KEY POINTS

1. Systemic inflammation is characterized by exaggerated immune responses to either a sterile or infectious process. The cause of inflammatory activation needs to be addressed to resolve the dysregulated immune state.

2. An understanding of the signaling mechanisms and pathways underlying systemic inflammation can help guide therapeutic interventions in injured and/or septic patients.

3. Management of such patients is optimized with the use of evidence-based and algorithm-driven therapy.

4. Nutritional assessments, whether clinical or laboratory guided, and intervention should be considered at an early juncture in all surgical and critically ill patients.

5. Excessive feeding should be avoided in an effort to limit complications, including ventilator dependency, aspiration events, and infections.

SYSTEMIC RESPONSE TO INJURY AND METABOLIC SUPPORT: INTRODUCTION

The immune system has developed to respond to and neutralize pathogenic micro-organisms as well as coordinate tissue repair. The inflammatory response to injury or infection involves cell signaling, cell migration, and mediator release. Minor host insults instigate a local inflammatory response that is transient and in most cases beneficial. Major host insults may propagate reactions that can become amplified, resulting in systemic inflammation and potentially detrimental responses. This topic is highly relevant because systemic inflammation is a central feature of both sepsis and severe trauma. Understanding the complex pathways that regulate local and systemic inflammation is necessary to develop therapies to intervene during overwhelming sepsis or after severe injury. Sepsis, defined by a systemic inflammatory response to infection, is a disease process with an increasing incidence of over 900,000 cases per year. Trauma is the leading cause of mortality and morbidity for individuals under 50 years of age.

This chapter reviews the autonomic, cellular, and hormonal responses to injury. These facets of the inflammatory response to injury and infection are discussed in reference to the specific response being considered.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The systemic inflammatory response syndrome (SIRS) is characterized by a sequence of host phenotypic and metabolic responses to systemic inflammation that includes changes in heart rate, respiratory rate, blood pressure, temperature regulation, and immune cell activation (Table 2-1). The systemic inflammatory response includes two general phases: (1) an acute proinflammatory state resulting from innate immune system recognition of ligands, and (2) an anti-inflammatory phase that may serve to modulate the proinflammatory phase. Under normal circumstances, these coordinated responses direct a return to homeostasis (Fig. 2-1).

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Identifiable source of microbial insult</td>
</tr>
<tr>
<td>SIRS</td>
<td>Two or more of following criteria are met:</td>
</tr>
<tr>
<td></td>
<td>Temperature ≥38°C (100.4°F) or ≤36°C (96.8°F)</td>
</tr>
<tr>
<td></td>
<td>Heart rate ≥90 beats per minute</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate ≥20 breaths per minute or PaCO₂ ≤32 mmHg or mechanical ventilation</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Identifiable source of infection + SIRS</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis + organ dysfunction</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis + cardiovascular collapse (requiring vasopressor support)</td>
</tr>
</tbody>
</table>

PaCO₂ = partial pressure of arterial carbon dioxide.

Fig. 2-1.
Schematic representation of the systemic inflammatory response syndrome (SIRS) after injury, followed by a period of convalescence mediated by the counterregulatory anti-inflammatory response syndrome (CARS). Severe inflammation may lead to acute multiple organ failure (MOF) and early death after injury (dark blue arrow). A lesser inflammatory response followed by excessive CARS may induce a prolonged immunosuppressed state that can also be deleterious to the host (light blue arrow). Normal recovery after injury requires a period of systemic inflammation followed by a return to homeostasis (red arrow).

(Adapted with permission from Guirao X, Lowry SF: Biologic control of injury and inflammation: Much more than too little or too late. World J Surg 20:437, 1996. With kind permission from Springer Science + Business Media.)

CENTRAL NERVOUS SYSTEM REGULATION OF INFLAMMATION

Afferent Signals to the Brain

The central nervous system (CNS) plays a key role in orchestrating the inflammatory response. The CNS influences multiple organs through both neurohormonal and endocrine signals. Injury or infection signals are recognized by the CNS through afferent signal pathways (Fig. 2-2). The CNS may respond to peripheral inflammatory stimuli through both circulatory and neuronal pathways. Inflammatory mediators activate CNS receptors and establish phenotypic responses such as fever and anorexia. The vagus nerve has been described as highly influential in mediating afferent sensory input to the CNS. 3

Fig. 2-2.
Cholinergic Anti-Inflammatory Pathways

The vagus nerve exerts several homeostatic influences, including enhancing gut motility, reducing heart rate, and regulating inflammation. Central to this pathway is the understanding of neurally controlled anti-inflammatory pathways of the vagus nerve. Parasympathetic nervous system activity transmits vagus nerve efferent signals primarily through the neurotransmitter acetylcholine. This neurally mediated anti-inflammatory pathway allows for a rapid response to inflammatory stimuli and also for the potential regulation of early pro-inflammatory mediator release, specifically tumor necrosis factor (TNF). Vagus nerve activity in the presence of systemic inflammation may inhibit cytokine activity and reduce injury from disease processes such as pancreatitis, ischemia and reperfusion, and hemorrhagic shock. This activity is primarily mediated through nicotinic acetylcholine receptors on immune mediator cells such as tissue macrophages. Furthermore, enhanced inflammatory profiles are observed after vagotomy, during stress conditions. Experimental trials have studied this pathway to develop therapeutic interventions. Specifically, nicotine, which also activates nicotinic acetylcholine receptors on immune cells, has been shown to reduce cytokine release after endotoxemia in animal models.

Hormonal Response to Injury

Hormone Signaling Pathways

Hormones are chemical signals that are released to modulate the function of target cells. Humans release hormones in several chemical categories, including polypeptides (e.g., cytokines, glucagon, and insulin), amino acids (e.g., epinephrine, serotonin, and histamine), and fatty acids (e.g., glucocorticoids, prostaglandins, and leukotrienes). Hormone receptors are present on or within the target cells and allow signal transduction to progress intracellularly mostly through three major pathways: (1) receptor kinases such as insulin and insulin-like growth factor (IGF) receptors, (2) guanine nucleotide-binding or G-protein receptors such as neurotransmitter and prostaglandin receptors, and (3) ligand-gated ion channels that permit ion transport when activated. On activation, the signal is then amplified through the action of secondary signaling molecules. Intracellular signaling leads to downstream effects such as protein synthesis and further mediator release. Protein synthesis is mediated through intracellular receptor binding either by hormone ligands or through subsequently released secondary signaling molecules. These, together with the targeted DNA sequences, activate transcription. The prototype of the intracellular hormone receptor is the glucocorticoid receptor (Fig. 2-3). This receptor is regulated by the stress-induced protein known as heat shock protein (HSP), which maintains the glucocorticoid receptor in the cytosol; however, on ligand binding, HSP is released, and the receptor-ligand complex is transported to the nucleus for DNA transcription.

Fig. 2-3.

Simplified schematic of steroid transport into the nucleus. Steroid molecules (S) diffuse readily across cytoplasmic membranes. Intracellularly the receptors (R) are rendered inactive by being coupled to heat shock protein (HSP). When S and R bind, HSP dissociates, and the S-R complex enters the nucleus, where the S-R complex induces DNA transcription, resulting in protein synthesis. mRNA = messenger RNA.

Virtually every hormone of the hypothalamic-pituitary-adrenal axis influences the physiologic response to injury and stress (Table 2-2), but some with direct influence on the inflammatory response or immediate clinical impact are highlighted here.

Table 2-2 Hormones Regulated by the Hypothalamus, Pituitary, and Autonomic System

<table>
<thead>
<tr>
<th>Hypothalamic Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone</td>
</tr>
<tr>
<td>Growth hormone–releasing hormone</td>
</tr>
<tr>
<td>Luteinizing hormone–releasing hormone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anterior Pituitary Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropic hormone</td>
</tr>
</tbody>
</table>

accessmedicine.com/popup.aspx?alD...
Adrenocorticotropic Hormone

Adrenocorticotropic hormone (ACTH) is a polypeptide hormone released by the anterior pituitary gland. ACTH binds with receptors in the zona fasciculata of the adrenal gland, which mediate intracellular signaling and subsequent cortisol release. ACTH release follows circadian rhythms in healthy humans; however, during times of stress this diurnal pattern becomes blunted because ACTH release is elevated in proportion to the severity of injury. Several important stimuli for ACTH release are present in the injured patient, including corticotropin-releasing hormone, pain, anxiety, vasopressin, angiotensin II, cholecystokinin, vasoactive intestinal polypeptide, catecholamines, and proinflammatory cytokines. Within the zona fasciculata of the adrenal gland, ACTH signaling activates intracellular pathways that lead to glucocorticoid production (Fig. 2-4). Conditions of excess ACTH stimulation result in adrenocortical hypertrophy. 7

Fig. 2-4.

Cortisol and Glucocorticoids

Cortisol is a glucocorticoid steroid hormone released by the adrenal cortex in response to ACTH. Cortisol release is increased during times of stress and may be chronically elevated in certain disease processes. For example, burn-injured patients may exhibit elevated levels for 4 weeks.

Steroid synthesis from cholesterol. Adrenocorticotropic hormone (ACTH) is a principal regulator of steroid synthesis. The end products are mineralocorticoids, glucocorticoids, and sex steroids.
Metabolically, cortisol potentiates the actions of glucagon and epinephrine that manifest as hyperglycemia. Cortisol acts on liver enzymes by decreasing glycogenesis, while increasing gluconeogenesis. In skeletal muscle, cortisol facilitates the breakdown of protein and amino acids, and mediates the release of lactate. Subsequently, these substrates are used by the liver for gluconeogenesis. In adipose tissue cortisol stimulates the release of free fatty acids, triglycerides, and glycerol to increase circulating energy stores. Wound healing also is impaired, because cortisol reduces transforming growth factor beta (TGF-β) and insulin-like growth factor I (IGF-I) in the wound. This effect can be partially ameliorated by the administration of vitamin A.

Adrenal insufficiency represents a clinical syndrome highlighted largely by inadequate amounts of circulating cortisol and aldosterone. Classically, adrenal insufficiency is described in patients with atrophic adrenal glands caused by exogenous steroid administration who undergo a stress such as surgery. These patients subsequently manifest signs and symptoms such as tachycardia, hypotension, weakness, nausea, vomiting, and fever. Critical illness may be associated with a relative adrenal insufficiency such that the adrenal gland cannot mount an effective cortisol response to match the degree of injury. Laboratory findings in adrenal insufficiency include hypoglycemia from decreased gluconeogenesis, hyponatremia from impaired renal tubular sodium resorption, and hyperkalemia from diminished kaliuresis. Diagnostic tests include baseline cortisol levels and ACTH-stimulated cortisol levels, both of which are lower than normal during adrenal insufficiency. Treatment strategies are controversial; however, they include low-dose steroid supplementation.

Glucocorticoids have immunosuppressive properties that have been used when needed, as in organ transplantation. Immunologic changes associated with glucocorticoid administration include thymic involution, depressed cell-mediated immune responses reflected by decreases in T-killer and natural killer cell function, T-lymphocyte blastogenesis, mixed lymphocyte responsiveness, graft-versus-host reactions, and delayed hypersensitivity responses. In addition glucocorticoids inhibit leukocyte migration to sites of inflammation by inhibiting the expression of adhesion molecules. In monocytes, glucocorticoids inhibit intracellular killing while maintaining chemotactic and phagocytic properties. Glucocorticoids inhibit neutrophil superoxide reactivity, suppress chemotaxis, and normalize apoptosis signaling mechanisms but maintain neutrophil phagocytic function. In clinical settings manifested by hypoperfusion, such as septic shock, trauma, and coronary artery bypass grafting, glucocorticoid administration is associated with attenuation of the inflammatory response.

**Macrophage Migration–Inhibiting Factor**

Macrophage migration–inhibiting factor (MIF) is a neurohormone that is stored and secreted by the anterior pituitary and by intracellular pools within macrophages. MIF is a counterregulatory mediator that potentially reverses the anti-inflammatory effects of cortisol. During times of stress, hypercortisolemia, and host immunosuppression, MIF may modulate the inflammatory response by inhibiting the immunosuppressive effect of cortisol on immunocytes and thereby increasing their activity against foreign pathogens.

**Growth Hormones and Insulin-Like Growth Factors**

Growth hormone (GH) is a neurohormone expressed primarily by the pituitary gland that has both metabolic and immunomodulatory effects. GH promotes protein synthesis and insulin resistance, and enhances the mobilization of fat stores. GH secretion is upregulated by hypothalamic GH–releasing hormone and downregulated by somatostatin. GH primarily exerts its downstream effects through direct interaction with GH receptors and secondarily through the enhanced hepatic synthesis of IGF-I. IGF circulates primarily bound to various IGF-binding proteins and also has anabolic effects, including increased protein synthesis and lipogenesis. In the liver, IGF stimulates protein synthesis and glycogenesis; in adipose tissue, it increases glucose uptake and lipid utilization; and in skeletal muscle, it mediates glucose uptake and protein synthesis. Critical illness is associated with an acquired GH resistance and contributes to decreased levels of IGF. This effect in part mediates the overall catabolic phenotype manifested during critical illness. In addition, GH enhances phagocytic activity of immunocytes through increased lysosomal superoxide production. GH also increases the proliferation of T-cell populations. Exogenous GH administration has been studied in critically ill patients and may be associated with worse outcomes, including increased mortality, prolonged ventilator dependence, and increased susceptibility to infection. The mechanisms through which GH is associated with these outcomes are unclear, although GH-induced insulin resistance and hyperglycemia may contribute.

**Catecholamines**

Catecholamines are hormones secreted by the chromaffin cells of the adrenal medulla and function as neurotransmitters in the CNS. The most common catecholamines are epinephrine, norepinephrine, and dopamine, which have metabolic, immunomodulatory, and vasoactive effects. After severe injury, plasma catecholamine levels are increased threefold to fourfold, with elevations lasting 24 to 48 hours before returning toward baseline levels.

Catecholamines act on both alpha and beta receptors, which are widely distributed on several cell types, including vascular endothelial cells, immunocytes, myocytes, adipose tissue, and hepatocytes. Epinephrine has been shown to induce a catabolic state and hyperglycemia through hepatic gluconeogenesis and glycogenolysis as well as by peripheral lipolysis and proteinolysis. In addition epinephrine promotes insulin resistance in skeletal muscle. Catecholamines also increase the secretion of thyroid hormone, parathyroid hormones, and renin, but inhibit the release of aldosterone.

Epinephrine also has immunomodulatory properties mediated primarily through the activation of beta2 receptors on immunocytes. Epinephrine has been shown to inhibit the release of inflammatory cytokines, including TNF, interleukin-1, and interleukin-6, while also enhancing the release of the anti-inflammatory mediator interleukin-10. Similar to cortisol, epinephrine increases leukocyte demargination with resultant neutrophilia and lymphocytosis. The immunomodulatory sequelae of catecholamines in patients during septic shock have yet to be clearly elucidated.

Catecholamines exert several hemodynamic effects, including increased cardiac oxygen demand, vasoconstriction, and increased cardiac output. Catecholamines are used to treat systemic hypotension during septic shock. Because of the increased cardiac stress induced by catecholamines, however, cardioprotective strategies, including beta blockade for patients undergoing surgery, have shown significant benefit in reducing cardiac-related deaths.

**Aldosterone**

Aldosterone is a mineralocorticoid released by the zona glomerulosa of the adrenal cortex. Aldosterone increases intravascular volume by acting on the renal mineralocorticoid receptor of the distal convoluted tubules to retain sodium and eliminate potassium and hydrogen ions. Aldosterone secretion is stimulated by ACTH, angiotensin II, decreased intravascular volume, and hyperkalemia. Aldosterone deficiency is manifested by hypotension and hyperkalemia, whereas aldosterone excess is manifested by edema, hypertension, hypokalemia, and...
metabolic alkalosis.

**Insulin**

Hyperglycemia and insulin resistance are hallmarks of critical illness due to the catabolic effects of circulating mediators, including catecholamines, cortisol, glucagon, and growth hormone. Insulin is secreted by the islets of Langerhans in the pancreas. Insulin mediates an overall host anabolic state through hepatic glycogenesis and glycolysis, peripheral glucose uptake, lipogenesis, and protein synthesis.\(^3\)

Hyperglycemia during critical illness has immunosuppressive effects, including glycosylation of immunoglobulins and decreased phagocytosis and respiratory burst of monocytes, and thus is associated with an increased risk for infection. Insulin therapy to manage hyperglycemia has grown in favor and has been shown to be associated with both decreased mortality and a reduction in infectious complications in select patient populations; however, caution should be exercised to avoid the deleterious sequelae of hypoglycemia from overaggressive glycemic control.\(^4\) The ideal blood glucose range within which to maintain critically ill patients and avoid hypoglycemia has yet to be determined.

**ACUTE PHASE PROTEINS**

Acute phase proteins are a class of proteins produced by the liver that manifest either increased or decreased plasma concentration in response to inflammatory stimuli such as traumatic injury and infection. Specifically, C-reactive protein has been studied as a marker of proinflammatory response in many clinical settings, including appendicitis, vasculitis, and ulcerative colitis. Importantly, C-reactive protein levels do not show diurnal variations and are not modulated by feeding. Acute phase protein levels may be unreliable as an index of inflammation in the setting of hepatic insufficiency.

**MEDIATORS OF INFLAMMATION**

**Cytokines**

Cytokines are a class of protein signaling compounds that are essential for both innate and adaptive immune responses. Cytokines mediate a broad sequence of cellular responses, including cell migration, DNA replication, cell turnover, and immunocyte proliferation (Table 2-3).

When functioning locally at the site of injury and infection, cytokines mediate the eradication of invading micro-organisms and also promote wound healing. However, an exaggerated proinflammatory cytokine response to inflammatory stimuli may result in hemodynamic instability (i.e., septic shock) and metabolic derangements (i.e., muscle wasting).

