screening Tool (MUST) and the Malnutrition Screening Tool (MST) for in-hospital, Seniors in the Community: Risk Evaluation for Eating and Nutrition Questionnaire (SCREEN-II) for those in the community, the Short Nutritional Assessment Questionnaire-Residential Care (SNAQ-RC) for those in residential care, and the Nutritional Form for the Elderly (NUFFE) for those in rehabilitation. The SGA includes medical history and a physical examination. The MNA-FF and MNA-SF (short form) had a sensitivity of 97.9% and a sensitivity closer to 100% when compared to the SGA. The MST has a sensitivity of approximately 93%, while the MUST score was used to predict mortality as well as length of stay and discharge destination in acute patients. Although a large number of screening tools are available, due to poor validation study design and results, it is not possible to make recommendations for one universal screening tool [17].

Biochemical Markers

Historically, serum proteins such as albumin and prealbumin have been used to help determine the nutritional status of patients. Other markers such as transferrin, retinol-binding protein (RBP), and indicators of inflammation such as C-reactive protein (CRP) and total lymphocyte count (TLC) have been used. These biochemical markers and their roles in the assessment of nutrition are discussed in this section.

Serum albumin concentration can help assess visceral protein stores in the nonacute care setting. Albumin is a plasma protein that maintains plasma oncotic pressure and is a carrier protein for multiple elements and medications. Testing serum levels is routinely available and the normal range is between 3.5 and 5 g/dl. The half-life of serum albumin is approximately 20–21 days. Therefore, albumin levels are not useful in the short term. Serum albumin is a reliable marker in the absence of liver disease, renal disease, prolonged bed rest, infection/sepsis, and cancer. However, many of these conditions are present in the hospitalized elderly [18, 19].

Measurement of C-reactive protein may help in interpreting albumin levels in the presence of an inflammatory process. An elevated C-reactive protein indicates an active inflammatory response, which calls into question the serum albumin level in the assessment of nutritional status. Serum albumin may distinguish between two forms of malnutrition: that due to a deficiency in food intake (albumin may be normal) and that due to inflammation and a catabolic state (a rapid fall in albumin) [14].

Retinol-binding protein is a part of the retinol-circulation complex, which utilizes vitamin A and zinc in order to function properly. It has been concluded that RBP and prealbumin are better tools for evaluating the short-term effects of nutrition based on their rapid turnover. RBP may not be as accurate in patients with renal insufficiency as the RBP complex is degraded by the kidneys [20].

Transferrin is an iron-binding plasma glycoprotein that binds iron for transport to the bone. Levels are affected by total body iron storage [19]. Normal serum levels are from 200 to 400 mg/dl [19]. Body tissue iron stores increase with aging, which leads to a decrease in transferrin levels in healthy individuals. If elderly patients are malnourished with decreased protein and low iron stores, they may express a falsely normal transferrin level. In younger patients, the 8–10 day half-life makes transferrin a good choice to assess the nutritional status, but should not be used in the geriatric population due to the changes with aging [6].

Prealbumin is a protein made in the liver and functions as a carrier, binding thyroxine, and retinol-binding protein. Normal serum levels are between 18 and 40 mg/dl [7, 19]. Its short half-life of 2 days makes it a promising marker of protein storage and short-term nutritional status.

The TLC is a marker of immunocompetence. Normal TLC is greater than 1500 cells per cubic millimeter [7]. Depression of this count may be associated with malnutrition, but can be altered by a host of other factors. These factors include hypoalbuminemia, infection, chronic comorbid conditions, and malignancy. For this reason, the TLC is not an adequate indicator of nutritional status and should not be used in the geriatric population [21].

Nitrogen Balance

Historically, nitrogen balance has been the gold standard in measuring protein intake. It is calculated as nitrogen intake minus nitrogen loss from the body. A negative nitrogen balance means there is more protein loss, than intake, which can help assess for malnutrition. Nitrogen balance can be evaluated by measuring the concentration of urea in the urine and by calculating the urinary creatinine/height index. Values of 60–80% and 40% indicate mild and severe protein malnutrition, respectively. One drawback of this technique is collecting the 24-hour urine sample which can be burdensome [20].

