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Implications of Immune Function to Anesthesia Care

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Multiple aspects of perianesthesia care and the perioperative environment can influence the functions of the immune system. This course reviews basic immune system functions and potential sources of immune system–altering perioperative stress. The effects of commonly used anesthesia drugs, opioids, and adjunct drugs on immune function are discussed. Patient populations at risk for increased morbidity due to perioperative immune depression are identified, along with patient-specific measures nurse anesthetists can take to reduce postoperative immune dysfunction.

Keywords: *Drug-induced immunosuppression, immune system, opioids, pain, perioperative metabolic stress response.*

Objectives

At the completion of this course, the reader should be able to:

1. Discuss basic immune function as it relates to perianesthesia care.
2. Describe potential sources of perioperative immune stress.
3. Discuss the effect of perianesthesia drug therapy on immune function.
4. List patient-specific and procedure-specific measures anesthesia providers may take to support postoperative immune function.
5. Identify patient populations at risk for serious immune suppression in the perioperative period.

The purpose of this course is to examine the influence of perianesthesia care on postoperative immune function. With so many other priorities competing for the anesthesia practitioner's attention—airway, blood pressure, cardiac status, pain—it is tempting to ask whether immune function should even be considered in the patient's plan of anesthesia care. However, immune dysfunction can contribute to increased risk of perioperative complications such as infection, poor transplant graft survival, and recurrence of neoplasms. Thus, this course reviews basic immune physiology, effects of surgical stress and anesthesia drugs on immune function, and implications for anesthesia care.

Innate Immune Function

The innate subdivision of the immune system is the most primitive. An important component consists of anatomic barriers such as intact skin and mucous membranes.[1] Perianesthesia procedures such as central line insertion, intubation, and surgical incision breach these barriers. The most important cells of the innate immune system are the neutrophils (polymorphonuclear cells), macrophages (transformed monocyte cells located in tissues), and lymphocytes known as natural killer cells.[1] These cells roam in all body tissues and are able to identify microbes via recognition signals of patterns of surface molecules indigenous to microorganisms. Invading microbes are identified and attacked by the release of toxic molecules or by phagocytosis and destruction following ingestion.

Innate cells initiate the process of inflammation following infection or tissue damage.[2] Inflammatory mediator molecules such as histamine are released that produce local vasodilation and increased blood flow, accompanied by increased capillary permeability. Circulating complement protein molecules are also activated and turn into complexes that enhance inflammation

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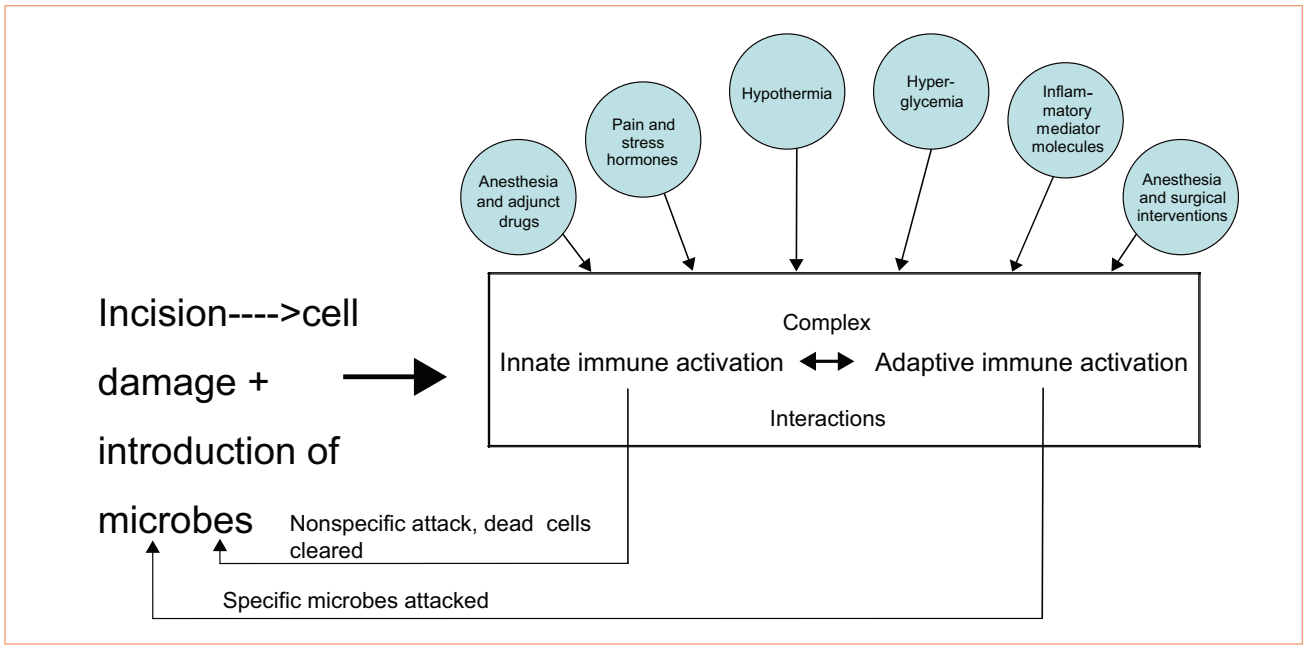