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>Macrophages/monocytes</td>
<td>Among earliest responders after injury; half-life &lt;20 min; activates TNF receptors 1 and 2; induces significant shock and catabolism</td>
</tr>
<tr>
<td></td>
<td>Kupffer cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NK cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Astrocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endothelial cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T lymphocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenal cortical cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adipocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Keratinocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteoblasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mast cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dendritic cells</td>
<td></td>
</tr>
<tr>
<td>IL-1</td>
<td>Macrophages/monocytes</td>
<td>Two forms (IL-1(\alpha) and IL-1(\beta)); similar physiologic effects as TNF; induces fevers through prostaglandin activity in anterior hypothalamus; promotes (\beta)-endorphin release from pituitary; half-life &lt;6 min</td>
</tr>
<tr>
<td></td>
<td>B and T lymphocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NK cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endothelial cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epithelial cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Keratinocytes</td>
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</tr>
<tr>
<td></td>
<td>Fibroblasts</td>
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</tr>
<tr>
<td></td>
<td>Osteoblasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dendritic cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Astrocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenal cortical cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Megakaryocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuronal cells</td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>T lymphocytes</td>
<td>Promotes lymphocyte proliferation, immunoglobulin production, gut barrier integrity; half-life &lt;10 min; attenuated production after major blood loss leads to immunocompromise; regulates lymphocyte apoptosis</td>
</tr>
<tr>
<td>IL-3</td>
<td>T lymphocytes</td>
<td></td>
</tr>
<tr>
<td>IL-4</td>
<td>T lymphocytes</td>
<td>Macrophages, Mast cells, Basophils, Macrophages, B lymphocytes, Eosinophils, Stromal cells</td>
</tr>
<tr>
<td>------</td>
<td>---------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>IL-5</td>
<td>T lymphocytes</td>
<td>Eosinophils, Mast cells, Basophils</td>
</tr>
<tr>
<td>IL-6</td>
<td>Macrophages</td>
<td>Eosinophils, Mast cells, Basophils, B lymphocytes, Neutrophils, Basophils, Mast cells, Fibroblasts, Endothelial cells, Astrocytes, Synovial cells, Adipocytes, Osteoblasts, Megakaryocytes, Chromaffin cells, Keratinocytes</td>
</tr>
<tr>
<td>IL-8</td>
<td>Macrophages/monocytes</td>
<td>T lymphocytes, Basophils, Mast cells, Epithelial cells, Platelets</td>
</tr>
<tr>
<td>IL-10</td>
<td>T lymphocytes</td>
<td>B lymphocytes, Macrophages, Basophils, Mast cells, Keratinocytes</td>
</tr>
<tr>
<td>IL-12</td>
<td>Macrophages/monocytes</td>
<td>Neutrophils, Keratinocytes, Dendritic cells, B lymphocytes</td>
</tr>
<tr>
<td>IL-13</td>
<td>T lymphocytes</td>
<td></td>
</tr>
<tr>
<td>IL-15</td>
<td>Macrophages/monocytes</td>
<td>Epithelial cells</td>
</tr>
<tr>
<td>IL-18</td>
<td>Macrophages</td>
<td>Kupffer cells, Keratinocytes, Adrenal cortical cells, Osteoblasts, Keratinocytes, Adipocytes, Osteoblasts, Osteoclasts, Megakaryocytes, Keratinocytes</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>T lymphocytes</td>
<td>NK cells, Macrophages</td>
</tr>
</tbody>
</table>
GM-CSF  
T lymphocytes  
Promotes wound healing and inflammation through activation of leukocytes

Fibroblasts
Endothelial cells
Stromal cells

IL-21  
T lymphocytes  
Preferentially secreted by Th2 cells; structurally similar to IL-2 and IL-15; activates NK cells, B and T lymphocytes; influences adaptive immunity

HMGB1  
Monocytes/lymphocytes  
High mobility group box chromosomal protein; DNA transcription factor; late (downstream) mediator of inflammation (ARDS, gut barrier disruption); induces "sickness behavior"

ARDS = acute respiratory distress syndrome; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; Ig = immunoglobulin; IL = interleukin; NK = natural killer; Th1 = helper T cell subtype 1; Th2 = helper T cell subtype 2; TNF = tumor necrosis factor.

Anti-inflammatory cytokines also are released, at least in part as an opposing influence to the proinflammatory cascade. These anti-inflammatory mediators also may result in immunocyte dysfunction and host immunosuppression. Cytokine signaling after an inflammatory stimulus is manifested by a fluctuating and counterregulated balance of opposing influences and should not be oversimplified into dichotomic proinflammatory and anti-inflammatory responses. 

Heat Shock Proteins
Heat shock proteins (HSPs) are a group of intracellular proteins that are increasingly expressed during times of stress, such as burn injury, inflammation, and infection. HSPs participate in many physiologic processes, including protein folding and protein targeting. The formation of HSPs requires gene induction by the heat shock transcription factor. HSPs bind both autologous and foreign proteins and thereby function as intracellular chaperones for ligands such as bacterial DNA and endotoxin. HSPs are presumed to protect cells from the deleterious effects of traumatic stress and, when released by damaged cells, alert the immune system of the tissue damage.

Reactive Oxygen Species
Reactive oxygen species (ROS) are small molecules that are highly reactive due to the presence of unpaired outer orbit electrons. They can cause cellular injury to both host cells and invading pathogens through the oxidation of unsaturated fatty acids within cell membranes.

Oxygen radicals are produced as a by-product of oxygen metabolism as well as by anaerobic processes. Potent oxygen radicals include oxygen, superoxide, hydrogen peroxide, and hydroxyl radicals. The main areas of ROS production include mitochondrial electron transport, peroxisomal fatty acid metabolism, cytochrome P-450 reactions, and the respiratory burst of phagocytic cells. Host cells are protected from the damaging effects of ROS through the activity of endogenous antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. Under normal physiologic conditions ROS are balanced by antioxidative enzymes. During times of stress or ischemia, however, enzymatic clearance mechanisms are consumed, and on restoration of perfusion, the unbalanced production of ROS leads to reperfusion injury.

Eicosanoids
Eicosanoids are derived primarily by oxidation of the membrane phospholipid arachidonic acid (eicosatetraenoic acid) and are composed of subgroups, including prostaglandins, prostacyclins, hydroxyeicosatetraenoic acids (HETEs), thromboxanes, and leukotrienes. The synthesis of arachidonic acid from phospholipids requires the enzymatic activation of phospholipase A2 (Fig. 2-5). Products of the COX pathway include all of the prostaglandins and thromboxanes. The lipoxigenase pathway generates leukotrienes and HETE. Eicosanoids are not stored within cells but are instead generated rapidly in response to many stimuli, including hypoxic injury, direct tissue injury, endotoxin (lipopolysaccharide, or LPS), norepinephrine, vasopressin, angiotensin II, bradykinin, serotonin, acetylcholine, cytokines, and histamine.

Eicosanoid pathway activation also leads to the formation of the anti-inflammatory compound lipoxin, which inhibits chemotaxis and nuclear factor-κB (NF-κB) activation. Glucocorticoids, NSAIDs, and leukotriene inhibitors block the end products of eicosanoid pathways.

Fig. 2-5.
Schematic diagram of arachidonic acid metabolism. LT = leukotriene; PG = prostaglandin; TXA2 = thromboxane A2.

Eicosanoids have a broad range of physiologic roles, including neurotransmission, vasomotor regulation, and immune cell regulation (Table 2-4). Eicosanoids mostly generate a proinflammatory response with deleterious host effects and are associated with acute lung injury, pancreatitis, and renal failure. Leukotrienes are potent mediators of capillary leakage as well as leukocyte adherence, neutrophil activation, bronchoconstriction, and vasoconstriction. Experimental models of sepsis have shown a benefit to inhibiting eicosanoid production. However, human sepsis trials have failed to show a mortality benefit using NSAIDs. 17

### Table 2-4 Systemic Stimulatory and Inhibitory Actions of Eicosanoids

<table>
<thead>
<tr>
<th>Organ/Function</th>
<th>Stimulator</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Glucose-stimulated insulin secretion</td>
<td>12-HPETE, PGE2</td>
</tr>
<tr>
<td></td>
<td>Glucagon secretion</td>
<td>PGD2, PGE2</td>
</tr>
<tr>
<td>Liver</td>
<td>Glucagon-stimulated glucose production</td>
<td>PGE2</td>
</tr>
<tr>
<td>Fat</td>
<td>Hormone-stimulated lipolysis</td>
<td>PGE2</td>
</tr>
</tbody>
</table>
| Bone                    | Resorption                  | PGE2, PGE-m, 6-K-PGE1, PGF1\(
|                         |                             | PGI2          |
| Pituitary               | Prolactin                   | PGE1         |
|                         | Luteinizing hormone         | PGE1, PGE2, 5-HETE |
|                         | Thyroid-stimulating hormone | PGA1, PGB1, PGE1, PGE1 |
| Growth hormone          |                             | PGE1         |
| Parathyroid             | Parathyroid hormone         | PGE2         |
|                         |                             | PGF2         |
| Lung                    | Bronchoconstriction         | PGF2, TXA2, LTC4, LTD4, LTE4 |
| Kidney                  | Stimulation of renin secretion | PGE2, PGI2 |
| Gastrointestinal system |                             |               |
| Cytoprotective effect   |                             | PGE2         |
| Immune response         |                             |               |
5-HETE = 5-hydroxyeicosatetraenoic acid; 12-HPETE = 12-hydroperoxyeicosatetraenoic acid; 6-K-PGE1 = 6-keto-prostaglandin E1; LT = leukotriene; PG = prostaglandin; PGE-m = 13,14-dihydro-15-keto-PGE2 (major urine metabolite of PGE2); TXA2 = thromboxane A2.

Eicosanoids also have several recognized metabolic effects. Cyclooxygenase pathway products inhibit pancreatic β-cell release of insulin, whereas lipooxygenase pathway products stimulate β-cell activity. Prostaglandins such as prostaglandin E2 can inhibit gluconeogenesis through the binding of hepatic receptors and also can inhibit hormone-stimulated lipolysis. 18

**Fatty Acid Metabolites**

Fatty acid metabolites function as inflammatory mediators and as such have significant roles in the inflammatory response. As previously discussed, eicosanoids participate in inflammatory signaling; however, dietary omega-3 and omega-6 fatty acids also influence inflammation. Eicosanoids are produced primarily through two major pathways: (1) with arachidonic acid (omega-6 fatty acid) as substrate and (2) eicosapentaenoic acid (omega-3 fatty acid) as substrate. Many lipid preparations are soy based and are primarily composed of omega-6 fatty acids. Nutritional supplementation with either omega-6 or omega-3 fatty acids can significantly modulate the inflammatory response, because omega-6 substrate is associated with increased downstream mediator production. Omega-3 fatty acids have specific anti-inflammatory effects, including inhibition of NF-κB activity, TNF release from hepatic Kupffer cells, as well as leukocyte adhesion and migration. The anti-inflammatory effects of omega-3 fatty acids on chronic autoimmune diseases such as rheumatoid arthritis, psoriasis, and lupus have been documented in both animals and humans. In experimental models of sepsis, omega-3 fatty acids inhibit inflammation, ameliorate weight loss, increase small-bowel perfusion, and may increase gut barrier protection. In human studies, omega-3 supplementation is associated with decreased production of TNF, interleukin-1β, and interleukin-6 by endotoxin-stimulated monocytes. In a study of surgical patients, preoperative supplementation with omega-3 fatty acid was associated with reduced need for mechanical ventilation, decreased hospital length of stay, and decreased mortality with a good safety profile. 19

**Kallikrein-Kinin System**

The kallikrein-kinin system is a group of proteins that contribute to inflammation, blood pressure control, coagulation, and pain responses. Prekallikrein is activated by stimuli such as Hageman factor, trypsin, plasmin, factor XI, glass surfaces, kaolin, and collagen to produce the serine protease kallikrein, which subsequently plays a role in the coagulation cascade. High molecular weight kinogen is produced by the liver and is metabolized by kallikrein to form bradykinin.

Kinins mediate several physiologic processes, including vasodilation, increased capillary permeability, tissue edema, pain pathway activation, inhibition of gluconeogenesis, and increased bronchoconstriction. They also increase renal vasodilation and consequently reduce renal perfusion pressure. Decreased renal perfusion leads to activation of the renin-angiotensin-aldosterone system, which acts on the nephron to actively resorb sodium and subsequently increase intravascular volume.

Bradykinin and kallikrein levels are increased during gram-negative bacteremia, hypotension, hemorrhage, endotoxemia, and tissue injury. The degree of elevation in the levels of these mediators has been associated with the magnitude of injury and mortality. Clinical trials using bradykinin antagonists have shown some benefit in patients with gram-negative sepsis. 20

**Serotonin**

Serotonin is a monoamine neurotransmitter (5-hydroxytryptamine) derived from tryptophan. Serotonin is synthesized by neurons in the CNS as well as by enterochromaffin cells of the GI tract and platelets. This neurotransmitter stimulates vasoconstriction, bronchoconstriction, and platelet aggregation. Serotonin also increases cardiac inotropy and chronotropy through nonadrenergic cyclic adenosine monophosphate (cAMP) pathways. Serotonin receptors are located in the CNS, GI tract, and monocytes. 21 Ex vivo study has shown that serotonin receptor blockade is associated with decreased production of TNF and interleukin-1β in endotoxin-treated monocytes. Serotonin is released at sites of injury, primarily by platelets; however, its role in inflammatory modulation has yet to be clearly defined.

**Histamine**

Histamine is synthesized by the decarboxylation of the amino acid histidine. Histamine is either rapidly released or stored in neurons, skin, gastric mucosa, mast cells, basophils, and platelets. There are four histamine receptor (H) subtypes with varying physiologic roles. H1 binding mediates vasodilation, bronchoconstriction, intestinal motility, and myocardial contractility. H2 binding stimulates gastric parietal cell acid secretion. H3 is an autoreceptor found on presynaptic histamine-containing nerve endings and leads to downregulation of histamine release. H4 is expressed primarily in bone marrow, eosinophils, and mast cells. H4 binding interactions have not been fully delineated but have been associated with eosinophil and mast cell chemotaxis. Increased histamine release has been documented in hemorrhagic shock, trauma, thermal injury, endotoxemia, and sepsis. 22

**CYTOKINE RESPONSE TO INJURY**

**Tumor Necrosis Factor**

Tumor necrosis factor alpha (TNF) is a cytokine that is rapidly mobilized in response to stressors such as injury and infection, and is a potent mediator of the subsequent inflammatory response. TNF is primarily synthesized by macrophages, monocytes, and T cells, which are abundant in peritoneal and splanchic tissues. Although the circulating half-life of TNF is brief, the activity of TNF elicits many metabolic and immunomodulatory activities. TNF stimulates muscle breakdown and cachexia through increased catabolism, insulin resistance, and redistribution of amino acids to hepatic circulation as fuel substrates. In addition, TNF also mediates coagulation activation, cell migration, and macrophage phagocytosis, and enhances the expression of adhesion molecules, prostaglandin E2, platelet-activating factor, glucocorticoids, and eicosanoids. 23

Tumor necrosis factor receptors (TNFRs) are composed of two subtypes: TNFR-1 and TNFR-2. TNFR-1 is ubiquitously expressed in most tissues.
and, on ligand binding, mediates apoptosis through proteolytic caspases. TNFR-2 is expressed primarily on immunocytes and, on ligand binding, leads to NF-κB activation and subsequent amplification of the inflammatory signal. TNFRs exist in both transmembrane and soluble form. In response to inflammatory stimuli such as injury and infection, TNFRs are proteolytically cleaved from cell membranes and are readily detectable in soluble form. This may represent a mechanism of inflammatory regulation, because soluble TNFRs maintain their affinity for TNF and thereby compete with and limit the activation of transmembrane TNFR. 24

**Interleukin-1**

Interleukin-1 (IL-1) is represented by two active subtypes, IL-1α and IL-1β. IL-1α is primarily membrane associated and functions through cellular contact. IL-1β is readily detectable in soluble form and mediates an inflammatory sequence similar to that of TNF. IL-1 is primarily synthesized by monocytes, macrophages, endothelial cells, fibroblasts, and epidermal cells. IL-1 is released in response to inflammatory stimuli, including cytokines (TNF, IL-2, interferon-γ [IFN-γ]) and foreign pathogens, and requires the formation of the inflammatory cascade in the cell for processing and release. High doses of either IL-1 or TNF are associated with profound hemodynamic compromise. Interestingly, low doses of both IL-1 and TNF combined elicit hemodynamic events similar to those elicited by high doses of either mediator, which suggests a synergistic effect. IL-1 is an endogenous pyrogen because it acts on the hypothalamus by stimulating prostaglandin activity and thereby mediates a febrile response. IL-1 is auto-regulated by endogenous IL-1 receptor antagonists, which are released in response to inflammatory stimuli and compete with IL-1 at receptor binding sites. There are two primary receptor types for IL-1: IL-1R1 and IL-1R2. IL-1R1 is widely expressed and mediates inflammatory signaling on ligand binding. IL-1R2 is proteolytically cleaved from the membrane surface to soluble form on activation and thus serves as another mechanism for competition and regulation of IL-1 activity. 25

**Interleukin-2**

Interleukin-2 (IL-2) is upregulated in response to IL-1 and is primarily a promoter of T-lymphocyte proliferation and differentiation, immunoglobulin production, and gut barrier integrity. IL-2 binds to IL-2 receptors, which are expressed on leukocytes. Partly due to its short half-life of <10 minutes, IL-2 is not readily detectable after acute injury. IL-2 receptor blockade induces immunosuppressive effects and can be pharmacologically used for organ transplantation. Attenuated IL-2 expression observed during major injury or blood transfusion may contribute to the relatively immunosuppressed state of the surgical patient. 26

**Interleukin-4**

Interleukin-4 (IL-4) is released by activated helper T cells and stimulates the differentiation of T cells, and also stimulates T-cell proliferation and B-cell activation. It is also important in antibody-mediated immunity and in antigen presentation. IL-4 induces class switching of differentiating B lymphocytes to produce predominantly immunoglobulin G4 and immunoglobulin E, which are important immunoglobulins in allergic and anaphylactic responses. IL-4 has anti-inflammatory effects on macrophages, exhibited by an attenuated response to proinflammatory mediators such as IL-1, TNF, interleukin-6, and interleukin-8. In addition, IL-4 appears to increase macrophage susceptibility to the anti-inflammatory effects of glucocorticoids.