Nutritional Requirements

Carbohydrates

Carbohydrates comprise half of the calories consumed in the Western diet. The human body can store approximately 1200 calories in the liver and muscle in the form of glycogen. During stress and starvation, these stores are immediately available. If the stressor is not removed, these stores are depleted within 3 days. The storage process begins between 8 and 16 h postprandially. Glycogenolysis occurs as insulin levels decrease, mobilizing glucose from hepatic stores. Alanine is essential for this process in muscle and is used for gluconeogenesis since muscle cannot mobilize glucose from glycogen due to its lack of glucose-6-phosphatase [9]. Age-related changes in the ability to metabolize glucose lead to chronically elevated blood glucose levels and advanced glycosylation end products. These end products promote fibrosis, decrease connective tissue flexibility, and change the extracellular matrices of the heart, kidney, skin, and central nervous system. Many of the common comorbid conditions in the geriatric population stem from these advanced glycosylation end products: neuropathy, nephropathy, cardiomyopathy, atherosclerosis, etc. [9] Based on these facts, it is recommended that elderly individuals consume more complex carbohydrates and less simple sugars [7].

Proteins

The protein requirement in the average adult is 0.8 g of protein per kilogram body weight daily. Large amounts of protein can be stored in the human body, but only 50% can be utilized without serious consequences [9]. The body may require up to 1.5 g/kg/day in the stressed state to support wound healing, immune function, etc. Patients who are bedbound or institutionalized require more than average protein to maintain nitrogen balance. One may incorrectly draw the conclusion that since lean muscle mass decreases in the elderly population, protein requirements would follow suit. This is not the case. The amount of nitrogen retained by the body decreases with decreased caloric intake, and additional protein must be provided in order to maintain positive nitrogen balance. The average elderly person requires 1.0 g/kg/day of protein. Promotion of skeletal muscle protein metabolism requires a larger amount of essential amino acids [7, 22]. By day 4 of their hospitalization, only 25% of undernourished patients achieve protein and energy requirements [16]. Protein intake is essential and should not be overlooked or under-recognized.

Lipids

Fats comprise up to 40% of the calories that make up the average Western diet. A fair amount of these calories (10%) are in excess amounting to at least 600 unnecessary kilocalories each day. The greatest amount of energy storage in the body is in the form of fat. Free fatty acids are

released during starvation. However, the mobilization of fat does not occur as readily in the elderly population, leading to mobilization of protein stores, protein breakdown, and sarcopenia [7, 22]. Although fat is a requirement in every diet, it should not exceed 30% of total caloric intake. If fats are being administered via total parenteral nutrition, triglyceride levels should be monitored, and infusion should be reduced if levels become elevated.

Vitamins and Minerals

Certain vitamins and minerals have been shown to improve outcomes in critically ill surgical patients receiving nutritional support. They include vitamin E, vitamin C, zinc, copper, and selenium. The addition of selenium to the nutrition source being given has been shown to reduce mortality in patients with sepsis and septic shock [23, 24].

Calcium

Total body calcium content is affected by multiple factors. Osteoporosis is aggravated by age-related hormonal changes leading to decreased total body calcium, particularly in women. Total bone mass decreases with age and inadequate intake of calcium leads to hip, lower vertebral, femoral, and cervical spine fractures. Due to gender-specific hormonal changes, dieting, childbearing, breastfeeding, and longevity, women are more affected than men. Calcium requirements increase with age. Therefore, the recommended intake is 800–1200 mg per day. Supplementation is necessary if levels cannot be maintained with diet [5, 10].

Fluids

The recommended fluid intake is 30 mL of fluid per kilogram of body weight. Cellular dehydration and hypovolemia are the two main factors involved in thirst regulation. Thirst sensitivity decreases with age, increasing the risk of dehydration. Thus, dehydration is a major concern in the geriatric population. In the presence of vomiting or diarrhea, fluid requirements increase and should be based on clinical findings, such as skin turgor, urine output, laboratory values, etc. [7].