Figure. Effects of Perianesthesia Care on the Immune System

and, along with the mediator molecules released by the innate cells, act as chemoattractants, drawing more immune cells into the area. The outcome of inflammation is the destruction of invading microbes, clearance of damaged tissues, and activation of the adaptive immune system.[2] Surgical incision produces an inflammatory response proportional to the size and invasiveness of the surgical procedure.[3] An unfortunate side effect of inflammation is increased pain secondary to up-regulation of nociceptor fibers on exposure to mediator molecules such as prostaglandins.[4]

Adaptive Immune Function

The response of the adaptive division of lymphocyte immune cells is characterized by delay—lymphocytes must be activated in a days-long process before they can respond; specificity—cells and antibodies are generated targeted to unique proteins found on an invading microbe; and memory—dormant cells are generated that can quickly mount a defense against the invader on reexposure.[1] Each CD4 "helper" lymphocyte (T-helper or Th) carries T-cell receptors that respond to a single antigen microbial protein component; on exposure, the CD4 cells begin secreting activator "helper" molecules that can further enhance macrophage function and activate the CD8 (cellular immunity) and B-lymphocyte cells (humoral immunity).[2] CD8 lymphocytes ("cytotoxic" cells, cellular adaptive response) seek out and destroy body cells infected with the microbe specific to its T-cell receptor. These cells are the body's primary defense against intracellular invaders such as viruses and some bacteria.[1] B lymphocytes, when activated by the antigen specific to the B-cell receptor and molecules from Th cells, begin the process of secreting their receptors into the plasma as soluble antibodies (humoral adaptive response) that attack invading microbes.

To "turn on" the adaptive response, specialized antigen-presenting and innate macrophage cells present in tissues migrate to regional lymph nodes, therein displaying antigens bonded to major histocompatibility complex class I or class II surface molecules for recognition by antigenically specific lymphocyte T-cell receptors.[1] In the specialized environment of the lymph node, the interactions of these cells result in the clonal expansion of lymphocyte populations and antibodies, generated to attack and destroy invading microbes.[2]

In summary, the physiologic objective of the integrated innate and adaptive immune response is to detect and prevent infection and clear damaged cells (Figure). There is a complex and partially reciprocal relationship between these arms of the immune system: the first-line innate immune system response is necessary to activate the adaptive immune cells, yet produces inflammatory mediator molecules that restrain lymphocyte function.[5] Activated Th lymphocytes produce cytokines that enhance macrophage and neutrophil function.[1] The complex biological signaling pathways orchestrating this coordinated and balanced response can be enhanced, decreased, or completely obliterated by the neurohormonal responses to surgery and the perianesthesia milieu and the effects of anesthetic drugs discussed subsequently.

Perianesthesia Stressors

• *Stress Response to Surgical Intervention.* The perianesthesia period is associated with multiple events (Figure) that can induce a neurohormonal stress response, includ-

Drug	Reported Effects
All inhaled anesthetics	Macrophage exposure decreases mediator molecule release[13]
Sevoflurane, isoflurane	Transcription factors blocked in T lymphocytes, cell death (apoptosis) is induced[13,14]
Thiopental, etomidate, ketamine	Lymphocyte functions suppressed[15,16]
Propofol	Less suppressive in 2 studies[17,18]; other investigations found immune cell impairment on exposure[19]
Amide local anesthetics	Inflammation reduced; may favor adaptive immunity[13]
Opioids	Direct, μ-opioid-receptor–mediated depression of immune cell function; indirect support of adaptive immune function through decreasing stress hormone release; potential anti-inflammatory effects[11-13]