**Interleukin-6**

Interleukin-6 (IL-6) release by macrophages is stimulated by inflammatory mediators such as endotoxin, TNF, and IL-1. IL-6 is increasingly expressed during times of stress, as in septic shock. After injury, IL-6 levels in the circulation are detectable by 60 minutes, peak between 4 and 6 hours, and can persist for as long as 10 days. Plasma levels of IL-6 are proportional to the degree of injury during surgery. Interestingly, IL-6 has counter-regulatory effects on the inflammatory cascade through the inhibition of TNF and IL-1. IL-6 also promotes the release of soluble tumor necrosis factor receptors and IL-1 receptor antagonists, and stimulates the release of cortisol. High plasma IL-6 levels have been associated with mortality during intra-abdominal sepsis. 27

**Interleukin-8**

Interleukin-8 (IL-8) is synthesized by macrophages as well as other cell lines such as endothelial cells. Critical illness as manifested during sepsis is a potent stimulus for IL-8 expression. IL-8 stimulates the release of IFN-γ and functions as a potent chemoattractant for neutrophils. Elevated plasma IL-8 also has been associated with disease severity and end organ dysfunction during sepsis. 28

**Interleukin-10**

Interleukin-10 (IL-10) is an anti-inflammatory cytokine synthesized primarily by monocytes; however, it is also released by other lymphocytes. IL-10 is increasingly expressed during times of septicemic inflammation, and its release is specifically enhanced by TNF and IL-1. IL-10 inhibits the secretion of proinflammatory cytokines, including TNF and IL-1, partly through the downregulation of NF-κB and thereby functions as a negative feedback regulator of the inflammatory cascade. Experimental models of inflammation have shown that neutralization of IL-10 increases TNF production and mortality, whereas repletion of circulating IL-10 reduces TNF levels and subsequent deleterious effects. Increased plasma levels of IL-10 also have been associated with mortality and disease severity after traumatic injury. IL-10 may significantly contribute to the underlying immunosuppressed state during sepsis through the inhibition and subsequent anergy of immunocytes. 29

**Interleukin-12**

Interleukin-12 (IL-12) has been described as a regulator of cell mediated immunity. IL-12 is released by activated phagocytes, including monocytes, macrophages, neutrophils, and dendritic cells, and is increasingly expressed during endotoxemia and sepsis. IL-12 stimulates lymphocytes to increase secretion of IFN-γ with the costimulus of interleukin-18 and also stimulates natural killer cell cytolysis and helper T cell differentiation. IL-12 release is inhibited by IL-10. IL-12 deficiency inhibits phagocytosis in neutrophils. In experimental models of inflammatory stress, IL-12 neutralization conferred a mortality benefit in mice during endotoxemia. However, in a cecal ligation and puncture model of intraperitoneal sepsis, IL-12 blockade was associated with increased mortality. Furthermore, later studies of intraperitoneal sepsis observed no difference in mortality with IL-12 administration; however, IL-12 knockout mice exhibited increased bacterial counts and inflammatory cytokine release, which suggests that IL-12 may contribute to an antibacterial response. IL-12 administration in chimpanzees is capable of stabilizing the release of proinflammatory mediators such as IFN-γ and also anti-inflammatory mediators, including IL-10, soluble TNFR, and IL-1 receptor antagonists. In addition, IL-12 enhances coagulation as well as fibrinolysis. Despite evidence of both proinflammatory and anti-inflammatory pathway activation, most evidence suggests that IL-12 contributes to an overall proinflammatory response. 30
Interleukin-13

Interleukin-13 (IL-13) exerts many of the same immunomodulatory effects as does IL-4. IL-13 inhibits monocyte release of TNF, IL-1, IL-6, and IL-8, while increasing the secretion of IL-1R antagonist. However, unlike IL-4, IL-13 has no identifiable effect on T lymphocytes and only has influence on selected B-lymphocyte populations. Increased IL-13 expression is observed during septic shock and mediates neutropenia, monocytopenia, and leukopenia. In addition, IL-13 inhibits leukocyte interaction with activated endothelial surfaces. Similar to IL-4 and IL-10, IL-13 has a net anti-inflammatory effect.

Interleukin-15

Interleukin-15 (IL-15) is synthesized in many cell types, including macrophages and skeletal muscle after endotoxin administration. IL-15 stimulates natural killer cell activation as well as B-cell and T-cell proliferation and thus functions as a regulator of cellular immunity. IL-15 has immunomodulatory effects similar to those of IL-2, in part due to shared receptor subunits. Furthermore, IL-15 acts as a potent inhibitor of lymphocyte apoptosis by enhancing the expression of antiapoptotic molecules such as Bcl-2.

Interleukin-18

Interleukin-18 (IL-18), formerly IFN-γ-inducing factor, is synthesized primarily by macrophages. IL-18 and its receptor complex are members of the IL-1 superfamily. As with IL-1, macrophages release IL-18 in response to inflammatory stimuli, including endotoxin, TNF, IL-1, and IL-6. IL-18 level also is elevated during sepsis. IL-18 activates NF-κB through an Myeloid differentiation primary response gene (88) (MyD88)-dependent pathway with subsequent proinflammatory mediator release. IL-18 regulation is in part mediated through IL-18–binding protein (IL-18BP). This molecule is not a soluble receptor isoform but rather a specific endogenous antagonist. IL-18 also mediates hepatotoxicity associated with Fas ligand and TNF. The viral skin pathogen molluscum contagiosum secretes an IL-18BP–like protein, which neutralizes IL-18 and thereby inhibits the inflammatory response. IL-18 and IL-12 act synergistically to release IFN-γ from T cells. In a murine model of systemic inflammation, IL-18 neutralization reduced lethal endotoxia. IL-18 signaling also is associated with increased expression of intercellular adhesion molecule-1. Interestingly, in a murine model of systemic inflammation, a reversal of left ventricular dysfunction was observed with IL-18 blockade, which suggests that IL-18 may contribute to the hemodynamic compromise during septic shock.

Interferons

Interferons were first recognized as soluble mediators that inhibited viral replication through the activation of specific antiviral genes in infected cells. Interferons are categorized into two major subtypes based on receptor specificity and sequence homology. Type I interferons include IFN-α, IFN-β, and IFN-ω, which are structurally related and bind to a common receptor, IFN-ω receptor. Type I interferons are expressed in response to many stimuli, including viral antigens, double-stranded DNA, bacteria, tumor cells, and LPS. Type I interferons influence adaptive immune responses by inducing the maturation of dendritic cells and by stimulating class I MHC expression. IFN-ω and IFN-β also enhance immune responses by increasing the cytotoxicity of natural killer cells both in culture and in vivo. In murine models, the absence of IFN-ω receptor results in greater susceptibility to viral infection as well as diminished LPS-induced lethality. Furthermore, type I interferons have also been studied as therapeutic agents in hepatitis C and relapsing multiple sclerosis.

Many of the physiologic effects observed with increased levels of IL-12 and IL-18 are mediated through IFN-γ. IFN-γ is a type II interferon secreted by T lymphocytes, natural killer cells, and antigen-presenting cells in response to bacterial antigens. IL-2, IL-12, and IL-18. IFN-γ stimulates the release of IL-12 and IL-18. Negative regulators of IFN-γ include IL-4, IL-10, and glucocorticoids. IFN-γ binding with a cognate receptor activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, leading to subsequent induction of biologic responses. Macrophages stimulated by IFN-γ demonstrate enhanced phagocytosis and microbial killing, and increased release of oxygen radicals, partly through a nicotinamide adenine dinucleotide phosphate–dependent phagocyte oxidase. IFN-γ mediates macrophage stimulation and thus may contribute to acute lung injury after major surgery or trauma. Diminished IFN-γ level, as seen in knockout mice, is associated with increased susceptibility to both viral and bacterial pathogens. IFN-γ regulates trafficking of monocytes to sites of inflammation via upregulation of chemokinate receptors [e.g., monokine induced by IFN-γ (MIG), macrophage inflammatory protein 1-alpha and 1-beta] and adhesion molecules (e.g., intercellular adhesion molecule-1, vascular cell adhesion molecule-1). In addition, IFN-γ promotes differentiation of T cells to the helper T cell subtype 1 and also enhances B-cell isotype switching to immunoglobulin G.

Granulocyte-Macrophage Colony-Stimulating Factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF), as the name suggests, upregulates both granulocyte and monocyte cell lines from hematopoietic bone marrow stem cells. GM-CSF plasma levels are low to undetectable but rapidly increase in response to inflammatory stimuli such as TNF. GM-CSF inhibits both monocyte and neutrophil apoptosis and enhances macrophage cytokine release in response to inflammatory stimuli. GM-CSF also potentiates the release of neutrophil superoxide as well as the cytotoxicity of monocytes. Administration of GM-CSF has proven beneficial during the treatment of fungal infections in immunocompromised patients. GM-CSF may potentiate acute lung injury during critical illness, because GM-CSF blockade has been found to be associated with decreased alveolar macrophage activity and NF-κB intensity. This growth factor is effective in promoting the maturation and recruitment of functional leukocytes necessary for normal inflammatory cytokine responses and also may be effective in wound healing.

High Mobility Group Box 1

High mobility group box 1 (HMGB1) is a DNA transcription factor that facilitates the binding of regulatory protein complexes to DNA. HMGB1 is actively secreted by macrophages, natural killer cells, and enterocytes. Endotoxin, TNF, and IFN-γ promote the release of HMGB1, and in a murine model of intraperitoneal sepsis, increased circulating HMGB1 was associated with increased mortality. HMGB1 also appears to have cytokine-like activities, because it promotes the release of TNF from monocytes. Interestingly, elevation of plasma HMGB1 levels after experimental induction of endotoxia is delayed relative to that of other inflammatory mediators, with levels peaking at 16 hours and remaining elevated beyond 30 hours. This response contrasts with that of acute inflammatory mediators such as TNF, which peaks at 1 to 2 hours and becomes undetectable by 12 hours. Furthermore, HMGB1 blockade is associated with decreased mortality even when initiated 4 to 24 hours after the inflammatory stimulus. HMGB1 is passively released by necrotic cells. Thus, HMGB1 alone or in combination with other molecules may contribute to the regulation of inflammation after tissue injury. Receptors for HMGB1 are receptors for advanced glycation end products and toll-like receptor 4. Binding leads to the proinflammatory response through the activation of NF-κB. Clinical trials have demonstrated increased plasma HMGB1 during systemic inflammation, as in sepsis, hemorrhagic shock, pancreatitis, myocardial infarction, and major surgery.
CELLULAR RESPONSE TO INJURY

Gene Expression and Regulation

Many genes are regulated at the point of DNA transcription and thus influence whether messenger RNA (mRNA) and its subsequent product are expressed (Fig. 2-6). These mRNA transcripts are also regulated by modulation mechanisms, including (a) splicing, which can cleave mRNA and remove noncoding regions; (b) capping, which modifies the 5’ ends of the mRNA sequence to inhibit breakdown by exonucleases; and (c) the addition of a polyadenylated tail, which adds a noncoding sequence to the mRNA, effectively increasing the half-life of the transcript. Once out of the nucleus, the mRNA can be inactivated or translated to form proteins. Many protein products are also further modified for specific function or trafficking.

**Fig. 2-6.**

Gene expression and protein synthesis can occur within a 24-hour period. The process can be regulated at various stages: transcription, messenger RNA (mRNA) processing, or protein packaging. At each stage, it is possible to inactivate the mRNA or protein, rendering these molecules nonfunctional.

Gene expression relies on the coordinated action of transcription factors and coactivators (i.e., regulatory proteins), which are complexes that bind to highly specific DNA sequences upstream of the target gene known as the promoter region. Enhancer sequences of DNA mediate gene expression, whereas repressor sequences are noncoding regions that bind proteins to inhibit gene expression. During systemic inflammation, transcription factors are highly important, because regulation of cytokine gene expression may have profound effects on the clinical phenotype.

CELL SIGNALING PATHWAYS

G-Protein Receptors

G-protein receptors (GPRs) are a large family of transmembrane receptors. They bind a multitude of ligands (e.g., epinephrine, bradykinin, leukotriene) and are involved in signal transduction during the inflammatory response. Extracellular ligands bind to GPR, which result in a conformational change and activation of associated proteins. The two major second messengers of the G-protein pathway are (1) cAMP, and (2) calcium, released from the endoplasmic reticulum (Fig. 2-7). Increased intracellular cAMP can activate gene transcription through the activity of intracellular signal transducers such as protein kinase A. Increased intracellular calcium can activate the intracellular signal transducer phospholipase C with further subsequent downstream effects. GPR binding also can promote the activity of protein kinase C, which can subsequently stimulate NF-κB as well as other transcription factors.

**Fig. 2-7.**
G-protein–coupled receptors are transmembrane proteins. The G-protein receptors respond to ligands such as adrenaline and serotonin. On ligand binding to the receptor (R), the G protein (G) undergoes a conformational change through guanosine triphosphate–guanosine diphosphate conversion and in turn activates the effector (E) component. The E component subsequently activates second messengers. The role of inositol triphosphate (IP₃) is to induce release of calcium from the endoplasmic reticulum (ER). cAMP = cyclic adenosine monophosphate.

Ligand-Gated Ion Channels

Ligand-gated ion channels (LGICs) are transmembrane receptors that allow the rapid influx of ions (e.g., sodium, calcium, potassium, chloride) and are central to the signal transduction of neurotransmitters. On ligand binding LGICs effectively convert a chemical signal into an electrical signal. The prototypical LGIC is the nicotinic acetylcholine receptor (Fig. 2-8).

Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs) are transmembrane receptors that are involved in cell signaling for several growth factors, including platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, and vascular endothelial growth factor. On ligand binding, RTKs dimerize with adjacent receptors, undergo autophosphorylation, and recruit secondary signaling molecules (e.g., phospholipase C) (Fig. 2-9). Activation of RTK is important for gene transcription as well as cell proliferation and may have influence in the development of many types of cancer.
The receptor tyrosine kinase requires dimerization of monomeric units. These receptors possess intrinsic enzymatic activity that requires multiple autophosphorylation steps to recruit and activate intracellular signaling molecules. ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

**Janus Kinase/Signal Transducer and Activator of Transcription Signaling**

The Janus kinases (JAKs) represent a family of tyrosine kinases that mediate signal transduction of several cytokines, including IFN-γ, IL-6, IL-10, IL-12, and IL-13. JAKs bind to cytokines, and upon ligand binding and dimerization, activated JAKs recruit and phosphorylate signal transducer and activator of transcription (STAT) molecules (Fig. 2-10). Activated STAT proteins further dimerize and translocate into the nucleus and modulate the transcription of target genes. Interestingly, STAT-DNA binding can be observed within minutes of cytokine binding. The JAK/STAT system is a rapid pathway for membrane to nucleus signal transduction. The JAK/STAT pathway is inhibited by the action of phosphatase, the export of STATs from the nucleus, as well as the interaction of antagonistic proteins. 37

**Fig. 2-9.**

![Diagram of receptor tyrosine kinase](source)

**Fig. 2-10.**

![Diagram of Janus kinase/Stat transduction](source)
factors. JAK/STAT activation occurs in response to cytokines (e.g., interleukin-6) and cell stressors, and has been found to induce cell proliferation and inflammatory function. Intracellular molecules that inhibit STAT function, known as suppressors of cytokine signaling (SOCSs), have been identified. P = phosphate.

Suppressors of Cytokine Signaling

Suppressors of cytokine signaling (SOCSs) molecules are a group of cytokine-induced proteins that function as a negative feedback loop by downregulating the JAK/STAT pathway. SOCSs exert an inhibitory effect partly by binding with JAK and thus competing with STAT. A deficiency of SOCS activity may render a cell hypersensitive to certain stimuli, such as inflammatory cytokines and growth hormones. Interestingly, in a murine model, SOCS knockout resulted in a lethal phenotype in part because of unregulated interferon-γ signaling. An example of this pathway is highlighted by an attenuated IL-6 response in macrophages via suppressor of cytokine signaling 3 (SOCS-3) inhibition of signal transducer and activator of transcription 3 (STAT3). 38

Mitogen-Activated Protein Kinases

Pathways mediated through mitogen-activated protein kinase (MAPK) contribute to inflammatory signaling and regulation of cell proliferation and cell death (Fig. 2-11). MAPK pathways involve sequential stages of mediator phosphorylation resulting in the activation of downstream effectors, including c-Jun N-terminal kinase (JNK), extracellular signal regulated protein kinase (ERK), and p38 kinase, with subsequent gene modulation. Dephosphorylation of MAPK pathway mediators inhibit their function. Activated JNK phosphorylates c-Jun, which dimerizes to form the transcription factor activated protein 1. The protein MAP/ERK kinase kinase (MEKK) has several functions, including protein kinase and ubiquitin ligase, and also has been shown to downregulate MAPK pathways. JNK is activated by TNF and IL-1 and is a regulator of apoptosis. Pharmacologic blockade of JNK was associated with decreased pulmonary injury and TNF and IL-1 secretion in an ischemia/reperfusion model. The p38 kinase is activated in response to endotoxin, viruses, IL-1, IL-2, IL-7, IL-17, IL-18, and TNF. The p38 also plays a role in immunocyte development, because p38 inactivation is a critical step in the differentiation of thymic T cells. These MAPK isoforms do not function independently but rather exhibit significant counteraction and crosstalk, which can influence the inflammatory response. 39

Fig. 2-11.

The mitogen-activated protein kinase (MAPK) signaling pathway requires multiple phosphorylation steps. Ras, Raf, and Mos are examples of the MAPK kinase kinase (MAPKKK) and are upstream molecules. Well-characterized downstream kinases are extracellular signal regulated kinases 1 and 2 (ERK 1/2), c-Jun N-terminal kinases (JNKs) or stress-activated protein kinases (SAPKs), and p38 MAPKs that target specific gene transcription sites in the nucleus. ATF2 = activating transcription factor 2; MAPKK = mitogen-activated protein kinase kinase; MEF2 = myocyte-enhancing factor 2; P = phosphate.