Glutamine

Glutamine is a conditionally essential amino acid used by intestinal epithelium for maintenance of function. During catabolic states of injury and critical illness, increased glutamine is necessary. Enterocytes, lymphocytes, and macrophages utilize glutamine to maintain intracellular levels of ATP. In critical illness, the gut is susceptible to loss of mucosal integrity secondary to decreased blood flow and disuse. This increases the risk of bacterial translocation which can lead to sepsis and death. The new ASPEN guidelines suggest that supplemental enteral glutamine not be added to an EN regimen routinely in critically ill patients [23]. Looking at data from 5 randomized controlled trials, involving 558 patients from burn, trauma, and mixed ICU populations, there was no significant difference in mortality, infections, or hospital length of stay [23].

Indications for Nutritional Support

A malnutrition screen should be performed on every patient that is admitted to the hospital, as there is an increased complication rate, mortality rate, and length of stay in malnourished patients. The maintenance of immunological integrity, preservation of lean body mass, and aversion of metabolic complications are the goals of early aggressive nutritional support [23, 25]. High nutrition risk can help identify patients most likely to benefit from early enteral nutrition.

Patients with loss of appetite, depression, decreased metabolism with aging, and decreased colonic motility lose the desire to eat. Patients with oral/esophageal obstructions, dysphagia, psychomotor diseases (Parkinson's disease, Huntington's disease, multiple sclerosis, dementia), polytrauma, poor dentition, and xerostomia have difficulty consuming nutrients orally. Even though patients may eat, their caloric intake may be inadequate. Infections (e.g., urinary tract), polypharmacy, and electrolyte imbalances contribute to this risk [7, 23, 26].

Patients deemed to be "at risk" by initial screening should then have their nutritional status assessed. The traditional nutritional assessment

should include evaluation of comorbid conditions, functionality of the GI tract, and risk of aspiration. Most recent guidelines suggest not using traditional nutrition indicators or surrogate markers, as they are not validated in critical care.

Anthropometric data obtained should include height (cm), weight (kg), body mass index (kg/cm^2), and skinfold measurements to determine fat and protein stores. The accuracy of these measurements has been questioned due to a great deal of variability between testers and even when repeated by the same tester. These measurements should be obtained by a trained technician or physician, with validity testing performed often. The measurements obtained are more useful in the outpatient setting assessing long-term nutritional status in serial fashion [7]. Specific laboratory values are discussed within the nutritional monitoring section of this chapter. The values are more applicable for nutritional monitoring rather than determination of nutritional status. Most of the substances are acute-phase reactants affected by a patient's metabolic state. Once a patient is identified as being malnourished, interventions should be made in the form of enteral nutrition, parenteral nutrition, or supplementation [23].

Enteral Nutrition

"If the gut works, use it." This simple dogmatic statement has been backed by many studies throughout the literature [2]. Using the patients' intestinal tract as the primary means of nutritional administration is preferred for multiple reasons. A decreased rate of infectious comorbidities including pneumonia, central venous catheter infection, and abdominal abscess in trauma has been shown with enteral nutrition versus parenteral nutrition. Decreases in length of stay and cost have also been shown. Other benefits include the preservation of intestinal mucosal integrity [23]. Feeding the enterocytes promotes the release of endogenous hormones, intestinal blood flow, and secretory IgA immunocytes. By not feeding the gut, these three factors decrease, leading to increasing gut permeability, breakdown of the mucosal defense system, and the theoretical risk of bacterial translocation, systemic infection, and multiorgan system failure [23]. Means of delivering enteral nutrition include nasogastric and nasojejunal tubes or gastrostomy and jejunostomy tubes.

