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The impact of anaesthesia on the immune system: understanding mechanisms and clinical implications – part I

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Abstract

Anaesthesia plays a crucial role in modern medicine. Recent research suggests that anaesthesia may also have significant effects on the immune system. This article provides a comprehensive review of the current understanding of how anaesthesia affects immune function. It is divided in two parts. The first one, explores the underlying mechanisms and discussing the clinical implications of leukocyte function, cell-mediated immunity, humoral immunity, gut microbiota and cytokine signaling pathways. The second part review the inflammatory response modulation, stress response and cancer recurrence rates. By elucidating these complex interactions, we aim to enhance our understanding of anaesthesia-related immunomodulation and facilitate the development of strategies to mitigate potential adverse effects. Advancing our knowledge of anaesthesia's immunomodulatory effects is a cornerstone to improve patient safety and the effectiveness of perioperative management. *Anestezjologia i Ratownictwo 2025; 19: 166-171. doi:10.53139/AIR.20251917*

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Introduction

Anaesthesia is a fundamental component of modern medicine in various surgical procedures, pain management and diagnostic interventions. The immune system, composed of innate and adaptive components, is a complex network of tissues, cells and molecules that together to protect the host against pathogens and maintain homeostasis (figure 1). Recent research has highlighted the potential impact of anaesthesia on the immune system, raising important questions about its implications for perioperative management and patient outcomes.

Applying the third law of logic (the principle of identity), we can establish that since surgery influences the patient's immune status, and anaesthesia influences surgery, in term of stress surgery response, therefore, anaesthesia influences the immune response. However, the reality is more complex, because it is difficult to quantify accurately the impact of different anaesthetic techniques on the immune system due to the influence of multiple confounding factors that take part in stress surgery modulation.

Thus, it is necessary to consider the coexistence of surgical trauma, the pre-existing comorbidities of the patient (e.g., malignancies, infections, transplantation…) and their influence on immune function, as well as the physiological stress response associated with the procedures (surgical trauma, preoperative and especially postoperative pain).

When evaluating the quality of published research, we should not focus solely on the study design (in vitro, in vivo, animal models, clinical trials) or the sample size. It is also important to analyze the study methodology, assessment and follow-up duration (particularly relevant in cancer recurrence studies), the

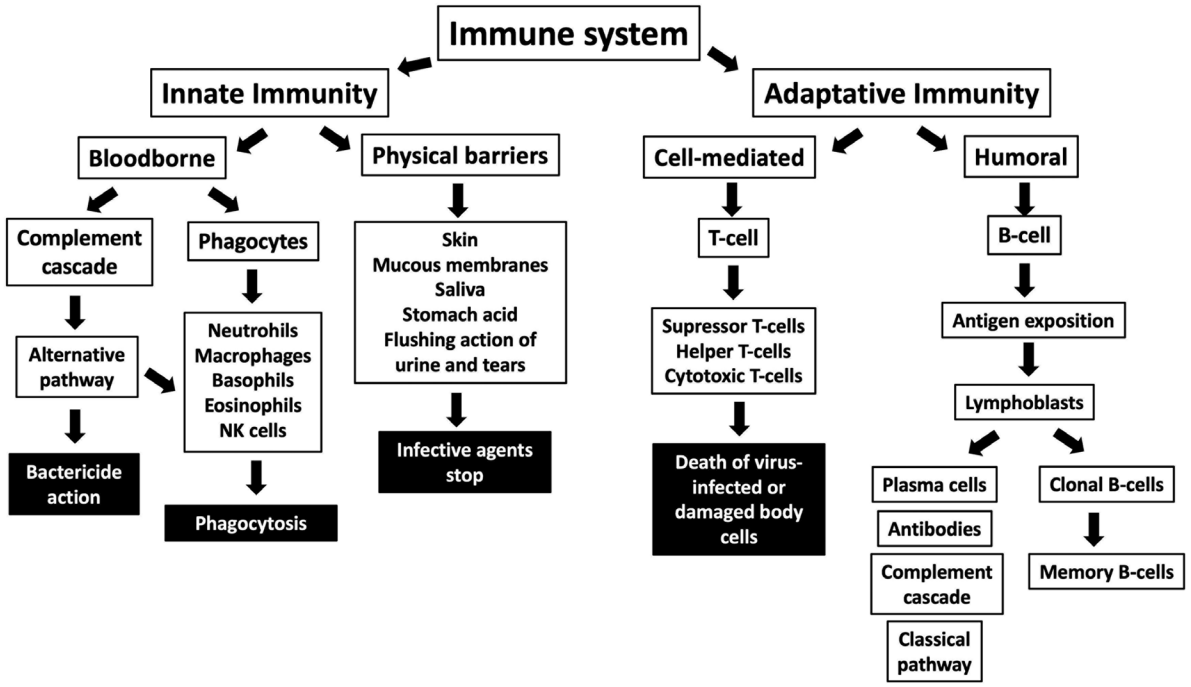

Figure 1. Scheme of the classification and functions of the different components of the immune system

type of pathology studied (e.g., gastric, colon, breast, brain cancers), as well as the patient's physical characteristics (age, sex, ASA classification, obesity). All these factors influence the true impact of anaesthesia on immune function.