Nuclear Factor κB

Nuclear factor κB (NF-κB) is a transcription factor that has a central role in regulating the gene products expressed after inflammatory stimuli...
NF-κB is composed of two smaller polypeptides, p50 and p65. NF-κB resides in the cytosol in the resting state primarily through the inhibitory binding of inhibitor of NF-κB (IκB). In response to an inflammatory stimulus such as TNF, IL-1, or endotoxin, a sequence of intracellular mediator phosphorylation reactions leads to the degradation of IκB and subsequent release of NF-κB. On release, NF-κB travels to the nucleus and promotes gene expression. NF-κB also stimulates the gene expression for IκB, which results in negative feedback regulation. In clinical appendicitis, for example, increased NF-κB activity was associated with initial disease severity, and levels returned to baseline within 18 hours after appendectomy in concert with resolution of the inflammatory response.  

Fig. 2-12.

NF-κB activation

Inhibitor of NF-κB (IκB) binding to the p50-p65 subunits of nuclear factor NF-κB inactivates the molecule. Ligand binding to the receptor activates a series of downstream signaling molecules, of which IκB kinase is one. The phosphorylated NF-κB complex further undergoes ubiquitination and proteosome degradation of IκB, activating NF-κB, which translocates into the nucleus. Rapid resynthesis of IκB is one method of inactivating the p50-p65 complex. IL-1 = interleukin-1; P = phosphate; TNF = tumor necrosis factor.

Toll-Like Receptors and CD14

The innate immune system responds to pathogen-associated molecular patterns (PAMPs) such as microbial antigens and LPS. Toll-like receptors (TLRs) are a group of pattern recognition receptors activated by PAMPs that function as effectors of the innate immune system and belong to the IL-1 superfamily. Immunocyte recognition of LPS is mediated primarily by TLR4. LPS-binding proteins chaperone LPS to the CD14/TLR4 complex, which sets into effect cellular mechanisms that activate MAPK, NF-κB, and cytokine gene expression (Fig. 2-13). In contrast to TLR4, TLR2 recognizes PAMPs from gram-positive bacteria, including lipoproteins, lipopeptides, peptidoglycans, and phenol-soluble modulin from Staphylococcus species. Interestingly, loss-of-function single nucleotide polymorphisms of TLR are associated with an increased risk of infection in susceptible critically ill patients. As multiligand receptors, TLRs also bind damage-associated molecular pattern molecules (DAMPs), which are endogenous cellular products released during times of stress or injury. DAMPs include products such as HMGB1, heat shock proteins, and hyaluronic acid. Innate immune activation by DAMPs stimulates the recruitment of inflammatory cells to the site of injury and also mediates proinflammatory signaling.
Lipopolysaccharide (LPS) recognition by immune cells is primarily by the toll-like receptor-4 (TLR4)/CD14/MD-2 complex. LPS is transported by LPS-binding protein (LBP) to the cell surface complex. Other cell surface LPS sensors include ion-gated channels, CD11b/CD18, and macrophage scavenger receptors. MAPK = mitogen-activated protein kinase; NF-κB = nuclear factor B.

**APOPTOSIS**

Apoptosis (regulated cell death) is an energy-dependent, organized mechanism for clearing senescent or dysfunctional cells, including macrophages, neutrophils, and lymphocytes, without promoting an inflammatory response. Conversely, cell necrosis results in a disorganized sequence of intracellular molecular releases with subsequent immune activation and inflammatory response. Systemic inflammation modulates apoptotic signaling in active immunocytes, which subsequently influences the inflammatory response through the loss of effector cells.

Apoptosis proceeds primarily through two pathways: the extrinsic pathway and the intrinsic pathway. The extrinsic pathway is activated through the binding of death receptors (e.g., Fas, TNFR), which leads to the recruitment of Fas-associated death domain protein and subsequent activation of caspase 3 (Fig. 2-14). On activation, caspases are the effectors of apoptotic signaling because they mediate the organized breakdown of nuclear DNA. The intrinsic pathway proceeds through protein mediators (e.g., Bcl-2, Bcl-2-associated death promoter, Bcl-2-associated X protein, Bim) that influence mitochondrial membrane permeability. Increased membrane permeability leads to the release of mitochondrial cytochrome C, which ultimately activates caspase 3 and thus induces apoptosis. These pathways do not function in a completely autonomous manner, because there is significant interaction and crosstalk between mediators of both extrinsic and intrinsic pathways. Apoptosis is modulated by several regulatory factors, including inhibitor of apoptosis proteins and regulatory caspases (e.g., caspases 1, 8, 10).

**Fig. 2-14.**
Signaling pathway for tumor necrosis factor receptor 1 (TNFR-1) (55 kDa) and TNFR-2 (75 kDa) occurs by the recruitment of several adapter proteins to the intracellular receptor complex. Optimal signaling activity requires receptor trimerization. TNFR-1 initially recruits TNFR-associated death domain (TRADD) and induces apoptosis through the actions of proteolytic enzymes known as caspases, a pathway shared by another receptor known as CD95 (Fas). CD95 and TNFR-1 possess similar intracellular sequences known as death domains (DDs), and both recruit the same adapter proteins known as Fas-associated death domains (FADDs) before activating caspase 8. TNFR-1 also induces apoptosis by activating caspase 2 through the recruitment of receptor-interacting protein (RIP). RIP also has a functional component that can initiate nuclear factor (NF)-κB (NF-κB) and c-Jun activation, both favoring cell survival and proinflammatory functions. TNFR-2 lacks a DD component but recruits adapter proteins known as TNFR-associated factors 1 and 2 (TRAF1, TRAF2) that interact with RIP to mediate NF-κB and c-Jun activation. TRAF2 also recruits additional proteins that are antiapoptotic, known as inhibitor of apoptosis proteins (IAPs). DED = death effector domain; I-B = inhibitor of B; I-B/NF-κB = inactive complex of NF-κB that becomes activated when the I-B portion is cleaved; JNK = c-Jun N-terminal kinase; MEKK1 = mitogen-activated protein/extracellular regulatory protein kinase kinase kinase-1; NIK = NF-κB–inducing kinase; RAIDD = RIP-associated interleukin-1b-converting enzyme and ced-homologue-1–like protein with death domain, which activates proapoptotic caspases.


Apoptosis during sepsis may influence the ultimate competency of the acquired immune response. In a murine model of peritoneal sepsis, increased lymphocyte apoptosis was associated with mortality, which may be due to a resultant decrease in IFN-γ release. In postmortem analysis of patients who expired from overwhelming sepsis, there was an increase in lymphocyte apoptosis, whereas macrophage apoptosis did not appear to be affected. Clinical trials have observed an association between the degree of lymphopenia and disease severity in sepsis. In addition, after the phagocytosis of apoptotic cells by macrophages, anti-inflammatory mediators such as IL-10 are released that may exacerbate immune suppression during sepsis. Neutrophil apoptosis is inhibited by inflammatory products, including TNF, IL-1, IL-3, IL-6, GM-CSF, and IFN-γ. This retardation in regulated cell death may prolong and exacerbate secondary injury through neutrophil free radical release as the clearance of senescent cells is delayed. 28

**CELL-MEDIATED INFLAMMATORY RESPONSE**

**Platelets**
Platelets are nonnucleated structures containing both mitochondria and mediators of coagulation and inflammatory signaling. Platelets are derived from bone marrow megakaryocytes. Platelets are critically important in the hemostatic response and are activated by several factors, including exposed collagen. Activated platelets at the site of injury release inflammatory mediators that serve as the principal chemoattractant for neutrophils and monocytes. The migration of platelets and neutrophils through the vascular endothelium occurs within 3 hours of injury and is enhanced by serotonin release, platelet-activating factor, and prostaglandin E2. Platelets are an important source of eicosanoids and vasoactive mediators. A hallmark of the septic response includes thrombocytopenia; however, the mechanism is unclear and likely multifactorial. Pharmaceutical agents such as NSAIDs inhibit platelet function through the blockade of COX. 43

**Lymphocytes and T-Cell Immunity**
Lymphocytes are circulating immune cells composed primarily of B cells, T cells, and natural killer cells. As mediators of adaptive immunity, T lymphocytes are recruited to sites of injury. Helper T lymphocytes are broadly categorized into two groups: Th1 and Th2. Th1 cells favor cellular immune responses and secrete IFN-γ, IL-2, and IL-12, whereas Th2 cells favor humoral responses and produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. Th1 activation is paramount in the defense against bacterial pathogens; however, during critical illness induced by severe trauma or sepsis, there appears to be a predominance of Th2 over Th1 cytokine responses, which may exacerbate immune dysregulation.
through amplified cytokine signaling (Fig. 2-15). In burn injury, T regulatory cells are associated with T-cell suppression via the release of transforming growth factor beta (TGF-β), which can downregulate T-cell function. Nutritional supplementation may confer a benefit in T-cell responses, because arginine is essential for T-cell proliferation and receptor function. 44

![Fig. 2-15.](source)

Specific immunity mediated by helper T lymphocytes subtype 1 (Th1) and subtype 2 (Th2) after injury. A Th1 response is favored in lesser injuries, with intact cell-mediated and opsonizing antibody immunity against microbial infections. This cell-mediated immunity includes activation of monocytes, B lymphocytes, and cytotoxic T lymphocytes. A shift toward the Th2 response from naïve helper T cells is associated with injuries of greater magnitude and is not as effective against microbial infections. A Th2 response includes the activation of eosinophils, mast cells, and B-lymphocyte immunoglobulin 4 and immunoglobulin E production. (Primary stimulants and principal cytokine products of such responses are in **bold** characters.) Interleukin-4 (IL-4) and IL-10 are known inhibitors of the Th1 response. Interferon-γ (IFN-γ) is a known inhibitor of the Th2 response. Although not cytokines, glucocorticoids are potent stimulants of a Th2 response, which may partly contribute to the immunosuppressive effects of cortisol. GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor. (Adapted with permission from Lin E, Calvano SE, Lowry SF: Inflammatory cytokines and cell response in surgery. Surgery 127:117, 2000. Copyright Elsevier.)

**Eosinophils**

Eosinophils are immunocytes whose primary functions are anthelminthic. Eosinophils are found mostly in tissues such as the lung and GI tract, which may suggest a role in immune surveillance. Eosinophils can be activated by IL-3, IL-5, GM-CSF, chemoattractants, and platelet-activating factor. Eosinophil activation can lead to subsequent release of toxic mediators, including reactive oxygen species, histamine, and peroxidase. 45

**Mast Cells**

Mast cells are important in the primary response to injury because they are located in tissues. TNF release from mast cells has been found to be crucial for neutrophil recruitment and pathogen clearance. Mast cells are also known to play an important role in the anaphylactic response to allergens. On activation from stimuli including allergen binding, infection, and trauma, mast cells produce histamine, cytokines, eicosanoids, proteases, and chemokines, which leads to vasodilatation, capillary leakage, and immunocyte recruitment. Mast cells are thought to be important cosignaling effector cells of the immune system via the release of IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-14, as well as macrophage migration–inhibiting factor. 46

**Monocytes**

Monocytes are mononuclear phagocytes that circulate in the bloodstream and can differentiate into macrophages, osteoclasts, and dendritic cells on migrating into tissues. Macrophages are the main effector cells of the immune response to infection and injury, primarily through mechanisms that include phagocytosis of microbial pathogens, release of inflammatory mediators, and clearance of apoptotic cells. In humans, downregulation of monocyte and neutrophil TNFR expression has been demonstrated experimentally and clinically during systemic inflammation. In clinical sepsis, nonsurviving patients with severe sepsis have an immediate reduction in monocyte surface TNFR expression with failure to recover, whereas surviving patients have normal or near-normal receptor levels from the onset of clinically defined sepsis. In patients with congestive heart failure, there is also a significant decrease in the amount of monocyte surface TNFR expression compared with control patients. In experimental models, endotoxin has been shown to differentially regulate over 1000 genes in murine macrophages with approximately 25% of these corresponding to cytokines and chemokines. During sepsis, macrophages undergo phenotypic reprogramming highlighted by decreased surface human leukocyte antigen DR (a critical receptor in antigen presentation), which also may contribute to host immunocompromise during sepsis. 47

**Neutrophils**

Neutrophils are among the first responders to sites of infection and injury and as such are potent mediators of acute inflammation. Chemotactic mediators from a site of injury induce neutrophil adherence to the vascular endothelium and promote eventual cell migration into the injured tissue. Neutrophils are circulating immunocytes with short half-lives (4 to 10 hours). On activation by inflammatory stimuli, including TNF, IL-1, and microbial pathogens, neutrophils are able to phagocytose, release lytic enzymes, and generate large amounts of toxic reactive oxygen species. 48
ENDOTHELIUM-MEDIATED INJURY

Vascular Endothelium

Under physiologic conditions, vascular endothelium has overall anticoagulant properties mediated via the production and cell surface expression of heparin sulfate, dermatan sulfate, tissue factor pathway inhibitor, protein S, thrombomodulin, plasmogen, and tissue plasminogen activator. Endothelial cells also perform a critical function as barriers that regulate tissue migration of circulating cells. During sepsis, endothelial cells are differentially modulated, which results in an overall procoagulant shift via decreased production of anticoagulant factors, which may lead to microthrombosis and organ injury.

Neutrophil-Endothelium Interaction

The regulated inflammatory response to infection facilitates neutrophil and other immunocyte migration to compromised regions through the actions of increased vascular permeability, chemoattractants, and increased endothelial adhesion factors referred to as selectins that are elaborated on cell surfaces (Table 2-5). Prolonged and unremitting neutrophil activation and mediator release can lead to tissue injury through the production of toxic oxygen metabolites and lysosomal enzymes that degrade tissue basal membranes, cause microvascular thrombosis, and activate myeloperoxidases. In response to inflammatory stimuli, including chemokines, thrombin, IL-1, histamine, and TNF, vascular endothelium increases surface expression of the adhesion molecule P-selectin, which is observable in 10 to 20 minutes and mediates neutrophil rolling (Fig. 2-16). After 2 hours, however, cell surface expression favors E-selectin expression. L-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) are responsible for over 85% of monocyte-to-monocyte and monocyte-to-endothelium adhesion activity. Endothelial selectins interact with leukocyte selectins (PSGL-1, L-selectin) to mediate leukocyte rolling, which allows targeted immunocyte migration. Also important are secondary leukocyte-leukocyte interactions in which PSGL-1 and L-selectin binding facilitates further leukocyte tethering. Although there are distinguishable properties among individual selectins in leukocyte rolling, effective rolling most likely involves a significant degree of functional overlap. 49

Table 2-5 Molecules that Mediate Leukocyte-Endothelial Adhesion, Categorized by Family

<table>
<thead>
<tr>
<th>Adhesion Molecule</th>
<th>Action</th>
<th>Origin</th>
<th>Inducers of Expression</th>
<th>Target Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-selectin</td>
<td>Fast rolling</td>
<td>Leukocytes</td>
<td>Native</td>
<td>Endothelium, platelets, eosinophils</td>
</tr>
<tr>
<td>P-selectin</td>
<td>Slow rolling</td>
<td>Platelets and endothelium</td>
<td>Thrombin, histamine</td>
<td>Neutrophils, monocytes</td>
</tr>
<tr>
<td>E-selectin</td>
<td>Very slow rolling</td>
<td>Endothelium</td>
<td>Cytokines</td>
<td>Neutrophils, monocytes, lymphocytes</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Firm adhesion/transmigration</td>
<td>Endothelium, leukocytes, fibroblasts, epithelium</td>
<td>Cytokines</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>ICAM-2</td>
<td>Firm adhesion</td>
<td>Endothelium, platelets</td>
<td>Native</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>Firm adhesion/transmigration</td>
<td>Endothelium</td>
<td>Cytokines</td>
<td>Monocytes, lymphocytes</td>
</tr>
<tr>
<td>PECAM-1</td>
<td>Adhesion/transmigration</td>
<td>Endothelium, platelets, leukocytes</td>
<td>Native</td>
<td>Endothelium, platelets, leukocytes</td>
</tr>
<tr>
<td>( \beta_2 ) (CD18) Integrins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD18/11a</td>
<td>Firm adhesion/transmigration</td>
<td>Leukocytes</td>
<td>Leukocyte activation</td>
<td>Endothelium</td>
</tr>
<tr>
<td>CD18/11b (Mac-1)</td>
<td>Firm adhesion/transmigration</td>
<td>Neutrophils, monocytes, natural killer cells</td>
<td>Leukocyte activation</td>
<td>Endothelium</td>
</tr>
<tr>
<td>CD18/11c</td>
<td>Adhesion</td>
<td>Neutrophils, monocytes, natural killer cells</td>
<td>Leukocyte activation</td>
<td>Endothelium</td>
</tr>
<tr>
<td>( \beta_1 ) (CD29) Integrins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLA-4</td>
<td>Firm adhesion/transmigration</td>
<td>Lymphocytes, monocytes</td>
<td>Leukocyte activation</td>
<td>Monocytes, endothelium, epithelium</td>
</tr>
</tbody>
</table>

ICAM-1 = intercellular adhesion molecule-1; ICAM-2 = intercellular adhesion molecule-2; Mac-1 = macrophage antigen 1; PECAM-1 = platelet-endothelial cell adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1; VLA-4 = very late antigen-4.

Fig. 2-16.
Simplified sequence of selectin-mediated neutrophil-endothelium interaction after an inflammatory stimulus. **CAPTURE** (tethering), predominantly mediated by cell L-selectin with contribution from endothelial P-selectin, describes the initial recognition between leukocyte and endothelium, in which circulating leukocytes marginate toward the endothelial surface. **FAST ROLLING** (20 to 50 μm/s) is a consequence of rapid L-selectin shedding from cell surfaces and formation of new downstream L-selectin to endothelium bonds, which occur in tandem. **SLOW ROLLING** (10 to 20 μm/s) is predominantly mediated by P-selectins. The slowest rolling (3 to 10 μm/s) before arrest is predominantly mediated by E-selectins, with contribution from P-selectins. **ARREST** (firm adhesion) leading to transmigration is mediated by β-integrins and the immunoglobulin family of adhesion molecules. In addition to interacting with the endothelium, activated leukocytes also recruit other leukocytes to the inflammatory site by direct interactions, which are mediated in part by selectins.