When should enteral nutrition be initiated? The general answer to this is the earlier the better. However, the practical answer has to do with the patient's nutritional status, timing of presentation to the hospital, and the procedure to be performed. If the patient is determined to be protein malnourished prior to elective surgery, nutritional support should begin 10 days preoperatively [27]. In the case of emergent/unplanned admissions, extensive preoperative planning is not possible. The answer as to when to begin then becomes the point at which the patient is hemodynamically stable and fully resuscitated. Patients who are unable to maintain volitional intake should have enteral nutrition initiated within 24–48 hours of admission to the hospital [24]. If the patient is hemodynamically unstable or under-resuscitated, or being started on vasopressor agents, feedings should not be started and should be held due to the risk of ischemic bowel. In patients requiring vasopressors to maintain adequate perfusion, reinitiating enteral nutrition may be started with caution once the vasopressor requirement has at least been stable or decreasing [24]. This requires close monitoring for intolerance as evidenced by high gastric residuals, abdominal pain/distention, and regurgitation of tube feeds if administered through a postpyloric feeding tube [23].

In the past, the presence of bowel sounds was used as criteria for the initiation of enteral nutrition. The absence of bowel sounds has not been shown to be associated with intolerance to enteral nutrition. Therefore, bowel sounds should not be used as criteria for initiation. During the infusion of tube feedings, gastric residuals are often checked as an indicator of tolerance. The literature has shown the range of aspirates in the literature is quite wide, with 200 and 500 cm^3 being elevated [8, 23]. Unless the patient is showing other signs of intolerance (pain, distention, absent flatus), tube feedings should not be held, and interventions to promote gastric emptying and decrease aspiration risk should be initiated in response to residuals in this range. These include administration of a prokinetic agent, elevation of

the head of the bed, and possibly inserting a small bowel feeding tube. Gastric residuals >500 cm^3 should prompt cessation of enteric feeding with the intent of reinitiating in the near future after the aforementioned interventions are performed [17]. Complications of enteral nutrition arise from the formulation, infection, or route of delivery. Formulation complications include diarrhea, vomiting, constipation, aspiration, hyperglycemia, and electrolyte imbalance. Patients may have diarrhea secondary to an infectious etiology while on tube feedings. Therefore, if a patient develops loose stools, an investigation into the cause is prudent. During the investigation into the etiology of the diarrhea, enteral nutrition should not be automatically stopped, but rather continued until the source has been found [24]. Diarrhea may be caused by hyperosmolar substances/formulation, recent broad-spectrum antibiotic usage, and *Clostridium difficile* colitis, to name a few. Workup should include physical exam, fecal white blood cell count, stool quantification, and a basic metabolic profile [17].

Aspiration is a serious complication and the most common cause of death after percutaneous gastrostomy tube insertion [8]. Patients who develop chronic cough with enteral access may have subclinical aspiration. Changing the nasogastric tube to a nasoenteric tube may decrease the incidence of aspiration.

The mechanics of the route of delivery can also lead to complications. The feeding tube may get clogged with inspissated tube feedings. This occurs in 18–45% of tubes placed. Attempts are made at flushing the tube or dissolving the tube feeds with warm water, cola, pancreatic enzyme, or meat tenderizer [28]. With percutaneous endoscopically or surgically placed tubes, mechanical obstructions can occur. The bowel may volvulize around the tube, or the balloon may cause a lead point of obstruction at the pylorus or within the small bowel lumen by migration [28, 29]. Also, patients may inadvertently pull the tube out. Reinsertion should only be attempted if the tube has been present long enough for a tract to form between the lumen of the bowel and the exit site (approximately 2 weeks). Reinsertion should then occur in a timely fashion as the gastrocutaneous tract may be lost if enough time passes. If dislodgement occurs shortly after placement, the tract has not had enough time to form. Leakage of gastric or small bowel contents is then likely to occur, which is a surgical emergency.