Table 1. Effect of Anesthetic Drugs and Opioids on Immune Cell Function

ing the psychological impact of fear and anxiety and the pain of surgical incision and intervention. These stimuli activate the hypothalamus and sympathetic nervous system, resulting in elevated plasma levels of cortisol and catecholamine molecules.[6] Cortisol molecules enter immune cells by passing through the lipoprotein cell membrane. Cortisol then combines with specific receptor molecules in the cytosol; the resulting biochemical signaling cascade depresses cellular functions and numbers of innate and adaptive immune cells, inducing a global immune suppression.[2] This rise in cortisol may be viewed as a negative feedback mechanism geared to control the strong innate immune system activation and concurrent inflammation (see "Inflammatory Response to Surgery"). Catecholamine molecules exert bidirectional but ultimately depressant immune effects via interactions with α and β receptors on the cell surface and through mediating a shift to T-helper cell subtypes less likely to generate an effective cellular immune response.[7,8] Thus, there is initial adrenergic receptor–mediated activation of innate natural killer cell numbers and cytotoxicity, in accordance with increased circulating numbers of lymphocytes (adaptive immune system).[7] However, as the length of stress exposure increases, immune cell function and numbers decrease accordingly.

• *Hyperglycemia.* The elevated concentrations of cortisol and catecholamines engendered by the perioperative stress response result in a catabolic state in which body protein, fat, and starch molecules are metabolized to glucose molecules, resulting in hyperglycemia, the magnitude of which is related to the invasiveness of the surgical intervention.[6] Chronic activation of endothelial cells lining the microvasculature by glucose molecules decreases crucial control of lymphocyte trafficking, impeding the effective movement of immune cells to areas of infection or inflammation.[9] The proliferation of immune cells is impaired by glucose-related alterations in critical enzyme functions.

• *Hypothermia and Altered Tissue Perfusion and Oxygenation.* Large, invasive surgery on major body organs or over large areas is associated with decreased core body temperature, fluid shifts, and altered vascular perfusion pressures that can jeopardize tissue oxygenation.[10] Even mild perioperative hypothermia may trigger thermoregulatory vasoconstriction, with resultant decreases in subcutaneous tissue oxygen partial pressure. Compensatory vasoconstriction during periods of rapid blood loss or hypovolemia exerts a similar effect. Tissue hypoxia impairs oxidative killing by neutrophils[2,10] and can reduce the deposition of collagen, prolonging wound healing. Furthermore, exposure of immune cells to hypothermic conditions directly impairs cellular functions.

• *Inflammatory Response to Surgery.* Tissue damage from the surgical intervention provokes a localized inflammatory response from the innate immune cells resident in the tissues as discussed. Proinflammatory biochemical pathways activated by cell damage produce prostanoid molecules via cyclooxygenase enzymes such as prostaglandin E_2, a direct depressant of lymphocyte (adaptive immune cell) function.[3] Cytokine mediator molecules such as interleukin-6 (IL-6) are produced and interact with liver hepatocytes to bring about the acute phase or systemic inflammatory response, in which proteins such as C-reactive protein are produced to fulfill a role in identification of microbial cells for phagocytosis. Proinflammatory cytokine molecules such as interleukin-1 may depress lymphocyte function, whereas IL-6 interacts with the central nervous system, causing fever and enhancing the neurohormonal stress response.[3] Indeed, IL-6 plasma levels have been identified as a marker of surgical invasiveness and the accompanying inflammatory reaction and as a predictor for survival following major surgery. In summary, surgical intervention produces inflammation related to surgical invasiveness; the subsequent depression of the adaptive immune response is directly proportional to the magnitude of the innate immune system activation.[3]

Anesthetic Agents and Immune Function

Numerous studies using clinical and in vitro techniques have examined the effects of inhaled and intravenous anesthetic agents on the function of immune cells (Table 1).[11-19] The resulting data reveal multiple and often conflicting effects on immune cells; however, the preponder-

ance of findings suggest that in most circumstances, volatile and intravenous anesthetics depress immune cell functions.