(Adapted with permission from Lin E, Calvano SE, Lowry SF: Selectin neutralization: Does it make biological sense? Crit Care Med 27:2050, 1999.)

**Nitric Oxide**

Nitric oxide (NO) was initially known as *endothelium-derived relaxing factor* due to its effect on vascular smooth muscle and has important functions in both physiologic and pathologic control of vascular tone. Normal vascular smooth muscle relaxation is maintained by a constant output of NO and subsequent activation of soluble guanylyl cyclase. NO also can reduce microthrombosis by reducing platelet adhesion and aggregation (Fig. 2-17). NO easily traverses cell membranes and has a short half-life of a few seconds and is oxidized into nitrate and nitrite.

Nitric oxide is constitutively expressed by endothelial cells; however, inducible NO synthase, which is normally not expressed, is upregulated in response to inflammatory stimuli, which increases NO production. Increased NO is detectable in septic shock and in response to TNF, IL-1, IL-2, and hemorrhage. NO mediates hypotension observed during septic shock; however, a clinical trial of a nonselective NOS inhibitor showed increased organ dysfunction and mortality.

**Fig. 2-17.**
Endothelial interaction with smooth muscle cells and with intraluminal platelets. Prostacyclin (prostaglandin \( I_2 \), or PGI2) is derived from arachidonic acid (AA), and nitric oxide (NO) is derived from L-arginine. The increase in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) results in smooth muscle relaxation and inhibition of platelet thrombus formation. Endothelins (ETs) are derived from "big ET," and they counter the effects of prostacyclin and NO.

**Prostacyclin**

Prostacyclin is a member of the eicosanoid family and is primarily produced by endothelial cells. Prostacyclin is an effective vasodilator and also inhibits platelet aggregation. During systemic inflammation, endothelial prostacyclin expression is impaired, and thus the endothelium favors a more procoagulant profile. Prostacyclin therapy during sepsis has been shown to reduce the levels of cytokines, growth factors, and adhesion molecules through a cAMP-dependent pathway. In clinical trials, prostacyclin infusion is associated with increased cardiac output, splanchnic blood flow, and oxygen delivery and consumption with no significant decrease in mean arterial pressure. However, further study is required before the widespread use of prostacyclin is recommended.  

**Endothelins**

Endothelins (ETs) are potent mediators of vasoconstriction and are composed of three members: ET-1, ET-2, and ET-3. ETs are 21-amino-acid peptides derived from a 38-amino-acid precursor molecule. ET-1, synthesized primarily by endothelial cells, is the most potent endogenous vasoconstrictor and is estimated to be 10 times more potent than angiotensin II. ET release is upregulated in response to hypotension, LPS, injury, thrombin, TGF-\( \beta \), IL-1, angiotensin II, vasopressin, catecholamines, and anoxia. ETs are primarily released to the abluminal side of endothelial cells, and very little is stored in cells; thus a plasma increase is associated with a marked increase in production. The half-life of plasma ET is between 4 and 7 minutes, which suggests that ET release is primarily regulated at the transcriptional level. Three endothelin receptors, referred to as ET\( _A \), ET\( _B \), and ET\( _C \), have been identified and function via the G-protein–coupled receptor mechanism. ET\( _B \) receptors are associated with increased NO and prostacyclin production, which may serve as a feedback mechanism. Atrial ET\( _A \) receptor activation has been associated with increased inotropy and chronotropy. ET-1 infusion is associated with increased pulmonary vascular resistance and pulmonary edema and may contribute to pulmonary abnormalities during sepsis. At low levels, in conjunction with NO, ETs regulate vascular tone. However, at increased concentrations, ETs can disrupt the normal blood flow and distribution and may compromise oxygen delivery to the tissue. In addition, increased plasma ET concentration correlates with the severity of injury after major trauma or major surgical procedures, and in patients with cardiogenic or septic shock.  

**Platelet-Activating Factor**

Another endothelium-derived product is platelet-activating factor (PAF), a natural phospholipid constituent of cell membranes that is minimally expressed under normal physiologic conditions. During acute inflammation, PAF is released by neutrophils, platelets, mast cells, and monocytes, and is expressed at the outer leaflet of endothelial cells. PAF can further activate neutrophils and platelets, and increase vascular permeability. Antagonists to PAF receptors have been experimentally shown to mitigate the effects of ischemia and reperfusion injury. Human sepsis is associated with a reduction in levels of PAF-acetylhydrolase, which is the endogenous inhibitor of PAF. Indeed, PAF-acetylhydrolase administration in patients with severe sepsis has yielded some reduction in multiple organ dysfunction and mortality.  

**Atrial Natriuretic Peptides**

Atrial natriuretic peptides (ANPs) are a family of peptides that are released primarily by atrial tissue but are also synthesized by the gut, kidney, brain, adrenal glands, and endothelium. They induce vasodilation as well as fluid and electrolyte excretion. ANPs are potent inhibitors of aldosterone secretion and prevent reabsorption of sodium. There is some experimental evidence to suggest that ANP can reverse acute
renal failure or early acute tubular necrosis.

SURGICAL METABOLISM

The initial hours after surgical or traumatic injury are metabolically associated with a reduced total body energy expenditure and urinary nitrogen wasting. On adequate resuscitation and stabilization of the injured patient, a reprioritization of substrate use ensues to preserve vital organ function and to support repair of injured tissue. This phase of recovery also is characterized by functions that participate in the restoration of homeostasis, such as augmented metabolic rates and oxygen consumption, enzymatic preference for readily oxidizable substrates such as glucose, and stimulation of the immune system.

Understanding of the collective alterations in amino acid (protein), carbohydrate, and lipid metabolism characteristic of the surgical patient lays the foundation upon which metabolic and nutritional support can be implemented.

Metabolism during Fasting

Fuel metabolism during unstressed fasting states has historically served as the standard to which metabolic alterations after acute injury and critical illness are compared (Fig. 2-18). To maintain basal metabolic needs (i.e., at rest and fasting), a normal healthy adult requires approximately 22 to 25 kcal/kg per day drawn from carbohydrate, lipid, and protein sources. This requirement can be as high as 40 kcal/kg per day in severe stress states, such as those seen in patients with burn injuries.

![Fig. 2-18.](image)

In the healthy adult, principal sources of fuel during short-term fasting (<5 days) are derived from muscle protein and body fat, with fat being the most abundant source of energy (Table 2-6). The normal adult body contains 300 to 400 g of carbohydrates in the form of glycogen, of which 75 to 100 g are stored in the liver. Approximately 200 to 250 g of glycogen are stored within skeletal, cardiac, and smooth muscle cells. The greater glycogen stores within the muscle are not readily available for systemic use due to a deficiency in glucose-6-phosphatase but are available for the energy needs of muscle cells. Therefore, in the fasting state, hepatic glycogen stores are rapidly and preferentially depleted, which results in a fall of serum glucose concentration within hours (<16 hours).

![Table 2-6 A. Body Fuel Reserves in a 70-kg Man](table)

<table>
<thead>
<tr>
<th>Component</th>
<th>Mass (kg)</th>
<th>Energy (kcal)</th>
<th>Days Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water and minerals</td>
<td>49</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Protein</td>
<td>6.0</td>
<td>24,000</td>
<td>13.0</td>
</tr>
<tr>
<td>Glycogen</td>
<td>0.2</td>
<td>800</td>
<td>0.4</td>
</tr>
<tr>
<td>Fat</td>
<td>15.0</td>
<td>140,000</td>
<td>78.0</td>
</tr>
<tr>
<td>Total</td>
<td>70.2</td>
<td>164,800</td>
<td>91.4</td>
</tr>
</tbody>
</table>

![Table 2-6 B. Energy Equivalent of Substrate Oxidation](table)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>O₂ Consumed (L/g)</th>
<th>CO₂ Produced (L/g)</th>
<th>Respiratory Quotient</th>
<th>kcal/g</th>
<th>Recommended Daily Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>0.75</td>
<td>0.75</td>
<td>1.0</td>
<td>4.0</td>
<td>7.2 g/kg per day</td>
</tr>
</tbody>
</table>
During fasting, a healthy 70-kg adult will utilize 180 g of glucose per day to support the metabolism of obligate glycolytic cells such as neurons, leukocytes, erythrocytes, and the renal medullae. Other tissues that use glucose for fuel are skeletal muscle, intestinal mucosa, fetal tissues, and solid tumors.

Glucagon, norepinephrine, vasopressin, and angiotensin II can promote the utilization of glycogen stores (glycogenolysis) during fasting. Although glucagon, epinephrine, and cortisol directly promote gluconeogenesis, epinephrine and cortisol also promote pyruvate shuttling to the liver for gluconeogenesis. Precursors for hepatic gluconeogenesis include lactate, glycerol, and amino acids such as alanine and glutamine. Lactate is released by glycolysis within skeletal muscles, as well as by erythrocytes and leukocytes. The recycling of lactate and pyruvate for gluconeogenesis is commonly referred to as the Cori cycle, which can provide up to 40% of plasma glucose during starvation (Fig. 2-19).

**Fig. 2-19.**

Lactate production from skeletal muscle is insufficient to maintain systemic glucose needs during short-term fasting (simple starvation). Therefore, significant amounts of protein must be degraded daily (75 g/d for a 70-kg adult) to provide the amino acid substrate for hepatic gluconeogenesis. Proteolysis during starvation, which results primarily from decreased insulin and increased cortisol release, is associated with elevated urinary nitrogen excretion from the normal 7 to 10 g per day up to 30 g or more per day. Although proteolysis during starvation occurs mainly within skeletal muscles, protein degradation in solid organs also occurs.

In prolonged starvation, systemic proteolysis is reduced to approximately 20 g/d and urinary nitrogen excretion stabilizes at 2 to 5 g/d (Fig. 2-20). This reduction in proteolysis reflects the adaptation by vital organs (e.g., myocardium, brain, renal cortex, and skeletal muscle) to using ketone bodies as their principal fuel source. In extended fasting, ketone bodies become an important fuel source for the brain after 2 days and gradually become the principal fuel source by 24 days.

**Fig. 2-20.**
Enhanced deamination of amino acids for gluconeogenesis during starvation consequently increases renal excretion of ammonium ions. The kidneys also participate in gluconeogenesis by the use of glutamine and glutamate, and can become the primary source of gluconeogenesis during prolonged starvation, accounting for up to one half of systemic glucose production.

Lipid stores within adipose tissue provide 40% or more of caloric expenditure during starvation. Energy requirements for basal enzymatic and muscular functions (e.g., gluconeogenesis, neural transmission, and cardiac contraction) are met by the mobilization of triglycerides from adipose tissue. In a resting, fasting, 70-kg person, approximately 160 g of free fatty acids and glycerol can be mobilized from adipose tissue per day. Free fatty acid release is stimulated in part by a reduction in serum insulin levels and in part by the increase in circulating glucagon and catecholamine. Such free fatty acids, like ketone bodies, are used as fuel by tissues such as the heart, kidney (renal cortex), muscle, and liver. The mobilization of lipid stores for energy importantly decreases the rate of glycolysis, gluconeogenesis, and proteolysis, as well as the overall glucose requirement to sustain the host. Furthermore, ketone bodies spare glucose utilization by inhibiting the enzyme pyruvate dehydrogenase.

**Metabolism after Injury**

Injuries or infections induce unique neuroendocrine and immunologic responses that differentiate injury metabolism from that of unstressed fasting (Fig. 2-21). The magnitude of metabolic expenditure appears to be directly proportional to the severity of insult, with thermal injuries and severe infections having the highest energy demands (Fig. 2-22). The increase in energy expenditure is mediated in part by sympathetic activation and catecholamine release, which has been replicated by the administration of catecholamines to healthy human subjects. Lipid metabolism after injury is intentionally discussed first, because this macronutrient becomes the primary source of energy during stressed states. 55

**Fig. 2-21.**
Acute injury is associated with significant alterations in substrate utilization. There is enhanced nitrogen loss, indicative of catabolism. Fat remains the primary fuel source under these circumstances. RBC = red blood cell; WBC = white blood cell.

**Fig. 2-22.**

Influence of injury severity on resting metabolism (resting energy expenditure, or REE). The shaded area indicates normal REE.

(Adapted with permission from Long CL 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* 3:452, 1979.)

**LIPID METABOLISM AFTER INJURY**

Lipids are not merely nonprotein, noncarbohydrate fuel sources that minimize protein catabolism in the injured patient. Lipid metabolism potentially influences the structural integrity of cell membranes as well as the immune response during systemic inflammation. Adipose stores within the body (triglycerides) are the predominant energy source (50 to 80%) during critical illness and after injury. Fat mobilization (lipolysis) occurs mainly in response to catecholamine stimulus of the hormone-sensitive triglyceride lipase. Other hormonal influences which potentiate lipolysis include adrenocorticotropic hormone (ACTH), catecholamines, thyroid hormone, cortisol, glucagon, growth hormone release, reduction in insulin levels, and increased sympathetic stimulus. 56

**Lipid Absorption**

Although the process is poorly understood, adipose tissue provides fuel for the host in the form of free fatty acids and glycerol during critical illness and injury. Oxidation of 1 g of fat yields approximately 9 kcal of energy. Although the liver is capable of synthesizing triglycerides from carbohydrates and amino acids, dietary and exogenous sources provide the major source of triglycerides. Dietary lipids are not readily absorbable in the gut but require pancreatic lipase and phospholipase within the duodenum to hydrolyze the triglycerides into free fatty acids and monoglycerides. The free fatty acids and monoglycerides are then readily absorbed by gut enterocytes, which resynthesize triglycerides by esterification of the monoglycerides with fatty acyl coenzyme A (acyl-CoA) (Fig. 2-23). Long-chain triglycerides (LCTs), defined...
as those with 12 carbons or more, generally undergo this process of esterification and enter the circulation through the lymphatic system as chylomicrons. Shorter fatty acid chains directly enter the portal circulation and are transported to the liver by albumin carriers. Hepatocytes use free fatty acids as a fuel source during stress states but also can synthesize phospholipids or triglycerides (i.e., very-low-density lipoproteins) during fed states. Systemic tissue (e.g., muscle and the heart) can use chylomicrons and triglycerides as fuel by hydrolysis with lipoprotein lipase at the luminal surface of capillary endothelium. Trauma or sepsis suppresses lipoprotein lipase activity in both adipose tissue and muscle, presumably mediated by TNF.

Fig. 2-23.

Pancreatic lipase within the small intestinal brush borders hydrolyzes triglycerides into monoglycerides and fatty acids. These components readily diffuse into the gut enterocytes, where they are re-esterified into triglycerides. The resynthesized triglycerides bind carrier proteins to form chylomicrons, which are transported by the lymphatic system. Shorter triglycerides (those with <10 carbon atoms) can bypass this process and directly enter the portal circulation for transport to the liver. CoA = coenzyme A.

Lipolysis and Fatty Acid Oxidation

Periods of energy demand are accompanied by free fatty acid mobilization from adipose stores. This is mediated by hormonal influences (e.g., catecholamines, ACTH, thyroid hormones, growth hormone, and glucagon) on triglyceride lipase through a cAMP pathway (Fig. 2-24). In adipose tissues, triglyceride lipase hydrolyzes triglycerides into free fatty acids and glycerol. Free fatty acids enter the capillary circulation and are transported by albumin to tissues requiring this fuel source (e.g., heart and skeletal muscle). Insulin inhibits lipolysis and favors triglyceride synthesis by augmenting lipoprotein lipase activity as well as intracellular levels of glycerol-3-phosphate. The use of glycerol for fuel depends on the availability of tissue glycerokinase, which is abundant in the liver and kidneys.

Fig. 2-24.
Fat mobilization in adipose tissue. Triglyceride lipase activation by hormonal stimulation of adipose cells occurs through the cyclic adenosine monophosphate (cAMP) pathway. Triglycerides are serially hydrolyzed with resultant free fatty acid (FFA) release at every step. The FFAs diffuse readily into the capillary bed for transport. Tissues with glycerokinase can use glycerol for fuel by forming glycerol-3-phosphate. Glycerol-3-phosphate can esterify with FFAs to form triglycerides or can be used as a precursor for renal and hepatic gluconeogenesis. Skeletal muscle and adipose cells have little glycerokinase and thus do not use glycerol for fuel.

Free fatty acids absorbed by cells conjugate with acyl-CoA within the cytoplasm. The transport of fatty acyl-CoA from the outer mitochondrial membrane across the inner mitochondrial membrane occurs via the carnitine shuttle (Fig. 2-25). Medium-chain triglycerides (MCTs), defined as those 6 to 12 carbons in length, bypass the carnitine shuttle and readily cross the mitochondrial membranes. This accounts in part for the fact that MCTs are more efficiently oxidized than LCTs. Ideally, the rapid oxidation of MCTs makes them less prone to fat deposition, particularly within immune cells and the reticuloendothelial system—a common finding with lipid infusion in parenteral nutrition. However, exclusive use of MCTs as fuel in animal studies has been associated with higher metabolic demands and toxicity, as well as essential fatty acid deficiency.
Free fatty acids (FFAs) in the cells form fatty acyl coenzyme A (CoA) with CoA. Fatty acyl-CoA cannot enter the inner mitochondrial membrane and requires carnitine as a carrier protein (carnitine shuttle). Once inside the mitochondria, carnitine dissociates and fatty acyl-CoA is re-formed. The carnitine molecule is transported back into the cytosol for reuse. The fatty acyl-CoA undergoes beta oxidation to form acetyl-CoA for entry into the tricarboxylic acid cycle. "R" represents a part of the acyl group of acyl-CoA.