Parenteral Nutrition

Parenteral nutrition dates back to the work of Dudrick and Rhoads in the late 1960s. Research showed that infusion of hypertonic solution with nitrogen and nutrients could sustain nitrogen balance and stimulate growth and development [30, 31]. In patients who are unable to tolerate oral or enteral feedings, parenteral nutrition should be considered. The ideal time for the initiation of parenteral nutrition in the specific subset of patients that require it continues to be debated. The initiation of parenteral nutrition preoperatively in a patient with protein malnutrition and continuation postoperatively is beneficial in elective general surgery. However, in patients who are well-nourished preoperatively or prior to admission to the intensive care unit for those who cannot receive enteral nutrition, parenteral nutrition should be initiated only after 7 days without enteral nutrition [23, 27]. In patients determined to be at high risk for malnutrition (NRS 2002 >5, NUTRIC >5), or patients who are severely malnourished and enteral nutrition is not feasible, parenteral nutrition should be started as soon as possible following ICU admission [24].

Restoration of nitrogen balance and creation of an anabolic state are the goals of parenteral nutrition. Energy requirements are calculated by the equations that are beyond the scope of this chapter. Permissive underfeeding or hypocaloric alimentation is beneficial in the critical care setting. It is recommended that 80% of calculated energy expenditure be used as a goal for this. Benefits include avoidance of insulin resistance, decreased infectious morbidity, less time requiring mechanical ventilation, and decreased length of stay. Much literature has been written about tight glucose control. Maintenance of a blood glucose between 140 and 150–180 mg/dL has been shown to decrease rates of sepsis, ICU length of stay, and in-hospital mortality [17].

The administration of parenteral nutrition containing hypertonic solutions must be done through a central venous catheter. The complication rate of insertion of a central venous catheter is between 5% and 19%. Pneumothorax is one of the more frequent complications with a range of 1–1.5% and is also considered a "never event." The incidence of pneumothorax increases with multiple passes of the access needle, insertion of larger catheters, and emergent placement. Venous thrombosis, toxicity, and venous perforation can result from malpositioning of the catheter. Potential vascular injuries include arterial puncture and hematoma, hemothorax, cannulation of the artery leading to stroke or neurologic deficits with infusion, pseudoaneurysms, and arteriovenous fistulas. Cardiac arrhythmias may result from insertion of the guidewire. A small number of the arrhythmias become symptomatic, while most subside with removal of the guidewire. However, complete heart block and sudden death can occur. Infection is a major complication that can lead to a catheter-associated bloodstream infection/sepsis with a mortality rate of 18%. Thrombosis increases the rate of infectious complications as well. Measures have been taken to prevent catheter-associated bloodstream infections. These include strict hand hygiene, surgical preparation with chlorhexidine, full sterile precautions during insertion, and catheter removal when it is no longer required. The central venous thrombosis rate related to indwelling central venous catheters ranges between 33% and 59%. However, only a small percentage is symptomatic. Over time, mechanical forces on the catheter can lead to fracture and embolization of the catheter, which is a rare complication. This can also occur during removal of the catheter making it imperative to inspect the catheter integrity upon removal. Other catheter removal complications include air embolism and hemorrhage [32].

A popular technique for administration of TPN is via a peripherally inserted central catheter (PICC). This form of venous access does not come with some of the significant risks for central venous catheters, such as pneumothorax, hemothorax, etc. Though low risk, complications such as bleeding, infection, arrhythmia, catheter malposition, and venous thrombosis are still possible. PICC lines can be used for prolonged periods and commonly come in single-lumen and double-lumen forms. They can be inserted in a number of environments. The risk-benefit profile makes them very attractive for the administration of TPN.

Nutrition in Palliative Care and the Terminally Ill

Nutrition can still be used in palliative care. This should only occur when the goals of nutrition in palliative care are consistent with palliative care principles. Therefore, the use of nutrition must palliate symptoms and improve the quality of life. Nutrition may be indicated for the malnourished or those who may become malnourished during the remaining course of their disease.

Psychosocial Aspects

Loss of appetite can be quite distressing to patients and loved ones. Meals are often social events. Anorexia and cachexia near the end of life can be subject to many fears and misconceptions. Care can be refocused through education and reassurance. Eating will not reverse terminal illness. The body will only take what it needs in cases of terminal illness. The illness alters the body's needs and the ability to metabolize food. This manifests by decreased intake. This is simply a part of the natural process of terminal illness and does not shorten life.