Material and methods

Literature search

This review utilized bibliographic databases such as Medline (PubMed), Web of Science (WOS), the Cochrane Library (evidence-based medicine), and UpToDate, using search terms including "Anaesthesia," "Anaesthesiology," "Anaesthetics," "Immunology," "Immunity," "Immune effects," "Cancer," "Pain," "Perioperative care," and "Patient outcomes," combined with Boolean operators "AND" and "OR." The search was limited to articles published in English or Spanish, including meta-analyses, randomized controlled trials, reviews, or systematic reviews, covering the period from January 2000 to 2025.

Effects of anaesthesia on immune function

Recent research has highlighted the potential impact of anaesthesia on the immune system, influencing both innate and adaptive immunity and raising important questions about its implications for perioperative care and patient outcome.

Anaesthesia, particularly general anaesthesia, induced varied, complex and interrelated effects on the immune system (figure 2).

The precise etiopathogenic mechanisms underlying anaesthesia-induced immunomodulation are unknown. Due to its multifactorial nature, various non-exclusive hypotheses try to explain these effects: direct interactions between anaesthetics and immune cells, neuroendocrine-mediated pathways, alterations in the gut microbiota and indirect perioperative effects such as the surgical stress response, hypothermia and fluid management. All of them may contribute to anaesthesia-related immunological changes.

This article has been divided in two parts. The first one explores the underlying mechanisms and discussing the clinical implications of leukocyte function, cell-mediated immunity, humoral immunity, gut microbiota and cytokine signaling pathways, providing the pathophysiological basis to better address the inflammatory response modulation, stress response and cancer recurrence rates that are reviewed in the second part (figure 3).