Within the mitochondria, fatty acyl-CoA undergoes beta oxidation, which produces acetyl-CoA with each pass through the cycle. Each acetyl-CoA molecule subsequently enters the tricarboxylic acid (TCA) cycle for further oxidation to yield 12 adenosine triphosphate (ATP) molecules, carbon dioxide, and water. Excess acetyl-CoA molecules serve as precursors for ketogenesis. Unlike glucose metabolism, oxidation of fatty acids requires proportionally less oxygen and produces less carbon dioxide. This is frequently quantified as the ratio of carbon dioxide produced to oxygen consumed for the reaction and is known as the respiratory quotient (RQ). An RQ of 0.7 would imply greater fatty acid oxidation for fuel, whereas an RQ of 1 indicates greater carbohydrate oxidation (overfeeding). An RQ of 0.85 suggests the oxidation of equal amounts of fatty acids and glucose.

KETOGENESIS

Carbohydrate depletion slows the entry of acetyl-CoA into the TCA cycle secondary to depleted TCA intermediates and enzyme activity. Increased lipolysis and reduced systemic carbohydrate availability during starvation diverts excess acetyl-CoA toward hepatic ketogenesis. A number of extrahepatic tissues, but not the liver itself, are capable of using ketones for fuel. Ketosis represents a state in which hepatic ketone production exceeds extrahepatic ketone utilization.

The rate of ketogenesis appears to be inversely related to the severity of injury. Major trauma, severe shock, and sepsis attenuate ketogenesis by increasing insulin levels and by causing rapid tissue oxidation of free fatty acids. Minor injuries and infections are associated with modest elevations in plasma free fatty acid concentrations and ketogenesis. However, in minor stress states ketogenesis does not exceed that in nonstressed starvation.

CARBOHYDRATE METABOLISM

Ingested and enteral carbohydrates are primarily digested in the small intestine, where pancreatic and intestinal enzymes reduce the complex carbohydrates to dimeric units. Disaccharidases (e.g., sucrase, lactase, and maltase) within intestinal brush borders dismantle the complex carbohydrates into simple hexose units, which are transported into the intestinal mucosa. Glucose and galactose are primarily absorbed by energy-dependent active transport coupled to the sodium pump. Fructose absorption, however, occurs by concentration-dependent facilitated diffusion. Neither fructose and galactose within the circulation nor exogenous mannitol (for neurologic injury) evokes an insulin response. Intravenous administration of low-dose fructose in fasting humans has been associated with nitrogen conservation, but the clinical utility of fructose administration in human injury remains to be demonstrated.

Discussion of carbohydrate metabolism primarily refers to the utilization of glucose. The oxidation of 1 g of carbohydrate yields 4 kcal, but sugar solutions such as those found in intravenous fluids or parenteral nutrition provide only 3.4 kcal/g of dextrose. In starvation, glucose production occurs at the expense of protein stores (i.e., skeletal muscle). Hence, the primary goal for maintenance glucose administration in surgical patients is to minimize muscle wasting. The exogenous administration of small amounts of glucose (approximately 50 g/d) facilitates fat entry into the TCA cycle and reduces ketosis. Unlike in starvation in healthy subjects, in septic and trauma patients provision of exogenous glucose never has been shown to fully suppress amino acid degradation for gluconeogenesis. This suggests that during periods of stress, other hormonal and proinflammatory mediators have a profound influence on the rate of protein degradation and that some degree of muscle wasting is inevitable. The administration of insulin, however, has been shown to reverse protein catabolism during severe stress by stimulating protein synthesis in skeletal muscles and by inhibiting hepatocyte protein degradation. Insulin also stimulates the incorporation of elemental precursors into nucleic acids in association with RNA synthesis in muscle cells.

In cells, glucose is phosphorylated to form glucose-6-phosphate. Glucose-6-phosphate can be polymerized during glycosynthesis or catabolized in glycogenolysis. Glucose catabolism occurs by cleavage to pyruvate or lactate (pyruvic acid pathway) or by decarboxylation to form acetyl-CoA.
Excess glucose from overfeeding, as reflected by RQs >1.0, can result in conditions such as glucosuria, thermogenesis, and conversion to fat (lipogenesis). Excessive glucose administration results in elevated carbon dioxide production, which may be deleterious in patients with suboptimal pulmonary function, as well as hyperglycemia, which may contribute to infectious risk and immune suppression.

Injury and severe infections acutely induce a state of peripheral glucose intolerance, despite ample insulin production at levels severalfold above baseline. This may occur in part due to reduced skeletal muscle pyruvate dehydrogenase activity after injury, which diminishes the conversion of pyruvate to acetyl-CoA and subsequent entry into the TCA cycle. The three-carbon structures (e.g., pyruvate and lactate) that consequently accumulate are shunted to the liver as substrate for gluconeogenesis. Furthermore, regional tissue catheterization and isotope dilution studies have shown an increase in net splanchnic glucose production by 50 to 60% in septic patients and a 50 to 100% increase in burn patients. The increase in plasma glucose levels is proportional to the severity of injury, and this net hepatic gluconeogenic response is believed to be under the influence of glucagon. Unlike in the nonstressed subject, in the hypermetabolic, critically ill patient the hepatic gluconeogenic response to injury or sepsis cannot be suppressed by exogenous or excess glucose administration but rather persists.

Hepatic gluconeogenesis, arising primarily from alanine and glutamine catabolism, provides a ready fuel source for tissues such as those of the nervous system, wounds, and erythrocytes, which do not require insulin for glucose transport. The elevated glucose concentrations also provide a necessary energy source for leukocytes in inflamed tissues and in sites of microbial invasions.

The shunting of glucose away from nonessential organs such as skeletal muscle and adipose tissues is mediated by catecholamines. Experiments with infusing catecholamines and glucagon in animals have demonstrated increased plasma glucose levels as a result of increased hepatic gluconeogenesis and peripheral insulin resistance. Interestingly, although glucocorticoid infusion alone does not increase glucose levels, it does prolong and augment the hyperglycemic effects of catecholamines and glucagon when glucocorticoid is administered concurrently with the latter.

Glycogen stores within skeletal muscles can be mobilized by epinephrine activation of beta-adenrenergic receptors, GTP-binding proteins (G-proteins), which subsequently activates the second messenger, cAMP. The cAMP activates phosphorylase kinase, which in turn leads to conversion of glycogen to glucose-1-phosphate. Phosphorylase kinase also can be activated by the second messenger, calcium, through the breakdown of phosphatidylinositol phosphate, which is the case in vasopressin-mediated hepatic glycogenolysis.

### Glucose Transport and Signaling

Hydrophobic cell membranes are relatively impermeable to hydrophilic glucose molecules. There are two distinct classes of membrane glucose transporters in human systems. These are the facilitated diffusion glucose transporters (GLUTs) that permit the transport of glucose down a concentration gradient (Table 2-7) and the Na⁺/glucose secondary active transport system (SGLT), which transports glucose molecules against concentration gradients by active transport.

#### Table 2-7 Human Facilitated Diffusion Glucose Transporter (GLUT) Family

<table>
<thead>
<tr>
<th>Type</th>
<th>Amino Acids</th>
<th>Major Expression Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>492</td>
<td>Placenta, brain, kidney, colon</td>
</tr>
</tbody>
</table>
Five functional human GLUTs have been cloned since 1985. GLUT1 is the transporter in human erythrocytes. It is expressed on several other tissues, but little is found in the liver and skeletal muscle. Importantly, it is a constitutive part of the endothelium in the blood-brain barrier. GLUT2 is predominantly expressed in the sinusoidal membranes of liver, renal tubules, enterocytes, and insulin-secreting β-cells of the pancreas. GLUT2 is important for rapid export of glucose resulting from gluconeogenesis. GLUT3 is highly expressed in neuronal tissue of the brain, the kidney, and placenta, but GLUT3 mRNA has been detected in almost every human tissue. GLUT4 is significant to human metabolism because it is the primary glucose transporter of insulin-sensitive tissues, adipose tissue, and skeletal and cardiac muscle. These transporters are usually packaged as intracellular vesicles, but insulin induces rapid translocation of these vesicles to the cell surface. GLUT4 function has important implications in the physiology of patients with insulin-resistant diabetes. GLUT5 has been identified in several tissues but is primarily expressed in the jejunum. Although it possesses some capacity for glucose transport, it is predominantly a fructose transporter.

SGLTs are distinct glucose transport systems found in the intestinal epithelium and in the proximal renal tubules. These systems transport both sodium and glucose intracellularly, and glucose affinity for this transporter increases when sodium ions are attached. SGLT1 is prevalent on brush borders of small intestine enterocytes and primarily mediates the active uptake of luminal glucose. In addition, SGLT1 within the intestinal lumen also enhances gut retention of water through osmotic absorption. SGLT1 and SGLT2 are both associated with glucose reabsorption at proximal renal tubules.

### Protein and Amino Acid Metabolism

The average protein intake in healthy young adults ranges from 80 to 120 g/d, and every 6 g of protein yields approximately 1 g of nitrogen. The degradation of 1 g of protein yields approximately 4 kcal of energy, similar to the yield in carbohydrate metabolism.

After injury the initial systemic proteolysis, mediated primarily by glucocorticoids, increases urinary nitrogen excretion to levels in excess of 30 g/d, which roughly corresponds to a loss in lean body mass of 1.5% per day. An injured individual who does not receive nutrition for 10 days can theoretically lose 15% lean body mass. Therefore, amino acids cannot be considered a long-term fuel reserve, and indeed excessive protein depletion (i.e., 25 to 30% of lean body weight) is not compatible with sustaining life.

Protein catabolism after injury provides substrates for gluconeogenesis and for the synthesis of acute phase proteins. Radiolabeled amino acid incorporation studies and protein analyses confirm that skeletal muscles are preferentially depleted acutely after injury, whereas visceral tissues (e.g., the liver and kidney) remain relatively preserved. The accelerated urea excretion after injury also is associated with the excretion of intracellular elements such as sulfur, phosphorus, potassium, magnesium, and creatinine. Conversely, the rapid utilization of elements such as potassium and magnesium during recovery from major injury may indicate a period of tissue healing.

The net changes in protein catabolism and synthesis correspond to the severity and duration of injury (Fig. 2-27). Elective operations and minor injuries result in lower protein synthesis and moderate protein breakdown. Severe trauma, burns, and sepsis are associated with increased protein catabolism. The rise in urinary nitrogen and negative nitrogen balance can be detected early after injury and peak by 7 days. This state of protein catabolism may persist for as long as 3 to 7 weeks. The patient's prior physical status and age appear to influence the degree of proteolysis after injury or sepsis.

**Fig. 2-27.**

The effect of injury severity on nitrogen wasting.

Activation of the ubiquitin-proteosome system in muscle cells is one of the major pathways for protein degradation during acute injury. This response is accentuated by tissue hypoxia, acidosis, insulin resistance, and elevated glucocorticoid levels.

**NUTRITION IN THE SURGICAL PATIENT**

The goal of nutritional support in the surgical patient is to prevent or reverse the catabolic effects of disease or injury. Although several important biologic parameters have been used to measure the efficacy of nutritional regimens, the ultimate validation for nutritional support in surgical patients should be improvement in clinical outcome and restoration of function.

**Estimation of Energy Requirements**

Overall nutritional assessment is undertaken to determine the severity of nutrient deficiencies or excess and to aid in predicting nutritional requirements. Pertinent information is obtained by determining the presence of weight loss, chronic illnesses, or dietary habits that influence the quantity and quality of food intake. Social habits predisposing to malnutrition and the use of medications that may influence food intake or urination should also be investigated. Physical examination seeks to assess loss of muscle and adipose tissues, organ dysfunction, and subtle changes in skin, hair, or neuromuscular function reflecting frank or impending nutritional deficiency. Anthropometric data (i.e., weight change, skinfold thickness, and arm circumference muscle area) and biochemical determinations (i.e., creatinine excretion, albumin level, prealbumin level, total lymphocyte count, and transferrin level) may be used to substantiate the patient's history and physical findings. It is impracticable to rely on any single or fixed combination of the aforementioned findings to accurately assess nutritional status or morbidity. Appreciation for the stresses and natural history of the disease process, in combination with nutritional assessment, remains the basis for identifying patients in acute or anticipated need of nutritional support.

A fundamental goal of nutritional support is to meet the energy requirements for metabolic processes, core temperature maintenance, and tissue repair. Failure to provide adequate nonprotein energy sources will lead to consumption of lean tissue stores. The requirement for energy may be measured by indirect calorimetry and trends in serum markers (e.g., prealbumin level) and estimated from urinary nitrogen excretion, which is proportional to resting energy expenditure. However, the use of indirect calorimetry, particularly in the critically ill patient, is labor intensive and often leads to overestimation of caloric requirements.

Basal energy expenditure (BEE) may also be estimated using the Harris-Benedict equations:

\[
BEE \text{(men)} = 66.47 + 13.75(W) + 5.0(H) - 6.76(A) \text{ kcal/d}
\]

\[
BEE \text{(women)} = 655.1 + 9.56(W) + 1.85(H) - 4.68(A) \text{ kcal/d}
\]

where \(W\) = weight in kilograms; \(H\) = height in centimeters; and \(A\) = age in years.

These equations, adjusted for the type of surgical stress, are suitable for estimating energy requirements in the majority of hospitalized patients. It has been demonstrated that the provision of 30 kcal/kg per day will adequately meet energy requirements in most postsurgical patients, with a low risk of overfeeding. After trauma or sepsis, energy substrate demands are increased, necessitating greater nonprotein calories beyond calculated energy expenditure (Table 2-8). These additional nonprotein calories provided after injury are usually 1.2 to 2.0 times greater than calculated resting energy expenditure, depending on the type of injury. It is seldom appropriate to exceed this level of nonprotein energy intake during the height of the catabolic phase.

**Table 2-8 Caloric Adjustments above Basal Energy Expenditure (BEE) in Hypermetabolic Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>kcal/kg per Day</th>
<th>Adjustment above BEE</th>
<th>Grams of Protein/kg per Day</th>
<th>Nonprotein Calories: Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/moderate malnutrition</td>
<td>25–30</td>
<td>1.1</td>
<td>1.0</td>
<td>150:1</td>
</tr>
<tr>
<td>Mild stress</td>
<td>25–30</td>
<td>1.2</td>
<td>1.2</td>
<td>150:1</td>
</tr>
<tr>
<td>Moderate stress</td>
<td>30</td>
<td>1.4</td>
<td>1.5</td>
<td>120:1</td>
</tr>
<tr>
<td>Severe stress</td>
<td>30–35</td>
<td>1.6</td>
<td>2.0</td>
<td>90–120:1</td>
</tr>
<tr>
<td>Burns</td>
<td>35–40</td>
<td>2.0</td>
<td>2.5</td>
<td>90–100:1</td>
</tr>
</tbody>
</table>

The second objective of nutritional support is to meet the substrate requirements for protein synthesis. An appropriate nonprotein-calorie:nitrogen ratio of 150:1 (e.g., 1 g N = 6.25 g protein) should be maintained, which is the basal calorie requirement provided to limit the use of protein as an energy source. There is now greater evidence suggesting that increased protein intake, and a lower calorie:nitrogen ratio of 80:1 to 100:1, may benefit healing in selected hypermetabolic or critically ill patients. In the absence of severe renal or hepatic dysfunction precluding the use of standard nutritional regimens, approximately 0.25 to 0.35 g of nitrogen per kilogram of body weight should be provided daily. 64

**Vitamins and Minerals**

The requirements for vitamins and essential trace minerals usually can be met easily in the average patient with uncomplicated postoperative course. Therefore, vitamins usually are not given in the absence of preoperative deficiencies. Patients maintained on elemental diets or parenteral hyperalimentation require complete vitamin and mineral supplementation. Commercial enteral diets contain varying amounts of essential minerals and vitamins. It is necessary to ensure that adequate replacement is available in the diet or by supplementation. Numerous commercial vitamin preparations are available for intravenous or intramuscular use, although most do not contain vitamin K and some do not contain vitamin B12 or folic acid. Supplemental trace minerals may be given intravenously via commercial preparations. Essential fatty acid supplementation also may be necessary, especially in patients with depletion of adipose stores.

**Overfeeding**

Overfeeding usually results from overestimation of caloric needs, as occurs when actual body weight is used to calculate the BEE in postoperative populations such as the critically ill with significant fluid overload and the obese. Indirect calorimetry can be used to quantify energy requirements but frequently overestimates BEE by 10 to 15% in stressed patients, particularly if they are receiving ventilatory support. In these instances, estimated dry weight should be obtained from preinjury records or family members. Adjusted lean body weight also can be
Isotonic formulas with fiber contain soluble and insoluble fiber, which is most often soy based. Physiologically, fiber-based solutions delay intestinal transit time and may reduce the incidence of diarrhea compared with nonfiber solutions. Fiber stimulates pancreatic lipase activity and is degraded by gut bacteria into short-chain fatty acids, an important fuel for colonocytes. There are no contraindications for using fiber-containing formulas in critically ill patients.

**LOW-RESIDUE ISOTONIC FORMULAS**

Most low-residue isotonic formulas provide a caloric density of 1.0 kcal/mL, and approximately 1500 to 1800 mL are required to meet daily requirements. These low-osmolarity compositions provide baseline carbohydrates, protein, electrolytes, water, fat, and fat-soluble vitamins (some do not have vitamin K) and typically have a nonprotein-calorie:nitrogen ratio of 150:1. These contain no fiber bulk and therefore leave minimum residue. These solutions usually are considered to be the standard or first-line formulas for stable patients with an intact gastrointestinal tract.

**ISOTONIC FORMULAS WITH FIBER**

Isotonic formulas with fiber contain soluble and insoluble fiber, which is most often soy based. Physiologically, fiber-based solutions delay intestinal transit time and may reduce the incidence of diarrhea compared with nonfiber solutions. Fiber stimulates pancreatic lipase activity and is degraded by gut bacteria into short-chain fatty acids, an important fuel for colonocytes. There are no contraindications for using fiber-containing formulas in critically ill patients.