In attempting to understand the immune system effects of anesthesia-related drugs during surgery, it is important to consider the context of the evidence. Procopio et al[20] exposed healthy volunteers to mask thiopental-isoflurane-nitrous oxide general anesthesia and then to lidocaine lumbar epidural anesthesia in the absence of surgery, and the immune function of sampled ex vivo cells from these volunteers was unaffected. Clearly, the interaction among the stressors of surgery, the perianesthesia environment, and drugs of anesthesia is necessary to account for postoperative immune modulation. And in considering the extremely complex milieu of a surgical patient under anesthesia, the net immune effect of these drugs may not be deleterious, as it will be determined not just by the drug's propensity to directly depress immune cell function but also by its efficacy in suppressing various aspects of the stress response to the surgical intervention.

Opioids, Pain, and Immune Function

Opioid use is ubiquitous in anesthesia practice, as these drugs are most effective and essential in the treatment of acute surgical pain and are used as an important component of chronic pain management. For these reasons and because of their complex effects on perioperative immune function, extra space is devoted to presenting relevant evidence. Although nurse anesthetists focus on the important analgesic effects of opioids, review of the relevant literature reveals multiple and often conflicting reports of opioid effects on immune system functions (see Table 1).

Of great concern when using opioids to manage perioperative pain is evidence that opioid analgesics are immune suppressive. Animal studies have shown the prototypical opioid morphine to suppress natural killer cell activity, mitogen-induced lymphocyte proliferation, and inflammatory cytokine production.[21] Other drugs with mu-opioid receptor agonist effects, including buprenorphine and fentanyl also depress immune function in a naltrexone-reversible manner.[22] In contrast with these findings, a preclinical study found immune suppression associated with fentanyl was limited to the first 72 postoperative hours and was nonexistent for buprenorphine.[23] Interestingly, in postoperative animals, the immune suppression associated with surgery was ameliorated with morphine administration, while buprenorphine restored immune parameters to normal levels.[11] By using a well-demonstrated animal model of postoperative pain and tumor metastasis, researchers have shown that animals treated with fentanyl or intrathecal morphine/bupivacaine have a significantly lower tumor burden than animals without postoperative analgesia.[24] It is important to note that the fentanyl-associated immune cell depression seen in control animals was absent in the postoperative group. In contrast with the effects of morphine and fentanyl, tramadol—a novel opioid analgesic with inhibitory effects on norepinephrine and serotonin uptake—has been found to have no depressant effects on immune parameters in a study of postoperative pain treatment in patients with cancer.[25]

A discussion of receptor interactions is germane to understanding complex opioid effects. Most commonly used opioids exert their agonist effects at the mu opioid receptors (MORs) located on central and peripheral afferent sensory nerve pathways, resulting in analgesia.[26] However, MORs located in cardiac and other autonomic neural circuits activate parasympathetic (vagal) autonomic pathways, concurrently decreasing sympathetic outflow[12] with potential effects on immune function. Vagal activation causes release of acetylcholine molecules that restrain innate immune cell–driven inflammation, thus indirectly supporting adaptive immune cell function.[27] The reduction in pain-related neural signals accompanying opioid administration may reduce hypothalamic stress axis and sympathetic outflow, thus reducing circulating catecholamine and cortisol molecules.

In summary, the effects of opioid drugs in the complex milieu of anesthetized patients undergoing surgery are unclear and still under investigation. Clearly, exposure of immune cells to stress hormone molecules results in depressed function. Although the direct effect of immune cell MOR stimulation by opioid molecules in the absence of pain may be depressive, multiple studies of animals subjected to surgery have shown a lack of immune depression postoperatively or decreased tumor metastasis when opioid analgesia is used. Effective postoperative pain control is essential in anesthesia practice, and by limiting pain and sympathetic nervous system activation, opioid-induced analgesia likely serves to return the recovering host to a situation of autonomic balance and restoration of immune protection.

Clinical Implications: Immune Function and Perianesthesia Care

Thus far, this article has discussed the interactions of the perianesthesia environment, surgical intervention, and anesthetic drugs as these may affect immune function. Practitioners need also to consider the patient's medical history and status, age, and medication therapy. To guide anesthesia care that is supportive of immune function, all of these factors are brought together in the following list of clinical recommendations for the anesthesia care plan.