Anorexia

Reversible causes should be looked for in cases of reduced intake. These include xerostomia, nausea, constipation, electrolyte disturbances, and psychological issues such as depression. Altering the temperature or presentation of the food can compensate for altered taste sensation. Using different types of food that are lower in urea and spicing or marinating foods may also help. Commercial supplements may in reality contribute to appetite suppression. The best appetite stimulant is the patient's preferred foods themselves, when feasible. Pharmacologic

appetite stimulants do not affect prognosis but may improve quality of life [28]. The American Geriatrics Society recommends not using prescription appetite stimulants or high-calorie supplements for treatment of anorexia or cachexia in older adults; instead, optimize social supporters, discontinue medications that may interfere with eating, provide appealing meals and feeding assistance, and clarify patient goals and expectations. Megestrol acetate and dexamethasone are among the stimulants used.

Giving permission to the patient to eat less may be the most important and effective intervention providers can offer. Intake can be improved by reducing the stigma of loss of appetite and altering the way in which food is available and meals are offered. Smaller, more frequent meals, having food available at all times whenever the patient is hungry, and having patients take part in meal planning are some interventions that may help [33].

Cachexia

Wasting of protein and energy stores is an effect of disease called cachexia (Table 18.1 [34]). Hyper-caloric feedings do not help in these cases. Protein and energy deficiency that is not part of a disease process is called starvation [34]. In cachexia related to terminal illness, the process is mediated by cytokines, such as tumor necrosis factor, IL-1, and IL-6 [35–37]. This is most widely studied in cancer patients. Appetite is suppressed early, and hunger pains generally are not part of the clinical picture. Functionality or survival is not improved by refeeding. This may not be true of certain subsets of AIDS patients [38].

Table 18.1 Differences between starvation and cachexia of terminal illness [2]

	Starvation	Cachexia of terminal illness
Appetite	Suppressed late	Suppressed early
BMI	Not predictive of mortality	Predictive of mortality
Albumin	Low late	Low early
Cholesterol	May be normal	Low
Total lymphocyte count	Low, responds to refeeding	Low, no response to refeeding
Cytokines	N/A	Elevated
Response to refeeding	Reversible	Resistant

Ethical Decision-Making Regarding Artificial Nutrition

Controversy surrounds the use of artificial nutrition. Very few of the terminal illnesses most commonly encountered in the geriatric population show favorable response to artificial feeding. No improvement in outcomes is seen in patients with dementia and most patients with advanced cancer [34]. Patients with head and neck or esophageal cancer may show improvement in outcomes [39]. The National Institute for Health and Clinical Excellence in Britain recommended the following in their clinical guidelines with regard to patients with dementia [40]:

- Encourage people with dementia to eat and drink by mouth for as long as possible.
- Do not generally use tube feeding in severe dementia if dysphagia or disinclination to eat is a manifestation of disease severity.
- Consider nutritional support, including tube feeding, if dysphagia is thought to be transient.
- Apply ethical and legal principles to decisions to withhold or withdraw nutritional support.

Quality of life and the dying process may actually worsen with feeding. By-products of the malnourished state, mainly ketones, can produce a euphoric feeling and reduce hunger pains. Tube feed aspiration can lead to pneumonia. Patients with feeding tubes may require use of restraints and complications can result from their use [37].

In 2008, the Cochrane Collaborative review did not find enough good quality trials to make any recommendations with regard to the use of medically assisted nutrition in palliative care patients [41]. More recently in 2016, the ASPEN guidelines suggest that artificial nutrition and hydration is not obligatory in cases of futile care or end-of-life situations. The decision to provide artificial nutrition and hydration should be based

on evidence, best practices, clinical experience, and judgment: effective communication with the patient, patient's family, and/or an authorized surrogate decision-maker and respect for the patient's autonomy and dignity [24].