**IMMUNE-ENHANCING FORMULAS**

Immune-enhancing formulas are fortified with special nutrients that are purported to enhance various aspects of immune or solid organ function, but low-residue formulations may be preferred. Enteral feeding should also be offered to patients with short-bowel syndrome or clinical support withholding enteric feedings for patients after bowel resection or for those with low-output enterocutaneous fistulas of <500 mL/d, abdominal distention requires cessation of feeding and adjustment of the infusion rate. Concomitant gastric decompression with distal small-setting of gastroparesis feedings should be administered distal to the pylorus. Gastric residuals of 200 mL or more in a 4- to 6-hour period or intestinal permeability studies in well-nourished patients undergoing upper gastrointestinal cancer surgery demonstrated normalization of gastric residuals formula over parenteral nutrition in patients undergoing gastrointestinal surgery have demonstrated reduced infectious complications and acute phase protein production in those fed by the enteral route. Yet prospectively randomized studies of patients with adequate nutritional status (albumin ≥4 g/dL) undergoing gastrointestinal surgery demonstrate no differences in outcome and complications between those administered enteral nutrition and those given maintenance intravenous fluids alone in the initial days after surgery. Furthermore, intestinal permeability studies in well-nourished patients undergoing upper gastrointestinal cancer surgery demonstrated normalization of intestinal permeability and barrier function by the fifth postoperative day. At the other extreme, meta-analysis of studies involving critically ill patients demonstrates a 44% reduction in infectious complications in those receiving enteral nutritional support compared with those receiving parenteral nutrition. Most prospectively randomized studies in patients with severe abdominal and thoracic trauma demonstrate significant reductions in infectious complications in patients given early enteral nutrition compared with those who were unrepaired or received parenteral nutrition. The exception has been in studies of patients with closed-head injury, in which no significant differences in outcome were demonstrated between early jejunal feeding and other nutritional support modalities. Moreover, early gastric feeding after closed-head injury was frequently associated with underfeeding and calorie deficiency due to the difficulties in overcoming gastroparesis and the high risk of aspiration.

The early initiation of enteral feeding in burn patients, while sensible and supported by retrospective analysis, is an empiric practice supported by limited prospective trials. Recommendations for instituting early enteral nutrition in surgical patients with moderate malnutrition (albumin level of 2.9 to 3.5 g/dL) can only be made by inference due to a lack of data directly pertaining to this population. For these patients, it is prudent to offer enteral nutrition based on measured energy expenditure of the recovering patient, or if complications arise that may alter the anticipated course of recovery (e.g., anastomotic leaks, return to surgery, sepsis, or failure to wean from the ventilator). Other clinical scenarios for which the benefits of enteral nutritional support have been substantiated include permanent neurologic impairment, oropharyngeal dysfunction, short-bowel syndrome, and bone marrow transplantation. Collectively, the data support the use of early enteral nutritional support after major trauma and in patients who are anticipated to have prolonged recovery after surgery. Healthy patients without malnutrition undergoing uncomplicated surgery can tolerate 10 days of partial starvation (i.e., maintenance intravenous fluids only) before any clinically significant protein catabolism occurs. Earlier intervention is likely indicated in patients with poorer preoperative nutritional reserves.

Initiation of enteral nutrition should occur immediately after adequate resuscitation, most readily determined by adequate urine output. The presence of bowel sounds and the passage of flatus or stool are not absolute prerequisites for initiation of enteral nutrition, but in the setting of gastroparesis feedings should be administered distal to the pylorus. Gastric residuals of 200 mL or more in a 4- to 6-hour period or abdominal distention requires cessation of feeding and adjustment of the infusion rate. Concomitant gastric decompression with distal small-bowel feedings may be appropriate in certain patients such as closed-head injury patients with gastroparesis. There is no evidence to support withholding enteric feedings for patients after bowel resection or for those with low-output enteroenteral fistulas of <500 mL/d, but low-residue formulations may be preferred. Enteral feeding should also be offered to patients with short-bowel syndrome or clinical malabsorption, but necessary calories, essential minerals, and vitamins should be supplemented using parenteral modalities.

**Enferal Formulas**

The functional status of the gastrointestinal tract determines the type of enteral solutions to be used. Patients with an intact gastrointestinal tract will tolerate complex solutions, but patients who have not been fed via the gastrointestinal tract for prolonged periods are less likely to tolerate complex carbohydrates such as lactose. In patients with malabsorption, such as in inflammatory bowel diseases, absorption may be improved by provision of dipeptidase, tripeptidase, and MCTs. However, MCTs are deficient in essential fatty acids, which necessitates supplementation with some LCTs.

Factors that influence the choice of enteral formula include the extent of organ dysfunction (e.g., renal, pulmonary, hepatic, or gastrointestinal), the nutrients needed to restore optimal function and healing, and the cost of specific products. There are still no conclusive data to recommend one category of product over another, and nutritional support committees typically develop the most cost-efficient enteral formulary for the most commonly encountered disease categories within the institution.

**LOW-RESIDUE ISOTONIC FORMULAS**

Most low-residue isotonic formulas provide a caloric density of 1.0 kcal/mL, and approximately 1500 to 1800 mL are required to meet daily requirements. These low-osmolarity compositions provide baseline carbohydrates, protein, electrolytes, water, fat, and fat-soluble vitamins (some do not have vitamin K) and typically have a nonprotein-calorie:nitrogen ratio of 150:1. These contain no fiber bulk and therefore leave minimum residue. These solutions usually are considered to be the standard or first-line formulas for stable patients with an intact gastrointestinal tract.

**ISOTONIC FORMULAS WITH FIBER**

Isotonic formulas with fiber contain soluble and insoluble fiber, which is most often soy based. Physiologically, fiber-based solutions delay intestinal transit time and may reduce the incidence of diarrhea compared with nonfiber solutions. Fiber stimulates pancreatic lipase activity and is degraded by gut bacteria into short-chain fatty acids, an important fuel for colonocytes. There are no contraindications for using fiber-containing formulas in critically ill patients.

**IMMUNE-ENHANCING FORMULAS**

Immune-enhancing formulas are fortified with special nutrients that are purported to enhance various aspects of immune or solid organ
function. Such additives include glutamine, arginine, branched-chain amino acids, omega-3 fatty acids, nucleotides, and beta carotene. Although several trials have proposed that one or more of these additives reduce surgical complications and improve outcome, these results have not been uniformly corroborated by other trials. The addition of amino acids to these formulas generally doubles the amount of protein (nitrogen) found in standard formula; however, their cost can be prohibitive.

**CALORIE-DENSE FORMULAS**

The primary distinction of calorie-dense formulas is a greater caloric value for the same volume. Most commercial products of this variety provide 1.5 to 2 kcal/mL and therefore are suitable for patients requiring fluid restriction or those unable to tolerate large-volume infusions. As expected, these solutions have higher osmolality than standard formulas and are suitable for intragastric feedings.

**HIGH-PROTEIN FORMULAS**

High-protein formulas are available in isotonic and nonisotonic mixtures and are proposed for critically ill or trauma patients with high protein requirements. These formulas have nonprotein-calorie:nitrogen ratios between 80:1 and 120:1.

**ELEMENTAL FORMULAS**

Elemental formulas contain predigested nutrients and provide proteins in the form of small peptides. Complex carbohydrates are limited, and fat content, in the form of MCTs and LCTs, is minimal. The primary advantage of such a formula is ease of absorption, but the inherent scarcity of fat, associated vitamins, and trace elements limits its long-term use as a primary source of nutrients. Due to its high osmolality, dilution or slow infusion rates usually are necessary, particularly in critically ill patients. These formulas have been used frequently in patients with malabsorption, gut impairment, and pancreatitis, but their cost is significantly higher than that of standard formulas.

**RENAL-FAILURE FORMULAS**

The primary benefits of renal formulas are the lower fluid volume and concentrations of potassium, phosphorus, and magnesium needed to meet daily calorie requirements. This type of formulation almost exclusively contains essential amino acids and has a high nonprotein-calorie:nitrogen ratio; however, it does not contain trace elements or vitamins.

**PULMONARY-FAILURE FORMULAS**

In pulmonary-failure formulas, fat content is usually increased to 50% of the total calories, with a corresponding reduction in carbohydrate content. The goal is to reduce carbon dioxide production and alleviate ventilation burden for failing lungs.

**HEPATIC-FAILURE FORMULAS**

Close to 50% of the proteins in hepatic-failure formulas are branched-chain amino acids (e.g., leucine, isoleucine, and valine). The goal of such a formula is to reduce aromatic amino acid levels and increase the levels of branched-chain amino acids, which can potentially reverse encephalopathy in patients with hepatic failure. The use of these formulas is controversial, however, because no clear benefits have been proven by clinical trials. Protein restriction should be avoided in patients with end-stage liver disease, because such patients have significant protein energy malnutrition that predisposed them to additional morbidity and mortality.

**ACCESS FOR ENTERAL NUTRITIONAL SUPPORT**

The available techniques and repertoire for enteral access have provided multiple options for feeding the gut. Presently used methods and preferred indications are summarized in Table 2-9.

### Table 2-9 Options for Enteral Feeding Access

<table>
<thead>
<tr>
<th>Access Option</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasogastric tube</td>
<td>Short-term use only; aspiration risks; nasopharyngeal trauma; frequent dislodgment</td>
</tr>
<tr>
<td>Nasoduodenal/nasojejunal tube</td>
<td>Short-term use; lower aspiration risks in jejunum; placement challenges (radiographic assistance often necessary)</td>
</tr>
<tr>
<td>Percutaneous endoscopic gastrostomy (PEG)</td>
<td>Endoscopy skills required; may be used for gastric decompression or bolus feeds; aspiration risks; can last 12–24 mo; slightly higher complication rates with placement and site leaks</td>
</tr>
<tr>
<td>Surgical gastrostomy</td>
<td>Requires general anesthesia and small laparotomy; procedure may allow placement of extended duodenal/jejunal feeding ports; laparoscopic placement possible</td>
</tr>
<tr>
<td>Fluoroscopic gastrostomy</td>
<td>Blind placement using needle and T-prongs to anchor to stomach; can thread smaller catheter through gastrostomy into duodenum/jejunum under fluoroscopy</td>
</tr>
<tr>
<td>PEG-jejunal tube</td>
<td>Jejunal placement with regular endoscope is operator dependent; jejunal tube can be dislodged retrograde; two-stage procedure with PEG placement, followed by fluoroscopic conversion with jejunal feeding tube through PEG</td>
</tr>
<tr>
<td>Direct percutaneous endoscopic jejunostomy (DPEJ)</td>
<td>Direct endoscopic tube placement with enteroscope; placement challenges; greater injury risks</td>
</tr>
<tr>
<td>Surgical jejunostomy</td>
<td>Commonly carried out during laparotomy; general anesthesia; laparoscopic placement usually requires assistant to thread catheter; laparoscopy offers direct visualization of catheter placement</td>
</tr>
<tr>
<td>Fluoroscopic jejunostomy</td>
<td>Difficult approach with injury risks; not commonly done</td>
</tr>
</tbody>
</table>

### Nasoenteric Tubes

Nasogastric feeding should be reserved for those with intact mentation and protective laryngeal reflexes to minimize risks of aspiration. Even in intubated patients, nasogastric feedings often can be recovered from tracheal suction. Nasojejunal feedings are associated with fewer pulmonary complications, but access past the pylorus requires greater effort to accomplish. Blind insertion of nasogastric feeding tubes is fraught with misplacement, and air instillation with auscultation is inaccurate for ascertaining proper positioning. Radiographic confirmation is usually required to verify the position of the nasogastric feeding tube.
Several methods have been recommended for the passage of nasoenteric feeding tubes into the small bowel, including use of prokinetic agents, right lateral decubitus positioning, gastric insufflation, tube angulation, and application of clockwise torque. However, the successful placement of feeding tubes by these methods is highly variable and operator dependent. Furthermore, it is time consuming, and success rates for intubation past the duodenum into the jejunum by these methods are <20%. Fluoroscopy-guided intubation past the pylorus has a >90% success rate, and more than half of these intubations result in jejunal placement. Similarly, endoscopy-guided placement past the pylorus has high success rates, but attempts to advance the tube beyond the second portion of the duodenum using a standard gastroduodenoscope is unlikely to be successful.

Small-bowel feeding is more reliable for delivering nutrition than nasogastric feeding. Furthermore, the risks of aspiration pneumonia can be reduced by 25% with small-bowel feeding compared with nasogastric feeding. The disadvantages of the use of nasoenteric feeding tubes are clogging, kinking, and inadvertent displacement or removal of the tube, and nasopharyngeal complications. If nasoenteric feeding will be required for longer than 30 days, access should be converted to a percutaneous one.  

Percutaneous Endoscopic Gastrostomy

The most common indications for percutaneous endoscopic gastrostomy (PEG) include impaired swallowing mechanisms, oropharyngeal or esophageal obstruction, and major facial trauma. It is frequently used for debilitated patients requiring caloric supplementation, hydration, or frequent medication dosing. It is also appropriate for patients requiring passive gastric decompression. Relative contraindications for PEG placement include ascites, coagulopathy, gastric varices, gastric neoplasm, and lack of a suitable abdominal site. Most tubes are 18F to 28F in size and may be used for 12 to 24 months.

Identification of the PEG site requires endoscopic transillumination of the anterior stomach against the abdominal wall. A 14-gauge angiocatheter is passed through the abdominal wall into the fully insufflated stomach. A guidewire is threaded through the angiocatheter, grasped by snare or forceps, and pulled out through the mouth. The tapered end of the PEG tube is secured to the guidewire and is pulled into position out of the abdominal wall. The PEG tube is secured without tension against the abdominal wall, and many have reported using the tube within hours of placement. It has been the practice of some to connect the PEG tube to a drainage bag for passive decompression for 24 hours before use, allowing more time for the stomach to seal against the peritoneum.

If endoscopy is not available or technical obstacles preclude PEG placement, the interventional radiologist can attempt the procedure percutaneously under fluoroscopic guidance by first insufflating the stomach against the abdominal wall with a nasogastric tube. If this also is unsuccessful, surgical gastrostomy tube placement can be considered, particularly with minimally invasive methods. When surgery is contemplated, it may be wise to consider directly accessing the small bowel for nutrition delivery.

Although PEG tubes enhance nutritional delivery, facilitate nursing care, and are superior to nasogastric tubes, serious complications occur in approximately 3% of patients. These complications include wound infection, necrotizing fasciitis, peritonitis, aspiration, leaks, dislodgment, bowel perforation, enteric fistulas, bleeding, and aspiration pneumonia.  

For patients with significant gastroparesis or gastric outlet obstruction, feedings through PEG tubes are hazardous. In such cases, the PEG tube can be used for decompression and allow access for converting the PEG tube to a transpyloric feeding tube.

Percutaneous Endoscopic Gastrostomy-Jejunostomy and Direct Percutaneous Endoscopic Jejunostomy

Although gastric bolus feedings are more physiologic, patients who cannot tolerate gastric feedings or who have significant aspiration risks should be fed directly past the pylorus. In the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) method, a 9F to 12F tube is passed through an existing PEG tube, past the pylorus, and into the duodenum. This can be achieved by endoscopic or fluoroscopic guidance. With weighted catheter tips and guidewires, the tube can be further advanced past the ligament of Treitz. However, the incidence of long-term PEG-J tube malfunction has been reported to be >50% as a result of retrograde tube migration into the stomach, kinking, or clogging.

Direct percutaneous endoscopic jejunojejunoscopy (DPEJ) tube placement uses the same techniques as PEG tube placement but requires an enteroscope or colonoscope to reach the jejunum. DPEJ tube malfunctions are probably less frequent than PEG-J tube malfunctions, and kinking or clogging is usually averted by placement of larger-caliber catheters. The success rate of DPEJ tube placement is variable because of the complexity of endoscopic skills required to locate a suitable jejunal site. In such cases where endoscopic means are not feasible, surgical jejunojejunoscopy is more appropriate, especially when minimally invasive techniques are available.

Surgical Gastrostomy and Jejunostomy

For a patient undergoing complex abdominal or trauma surgery, thought should be given during surgery to the possible routes for subsequent nutritional support, because laparotomy affords direct access to the stomach or small bowel. The only absolute contraindication to feeding jejunostomy is distal intestinal obstruction. Relative contraindications include severe edema of the intestinal wall, radiation enteritis, inflammatory bowel disease, ascites, severe immunodeficiency, and bowel ischemia. Needle-catheter jejunostomies also can be done with a minimal learning curve. The biggest drawback usually is possible clogging and knotting of the 6F catheter.  

Abdominal distention and cramps are common adverse effects of early enteral nutrition. Some have also reported impaired respiratory mechanics as a result of intolerance to enteral feedings. These are mostly correctable by temporarily discontinuing feedings and resuming at a lower infusion rate.

Pneumatosis intestinalis and small-bowel necrosis are infrequent but significant problems in patients receiving jejunal tube feedings. Several contributing factors have been proposed, including the hyperosmolarity of enteral solutions, bacterial overgrowth, fermentation, and accumulation of metabolic breakdown products. The common pathophysiology is believed to be bowel distention and consequent reduction in bowel wall perfusion. Risk factors for these complications include cardiogenic and circulatory shock, vasopressor use, diabetes mellitus, and chronic obstructive pulmonary disease. Therefore, enteral feedings in the critically ill patient should be delayed until adequate resuscitation has been achieved. As alternatives, diluting standard enteral formula, delaying the progression to goal infusion rates, or using monomeric solutions with low osmolality requiring less digestion by the gastrointestinal tract all have been successfully used.