1. Take measures to reduce the metabolic stress response to surgery when possible, especially in patients with conditions associated with preexisting immune system alterations[28] such as extremes of age, inadequate nutritional status, cancer, diabetes mellitus, preoperative

Drug	Reported Effects
Erythromycin	Modulation of neutrophil function[33]
Proton pump inhibitors	Reduced bactericidal activity of neutrophils[34]
Adrenergic drugs	Mimic biphasic (activating, then suppressing) effects of catecholamine stress hormones[7,8,35]
Anticholinesterase drugs	Vagal activation may be anti-inflammatory[27]
Dexamethasone	Suppresses all immune cell function; brief nonsignificant effects with single dose for nausea prevention[32]
Cyclosporine, azathioprine	Suppresses all immune cell function; used to prevent allograft rejection[12]

Table 2. Supportive and/or Adjunct Drugs Commonly Used in Anesthesia Perioperative Care With Immunosuppressive Effects

sepsis or infection, human immunodeficiency virus disease, and iatrogenically induced immune depression associated with organ transplantation. Patients with these conditions are at increased risk of immune-deficiency–related increased postoperative morbidity, including infection and neoplasm.

The fear and anxiety accompanying the experience of surgery are well known. Preoperative emotional support and adequate sedation can ameliorate psychogenic sources of stress and reduce the influence of this activating afferent stimulus on the hypothalamic and sympathetic stress axes.[29]

Pain should be prevented when possible through the use of regional anesthesia and analgesia. Studies have demonstrated that regional anesthetics can abrogate the perioperative stress response for lower body surgeries with potential immune-sparing effects; the metabolic stress response to thoracoabdominal surgery is not as effectively blocked by regional anesthesia.[30] Neuraxial and systemic opioids should be administered in sufficient quantity to effectively treat pain. As previously discussed, although opioid molecules may exert a direct depressant effect on immune cells mediated through surface MORs, the indirect effects of blocking pain-driven stress hormone production may well serve to preserve immune function. Consider the use of drugs that limit inflammation, such as cyclooxygenase inhibitors for pain[31] and dexamethasone for nausea.[32] Although dexamethasone (Table 2)[7,8,12,27,33-35] may directly depress lymphocyte function in the doses used to treat perioperative nausea, no postoperative sequelae have been identified, and by limiting inflammation-associated production of prostaglandin E_2, the drug may indirectly support lymphocyte function.

2. Avoid hyperglycemia in patient populations at increased risk for immune suppression undergoing major surgery. Insulin therapy, guided by frequent blood glucose determination, should be considered when indicated.

3. Assess and prevent hypothermia by frequent core body temperature determinations, warming intravenous fluids, and using warm air circulation devices intraoperatively and postoperatively.

4. Ensure adequate tissue perfusion to ensure adequate oxygen and nutrient delivery to circulating immune cells. Maintain the mean arterial pressure at a level judged adequate based on the patient's history and status. Keep the fraction of inspired oxygen at a level adequate to maintain arterial P_{O_2} values within normal range to ensure adequate plasma partial pressure, driving delivery of oxygen molecules to immune cells via diffusion mechanisms.

5. Urge the surgical team to consider minimally invasive surgical approaches when appropriate and reasonable. Studies have consistently demonstrated that laparoscopic approaches result in limited inflammatory responses to surgical intervention, thus reducing the negative effects of excessive concentrations of prostaglandin and proinflammatory cytokine molecules on adaptive immune cell function.[3]

6. Administer antibiotic drugs in a timely manner before surgical incision or as previously scheduled. Take note of adjunctive or supportive nonanesthetic drugs with potential immunosuppressive effects administered during perioperative care (see Table 2), and choose less harmful alternatives when possible.

7. Limit invasive instrumentation as much as possible to prevent microbial colonization. Incorporate strict aseptic and reverse isolation techniques into the anesthesia care plan for populations at risk for immune suppression, such as organ transplant recipients and immune-depressed patients.

8. Unless clearly indicated clinically, avoid blood transfusion in populations at risk for immune suppression. Recipient leukocyte immune reaction to alloantigens on donor white blood cells in the transfused product can induce a variety of syndromes, including autoimmune reactions and immune depression.[36] Vulnerable patients may thus be predisposed to serious morbidity.

Conclusion

Transient depression of adaptive immune cell function is commonly observed in the perioperative period, proportional to the invasiveness of the surgical procedure. Although most likely not a significant source of compli-

cations in healthy populations, this phenomenon may contribute to the significant risk of morbidity and mortality in high-risk populations undergoing major surgery. Multiple risk factors for immune suppression discussed in this course can be modified by anesthesia providers by following the measures discussed herein, ensuring the best chance of successful recovery for patients at risk.

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