Conclusion

Our population is aging at a tremendous rate. The risk of malnutrition in our elderly population increases dramatically and costs our health-care systems billions of dollars per year. A stated earlier in this chapter, it is important to recognize the physiologic aspects of aging. Nutritional assessment should be performed on all patients admitted into the hospital. Patients determined to be at high risk of malnutrition should be started on enteral nutrition within 24–48 hours of admission. Although still frequently used throughout the ICU, nutritional assessment should focus more on comorbid conditions, functionality of the GI tract, and assessing the risk for aspiration rather than using traditional biochemical nutrition markers. Utilizing this information can help take care of this population effectively, lowering health-care costs and allowing these patients to not only have autonomy but dignity as well toward the end of their lives.

References

1. The Federal Interagency Forum on Aging-Related Statistics. Older Americans 2016: key indicators of well-being.http://www.agingstats.gov/agingstatsdotnet/main_site/default.aspx. Accessed August 2016.
2. Davis K, Rosenbaum S. Surgical metabolism: the metabolic care of the surgical patient, vol. 273. 1st ed. New York: Springer; 2014.
3. Bernstein L. U.S Life Expectancy Declines Again, a Dismal trend not seen since World War I. The Washington Post, November 29, 2018.
4. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th ed. December 2015. Available at https://health.gov/dietaryguidelines/2015/guidelines/.
5. Thompson M. Briefs: geriatric nutrition. J Natl Med Assoc. 1980;72(8):795–803.
6. Cutungo CL. The "graying" of trauma care: addressing traumatic injury in older adults. Am J Nurs. 2011;111(11):40–8.
7. Johnston RE, Chernoff R. Geriatrics. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice. 2nd ed. Philadelphia: Saunders; 2003. p. 377–83.
8. Dorner B, Pasthauer ME, Friedrich EK, Robinson GE. Enteral nutrition for older adults in nursing facilities. Nutr Clin Pract. 2011;26(3):261–72.
9. D'Olimpio JT. Physiology of nutrition and aging. In: Walsh DT, Caraceni AT, Fainsinger R, Foley KM, Glare P, Goh C, Lloyd-Williams M, Nunez Olarte J, Radbruch L, editors. Palliative medicine. 1st ed. Philadelphia: Saunders; 2009. [Chapter 104].
10. King M, Emery E. Nutrition management of the geriatric patient. Support Line. 2007;29(5):21–8.
11. Booth SL. Vitamin K status in the elderly. Curr Opin Clin Nutr Metab Care. 2007;10(1):20–3.
12. Erkkila AT, Booth SL, Hu FB, Jacques PF, Lichtenstein AH. Phylloquinone intake and risk of cardiovascular diseases in men. Nutr Metab Cardiovasc Dis. 2007;17(1):58–62.
13. Jensen GL, Cederholm T, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. JPEN. 2019;38(1):1–9. [PMID: 30175461 (http://ncbi.nlm.nih.gov/pubmed?term=30175461)].
14. Haute Autorité de Santé, Clinical Practice Guideline. Nutritional support strategy for protein-energy malnutrition in the elderly; April 2007. http://www.has-sante.fr/portail/upload/docs/application/pdf/malnutrition_elderly_guidelines.pdf.
15. Banks M. Economic analysis of malnutrition and pressure ulcers in Queensland hospitals and residential aged care facilities. Brisbane: Queensland University of Technology; 2008.
16. Leistra E, Willeboordse F, van Bokhorst MAE, Visser M, Haans-van der Oord A, Weijs PJM, Oostenbrink A, Evers AM, Kruizenga HM. Predictors for achieving protein requirements in undernourished hospital patients. Clin Nutr. 2011;30(4):484–9.
17. Power L, Mullaly D, Gibney E, Clarke M, Visser M, Volkert D, Bardon L, Schueren M, Corish C. A review of the validity of malnutrition screening tools used in older adults in community and healthcare settings - A MaNuEL study. Clin Nutr ESPEN. 2018;4:1–13.
18. Kagansky N, Berner Y, Koren-Morag N, Perelman L, Knobler H, Levy S. Poor nutritional habits are predictors of poor outcomes in very old hospitalized patients. Am J Clin Nutr. 2005;82:784–91.
19. Martindale RG, Cresci GA, Leibach FH. Nutrition and metabolism. In: O'Leary JP, Capote LR, editors. Physiologic basis of surgery. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 133–68.