PARENTERAL NUTRITION

Parenteral nutrition is the continuous infusion of a hyperosmolar solution containing carbohydrates, proteins, fat, and other necessary nutrients through an indwelling catheter inserted into the superior vena cava. To obtain the maximum benefit, the calorie:protein ratio must be adequate (at least 100 to 150 kcal/g nitrogen), and both carbohydrates and proteins must be infused simultaneously. When the sources

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of calories and nitrogen are given at different times, there is a significant decrease in nitrogen utilization. These nutrients can be given in quantities considerably greater than the basic caloric and nitrogen requirements, and this method has proved to be highly successful in achieving growth and development, positive nitrogen balance, and weight gain in a variety of clinical situations. Clinical trials and meta-analysis of studies of parenteral feeding in the perioperative period have suggested that preoperative nutritional support may benefit some surgical patients, particularly those with extensive malnutrition. Short-term use of parenteral nutrition in critically ill patients (i.e., duration of <7 days) when enteral nutrition may have been instituted is associated with higher rates of infectious complications. After severe injury, parenteral nutrition is associated with higher rates of infectious risks than is enteral feeding (Table 2-10). Clinical studies have demonstrated that parenteral feeding with complete bowel rest results in augmented stress hormone and inflammatory mediator response to an antigenic challenge. However, parenteral feeding still is associated with fewer infectious complications than no feeding at all. In cancer patients, delivery of parenteral nutrition has not been shown to benefit clinical response, prolong survival, or ameliorate the toxic effects of chemotherapy, and infectious complications are increased.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Blunt Trauma TEN n = 48</th>
<th>Penetrating Trauma TEN n = 38</th>
<th>Total TEN n = 44</th>
<th>TPN n = 84</th>
</tr>
</thead>
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<tr>
<td>Abdominal abscess</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>10</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Total complications</td>
<td>13</td>
<td>22</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>% Complications per patient group</td>
<td>27%</td>
<td>50%</td>
<td>30%</td>
<td>23%</td>
</tr>
</tbody>
</table>

TEN = total enteral nutrition; TPN = total parenteral nutrition.


Rationale for Parenteral Nutrition

The principal indications for parenteral nutrition are malnutrition, sepsis, or surgical or traumatic injury in seriously ill patients for whom use of the gastrointestinal tract for feedings is not possible. In some instances, intravenous nutrition may be used to supplement inadequate oral intake. The safe and successful use of parenteral nutrition requires proper selection of patients with specific nutritional needs, experience with the technique, and an awareness of the associated complications. As with enteral nutrition, the fundamental goals are to provide sufficient calories and nitrogen substrate to promote tissue repair and to maintain the integrity or growth of lean tissue mass. The following are patient groups for whom parenteral nutrition has been used in an effort to achieve these goals:

1. Newborn infants with catastrophic gastrointestinal anomalies, such as tracheoesophageal fistula, gastrochisis, omphalocele, or massive intestinal atresia
2. Infants who fail to thrive due to gastrointestinal insufficiency associated with short-bowel syndrome, malabsorption, enzyme deficiency, meconium ileus, or idiopathic diarrhea
3. Adult patients with short-bowel syndrome secondary to massive small-bowel resection (<100 cm without colon or ileocecal valve, or <50 cm with intact ileocecal valve and colon)
4. Patients with enterocolitis, enterocolitis, enterocolitis, or high-output enterocutaneous fistulas (>500 mL/d)
5. Surgical patients with prolonged paralytic ileus after major operations (>7 to 10 days), multiple injuries, or blunt or open abdominal trauma, or patients with reflex ileus complicating various medical diseases
6. Patients with normal bowel length but with malabsorption secondary to sprue, hypoproteinemia, enzyme or pancreatic insufficiency, regional enteritis, or ulcerative colitis
7. Adult patients with functional gastrointestinal disorders such as esophageal dyskinesia after cerebrovascular accident, idiopathic diarrhea, psychogenic vomiting, or anorexia nervosa
8. Patients with granulomatous colitis, ulcerative colitis, or tuberculous enteritis in which major portions of the absorptive mucosa are diseased
9. Patients with malignancy, with or without cachexia, in whom malnutrition might jeopardize successful use of a therapeutic option
10. Patients in whom attempts to provide adequate calories by enteral tube feedings or high residuals have failed
11. Critically ill patients who are hypermetabolic for >5 days or for whom enteral nutrition is not feasible

Patients in whom hyperalimentation is contraindicated: include the following:

1. Patients for whom a specific goal for patient management is lacking or for whom, instead of extending a meaningful life, inevitable dying would be delayed
2. Patients experiencing hemodynamic instability or severe metabolic derangement (e.g., severe hyperglycemia, azotemia, encephalopathy, hyperosmolality, and fluid-electrolyte disturbances) requiring control or correction before hypertonic intravenous feeding is attempted
3. Patients for whom gastrointestinal tract feeding is feasible; in the vast majority of instances, this is the best route by which to provide nutrition
4. Patients with good nutritional status
5. Infants with <8 cm of small bowel, because virtually all have been unable to adapt sufficiently despite prolonged periods of parenteral nutrition
6. Patients who are irreversibly decerebrate or otherwise dehumanized

**Total Parenteral Nutrition**

TPN, also referred to as central parenteral nutrition, requires access to a large-diameter vein to deliver the entire nutritional requirements of the individual. Dextrose content of the solution is high (15 to 25%), and all other macronutrients and micronutrients are deliverable by this route.

**Peripheral Parenteral Nutrition**

The lower osmolarity of the solution used for peripheral parenteral nutrition (PPN), secondary to reduced levels of dextrose (5 to 10%) and protein (3%), allows its administration via peripheral veins. Some nutrients cannot be supplemented because they cannot be concentrated into small volumes. Therefore, PPN is not appropriate for repleting patients with severe malnutrition. It can be considered if central routes are not available or if supplemental nutritional support is required. Typically, PPN is used for short periods (<2 weeks). Beyond this time, TPN should be instituted.

**Initiation of Parenteral Nutrition**

The basic solution for parenteral nutrition contains a final concentration of 15 to 25% dextrose and 3 to 5% crystalline amino acids. The solutions usually are prepared in sterile conditions in the pharmacy from commercially available kits containing the component solutions and transfer apparatus. Preparation in the pharmacy under laminar flow hoods reduces the incidence of bacterial contamination of the solution. Proper preparation with suitable quality control is absolutely essential to avoid septic complications.

The proper provision of electrolytes and amino acids must take into account routes of fluid and electrolyte loss, renal function, metabolic rate, cardiac function, and the underlying disease state.

Intravenous vitamin preparations also should be added to parenteral formulas. Vitamin deficiencies are rare occurrences if such preparations are used. In addition, because vitamin K is not part of any commercially prepared vitamin solution, it should be supplemented on a weekly basis. During prolonged parenteral nutrition with fat-free solutions, essential fatty acid deficiency may become clinically apparent and manifests as dry, scaly dermatitis and loss of hair. The syndrome may be prevented by periodic infusion of a fat emulsion at a rate equivalent to 10 to 15% of total calories. Essential trace minerals may be required after prolonged TPN and may be supplied by direct addition of commercial preparations. The most frequent presentation of trace mineral deficiencies is the eczematoid rash developing both diffusely and at intertriginous areas in zinc-deficient patients. Other rare trace mineral deficiencies include a microcytic anemia associated with copper deficiency, and glucose intolerance presumably related to chromium deficiency. The latter complications are seldom seen except in patients receiving parenteral nutrition for extended periods. The daily administration of commercially available trace mineral supplements will obviate most such problems.

Depending on fluid and nitrogen tolerance, parenteral nutrition solutions generally can be increased over 2 to 3 days to achieve the desired infusion rate. Insulin may be supplemented as necessary to ensure glucose tolerance. Administration of additional intravenous fluids and electrolytes may occasionally be necessary in patients with persistently high fluid losses. The patient should be carefully monitored for development of electrolyte, volume, acid-base, and septic complications. Vital signs and urinary output should be measured regularly, and the patient should be weighed regularly. Frequent adjustments of the volume and composition of the solutions are necessary during the course of therapy. Samples for measurement of electrolytes are drawn daily until levels are stable and every 2 or 3 days thereafter. Blood counts, blood urea nitrogen level, levels of liver function indicators, and phosphate and magnesium levels are determined at least weekly.

The urine or capillary blood glucose level is checked every 6 hours and serum glucose concentration is checked at least once daily during the first few days of the infusion and at frequent intervals thereafter. Relative glucose intolerance, which often manifests as glycosuria, may occur after initiation of parenteral nutrition. If blood glucose levels remain elevated or glycosuria persists, the dextrose concentration may be decreased, the infusion rate slowed, or regular insulin added to each bottle. The rise in blood glucose concentration observed after initiating parenteral nutrition may be temporary, as the normal pancreas increases its output of insulin in response to the continuous carbohydrate infusion. In patients with diabetes mellitus, additional insulin may be required.

Potassium is essential to achieve positive nitrogen balance and replace depleted intracellular stores. In addition, a significant shift of potassium ion from the extracellular to the intracellular space may take place because of the large glucose infusion, with resultant hypokalemia, metabolic alkalosis, and poor glucose utilization. In some cases as much as 240 mEq of potassium ion daily may be required. Hypokalemia may cause glycosuria, which would be treated with potassium, not insulin. Thus, before giving insulin, the serum potassium level must be checked to avoid exacerbating the hypokalemia.

Patients with insulin-dependent diabetes mellitus may exhibit wide fluctuations in blood glucose levels while receiving parenteral nutrition. This may require protocol-driven intravenous insulin therapy. In addition, partial replacement of dextrose calories with lipid emulsions may alleviate these problems in selected patients.

Lipid emulsions derived from soybean or safflower oils are widely used as an adjunctive nutrient to prevent the development of essential fatty acid deficiency. There is no evidence of enhanced metabolic benefit when >10 to 15% of calories are provided as lipid emulsions. Although the administration of 500 mL of 20% fat emulsion one to three times a week is sufficient to prevent essential fatty acid deficiency, it is common to provide fat emulsions on a daily basis to provide additional calories. The triple mix of carbohydrate, fat, and amino acids is infused at a constant rate during a 24-hour period. The theoretical advantages of a constant fat infusion rate include increased efficiency of lipid utilization and reduction in the impairment of reticuloendothelial function normally identified with bolus lipid infusions. The addition of lipids to an infusion bag may alter the stability of some micronutrients in a dextrose–amino acid preparation.

**INTRAVENOUS ACCESS METHODS**

Temporary or short-term access can be achieved with a 16-gauge percutaneous catheter inserted into a subclavian or internal jugular vein and threaded into the superior vena cava. More permanent access with the intention of providing long-term or home parenteral nutrition can be achieved by placement of a catheter with a subcutaneous port for access by tunneling a catheter with a substantial subcutaneous length or threading a long catheter through the basilic or cephalic vein into the superior vena cava.
COMPLICATIONS OF PARENTERAL NUTRITION

Technical Complications

One of the more common and serious complications associated with long-term parenteral feeding is sepsis secondary to contamination of the central venous catheter. Contamination of solutions should be considered, but is rare when proper pharmacy protocols have been followed. This problem occurs more frequently in patients with systemic sepsis and in many cases is due to hematogenous seeding of the catheter with bacteria. One of the earliest signs of systemic sepsis may be the sudden development of glucose intolerance (with or without temperature increase) in a patient who previously has been maintained on parenteral alimentation without difficulty. When this occurs, or if high fever (>38.5°C [101.3°F]) develops without obvious cause, a diligent search for a potential septic focus is indicated. Other causes of fever should also be investigated. If fever persists, the infusion catheter should be removed and submitted for culture. If the catheter is the cause of the fever, removal of the infectious source is usually followed by rapid defervescence. Some centers are now replacing catheters considered at low risk for infection over a guidewire. Should evidence of infection persist over 24 to 48 hours without a definable source, the catheter should be replaced into the opposite subclavian vein or into one of the internal jugular veins and the infusion restarted. It is prudent to delay reintervening the catheter by 12 to 24 hours, especially if bacteremia is present.

Other complications related to catheter placement include the development of pneumothorax, hemothorax, hydrothorax, subclavian artery injury, thoracic duct injury, cardiac arrhythmia, air embolism, catheter embolism, and cardiac perforation with tamponade. All of these complications may be avoided by strict adherence to proper techniques.

The use of multilumen catheters may be associated with a slightly increased risk of infection. This is most likely associated with greater catheter manipulation and intensive use. The rate of catheter infection is highest for those placed in the femoral vein, lower for those in the jugular vein, and lowest for those in the subclavian vein. When catheters are indwelling for <3 days, infection risks are negligible. If indwelling time is 3 to 7 days, the infection risk is 3 to 5%. Indwelling times of >7 days are associated with a catheter infection risk of 5 to 10%. Strict adherence to barrier precautions also reduces the rate of infection.

Metabolic Complications

Hyperglycemia may develop with normal rates of infusion in patients with impaired glucose tolerance or in any patient if the hypertonic solutions are administered too rapidly. This is a particularly common complication in patients with latent diabetes and in patients subjected to severe surgical stress or trauma. Treatment of the condition consists of volume replacement with correction of electrolyte abnormalities and the administration of insulin. This complication can be avoided with careful attention to daily fluid balance and frequent monitoring of blood glucose levels and serum electrolytes.

Increasing experience has emphasized the importance of not overfeeding the parenterally nourished patient. This is particularly true for the depleted patient in whom excess calorie infusion may result in carbon dioxide retention and respiratory insufficiency. In addition, excess feeding also has been related to the development of hepatic steatosis or marked glycogen deposition in selected patients. Cholestasis and formation of gallstones are common in patients receiving long-term parenteral nutrition. Mild but transient abnormalities of serum transaminase, alkaline phosphatase, and bilirubin levels occur in many parenterally nourished patients. Failure of the liver enzymes to plateau or return to normal over 7 to 14 days should suggest another etiology.

Intestinal Atrophy

Lack of intestinal stimulation is associated with intestinal mucosal atrophy, diminished villous height, bacterial overgrowth, reduced lymphoid tissue size, reduced immunoglobulin A production, and impaired gut immunity. The full clinical implications of these changes are not well realized, although bacterial translocation has been demonstrated in animal models. The most efficacious method to prevent these changes is to provide at least some nutrients enterally. In patients requiring TPN, it may be feasible to infuse small amounts of feedings via the gastrointestinal tract.

SPECIAL FORMULATIONS

Glutamine and Arginine

Glutamine is the most abundant amino acid in the human body, comprising nearly two thirds of the free intracellular amino acid pool. Of this, 75% is found within the skeletal muscles. In healthy individuals, glutamine is considered a nonessential amino acid, because it is synthesized within the skeletal muscles and the lungs. Glutamine is a necessary substrate for nucleotide synthesis in most dividing cells and hence provides a major fuel source for enterocytes. It also serves as an important fuel source for immunocytes such as lymphocytes and macrophages, and is a precursor for glutathione, a major intracellular antioxidant. During stress states such as sepsis, or in tumor-bearing hosts, peripheral glutamine stores are rapidly depleted, and the amino acid is preferentially shunted as a fuel source toward the visceral organs and tumors, respectively. These situations create, at least experimentally, a glutamine-depleted environment, with consequences including enterocyte and immunocyte starvation.

Glutamine metabolism during stress in humans, however, may be more complex than is indicated in previously reported animal data. Advanced methods of detecting glutamine traffic in patients with gastrointestinal cancer have not demonstrated more sequestration of glutamine in tumors than in normal intestine. There are data demonstrating decreased dependency on TPN in severe cases of short-bowel syndrome when glutamine therapy with modified diets and growth hormones are used. However, in patients with milder forms of short-bowel syndrome and better nutritional status, glutamine supplementation did not lead to appreciable enhancement in intestinal absorption. Although it is hypothesized that provision of glutamine may preserve immune cell and enterocyte function and enhance nitrogen balance during injury or sepsis, the clinical evidence in support of these phenomena in human subjects remains inconclusive.

Arginine, also a nonessential amino acid in healthy subjects, first attracted attention for its immunoenhancing properties, wound-healing benefits, and association with improved survival in animal models of sepsis and injury. As with glutamine, the benefits of experimental arginine supplementation during stress states are diverse. In clinical studies involving critically ill and injured patients and patients who have undergone surgery for certain malignancies, enteral administration of arginine has led to net nitrogen retention and protein synthesis, whereas isonitrogenous diets have not. Some of these studies also provide in vitro evidence of enhanced immunocyte function. The clinical utility of arginine supplementation in improving overall patient outcome remains an area of investigation.

Omega-3 Fatty Acids
The provision of omega-3 polyunsaturated fatty acids (canola oil or fish oil) displaces omega-6 fatty acids in cell membranes, which theoretically reduces the proinflammatory response from prostaglandin production.  

**Nucleotides**

RNA supplementation in solutions is purported, at least experimentally, to increase cell proliferation, provide building blocks for DNA synthesis, and improve helper T cell function.

**NUTRITION-INDUCED INFLAMMATORY MODULATION**

Studies have demonstrated that the mode of nutritional supplementation, either enteral or parenteral, may influence stress-induced inflammatory responses. Intravenously fed subjects demonstrate a heightened response to proinflammatory stimuli such as endotoxin. Enteral feedings have been regarded as the feeding mode of choice when possible, and although advantages have been suggested, including improved GI barrier function, the mechanisms through which enteral feedings mediate efficacious effects have yet to be fully determined.

Providing further insight into the benefit of enteral feedings, Luyer and colleagues have demonstrated that enteral fat maintains both afferent and efferent vagal pathway signaling via intestinal cholecystokinin receptor activation. They observed that consumption of a high-density fat meal before stress induced by hemorrhage resulted in reduced systemic inflammation and improved outcome.  

Thus, enteral nutrients may act as agonists for endogenous neuroendocrine anti-inflammatory pathways (Fig. 2-28).

**Fig. 2-28.**

![Diagram](https://accessmedicine.com/popup.aspx?aID=40/43)

Vagal afferent system senses peripheral inflammatory focus and also responses to intestinal luminal substrates, in this case enteral lipid signaling via cholecystokinin receptors (CCK-r). Efferent vagal signals limit proinflammatory cytokine production via activation of cholinergic nicotinic receptors on visceral immune cells. Clinical conditions that disrupt the integrity of this circuit may enhance inflammatory responses. Ach = acetylcholine; CCK = cholecystokinin; IL-6 = interleukin-6; TLR = toll-like receptor; TNF = tumor necrosis factor.


**REFERENCES**

Entries Highlighted in Bright Blue Are Key References.