20. Bharadwaj S, Ginoya S, Tandon P, Gohel T, Guirguis J, Vallabh H, Jevenn A, Hanouneh I. Malnutrition: laboratory markers vs nutritional assessment. Gastroenterol Rep (oxf.). 2016;4(4):272–80.
21. Kuzuya M, Kanda S, Koike T, Suzuki Y, Iguchi A. Lack of correlation between total lymphocyte count and nutritional status in the elderly. Clin Nutr. 2005;24(3):427–32.
22. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia: protein, amino acid metabolism and therapy. Curr Opin Clin Nutr Metab Care. 2009;12(1):86–90.
23. Mclave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Crescit GASPEN. Board of Directors, American College of Critically ill guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. J Parenter Enteral Nutr. 2009;33(3):277–316.
24. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Crescit G. ASPEN Board of Directors, American College of critical care medicine guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. J Parenter Enteral Nutr. 2017;41(1):104–43.
25. Read J, Clarke S. Clinical nutrition. In: Walsh DT, Caraceni AT, Fainsinger R, Foley KM, Glare P, Goh C, Lloyd-Williams M, Nunez Olarte J, Radbruch L, editors. Palliative medicine. 1st ed. Philadelphia: Saunders; 2009. [Chapter 107].
26. Jacobs DG, Jacobs DO, Kudsk KA, Moore FA, Oswanski MF, Poole GV, Sacks GS, Scherer LR, Sinclair KE. Practice management guidelines for nutritional support of the trauma patient. J Trauma. 2004;57:660–79.
27. Silk D, Green CJ. Perioperative nutrition: parenteral versus enteral. Curr Opin Clin Nutr Metab Care. 1998;1(1):21–7.
28. Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Ramierez-Perez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. J Clin Nurs. 2001;10:482–90.
29. Grant MJ, Martin S. Delivery of enteral nutrition. In: Vergeer JT, Schears G, Lord LM, editors. AACN Clin Issues Adv Pract Acute Crit Care, vol. 11(4); 2000. p. 507–16.
30. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Can intravenous feeding as the sole nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. Ann Surg. 1969;169(6):974–84.
31. Dudrick SJ, Wilmire DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery. 1968;64(1):134–42.
32. Kusminsky RE. Complications of central venous catheterization. J Am Coll Surg. 2007;204(4):681–96.
33. Dy M. Enteral and parenteral nutrition in terminally ill cancer patients: a review of the literature. Am J Hosp Palliat Med. 2006;23(5):369–77.
34. Thomas D. Distinguishing starvation from cachexia. Clin Geriatr Med. 2002;18:883–91.
35. Alexander H. Prevalence and pathophysiology of cancer cachexia. In: Portenoy RK, Bruera E, editors. Topics in palliative care. New York: Oxford University Press; 1998. p. 91–129.
36. Inui A. Cancer anorexia–cachexia syndrome: are neuropeptides the key? Cancer Res. 1999;59(18):4493–501.
37. Dunlop RJ, Campbell CW. Cytokines and advanced cancer. J Pain Symptom Manage. 2000;20(3):214–32.
38. Nemechek PM, Polsky B, et al. Treatment guidelines for HIV-associated wasting. Mayo Clin Proc. 2000;75(4):386–94.
39. Ganzini L. Artificial nutrition and hydration at the end of life: ethics and evidence. Palliat Support Care. 2006;4:135–43.
40. National Institute for Health and Care Excellence. Clinical Guideline 42: Dementia. http://www.nice.org.uk/guidance.nice.org.uk/CG42.
41. Good P, Cavenagh J, Mather M, Ravenscroft P. Medically assisted nutrition for palliative care in adult patients. Cochrane Database Syst Rev. 2008;4:CD006274.

Index

K. A. Davis, S. H. Rosenbaum (eds.), *Surgical Metabolism*,
https://doi.org/10.1007/978-3-030-39781-4