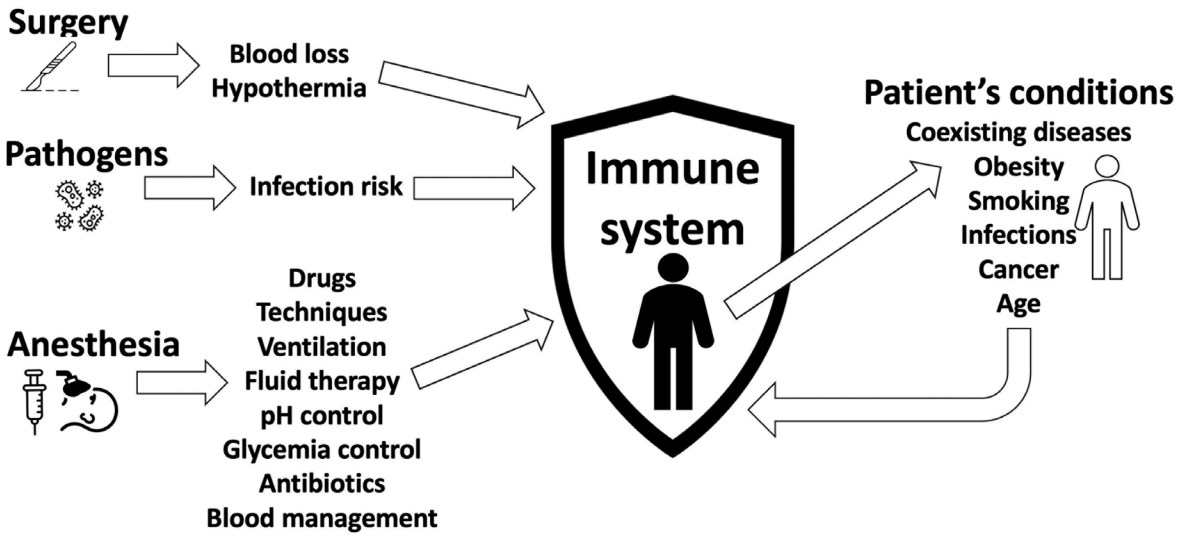

Figure 2. Perioperative factors that affect the immune system

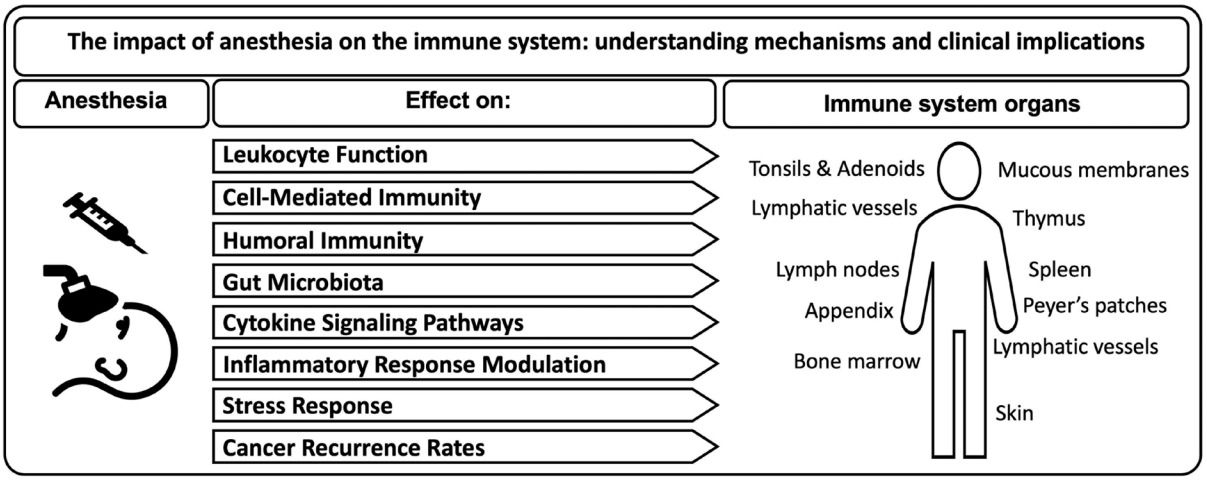

Figure 3. The impact of anesthesia on the immune system

Leukocyte function

Anaesthesia can influence the function of leukocytes, including neutrophils, macrophages, and lymphocytes.

Volatile anaesthetics have been involved in a significant reduction of neutrophil recruitment and phagocytosis by targeting multiple molecules in surgical patients [1]. A comparison of desflurane, sevoflurane, and propofol effects on phagocytosis and respiratory burst activity of human polymorphonuclear leukocytes in bronchoalveolar lavage showed increased respiratory burst function in propofol anaesthesia and no significant differences in phagocytic activity [2].

Anaesthetic technique (neuraxial vs. general) does not appear to significantly affect postoperative NK (**N**atural **K**iller) T lymphocyte function [3].

Cell-mediated immunity

Surgery-induced stress responses and surgical manipulation enhance tumor metastasis via release of angiogenic factors and suppression of NK cells and cell-mediated immunity [4,5]. Anaesthesia has been shown to influence the immune response to pathogens and tumor cells (function of cytotoxic T and NK cells),

and surveillance and antigen presentation [5] (NK cell and **A**ntigen-**P**resenting **C**ells (APCs) activity).

Local anaesthetics such as lidocaine increase NK cell activity. Ketamine and thiopental (not propofol) suppress NK cell function. Ketamine (not midazolam) induces T-lymphocyte apoptosis. Volatile anaesthetics suppress NK cell activity, induce T-lymphocyte apoptosis, and also enhance angiogenesis through HIF-1α activity [4]. However, other research found that changes in immune cells were similar with propofol and sevoflurane during breast cancer surgery, concluding that the effect of anaesthetics on perioperative immune activity may be minimal during cancer surgery [6,7].

Opioids suppress NK cell activity and increase regulatory T cells [4]. Morphine may promote tumor neovascularization and expansion. Fentanyl administration significantly diminishes NK cells and CD8+ cytotoxic T-cells [8].

Although the results are not consistent in all instances, the prevailing opinion is that both propofol and regional anaesthesia might cause less immunosuppression and reduce recurrence of certain types of cancer when compared to volatile anaesthetics and opioids (which may contribute to a pro-tumor metastasis environment, also known as cancer propagation) [4,8]. This is one of the main reasons for increasing interest in the development of **O**pioid-**F**ree **A**naesthesia (OFA) techniques.

Humoral immunity

Anaesthesia can also modify humoral immunity: B cell proliferation, antibody production, immunoglobulin secretion, vaccine responses, and antibody-mediated immunity.

Post-operative immunological complications (e.g., poor wound healing or infection) are rare in patients with normally functioning immune systems. However, there is an increased interaction of anaesthetics with receptors found on cytokine-producing cells in patients with immune disorders (e.g., AIDS, autoimmune diseases, active infections…), leading to modulations in the response to surgical stress. This is why pain relief therapy should be carefully considered regarding immune suppression [9]. Nonetheless, we should not consider anaesthetic drugs as the main cause of the effects on humoral immunity. Optimization of host immunity includes temperature regulation (normothermia), adequate oxygenation, and glucose management [5]. Older age, smoking and coexisting diseases morbidity such as diabetes and obesity [10] are considered to be associated with impaired immune functions (defective chemotaxis, bacterial killing, superoxide production, phagocytosis, ...) [5].

Concerning the interaction between anaesthesia for elective procedures and vaccines, Siebert et al. describe minor transitory effects in healthy children during a 2-day period. Therefore, they recommend waiting at least 2 days for inactivated vaccines or 2-3 weeks in case of live attenuated viral vaccines to avoid confusing the adverse effects of vaccination with post-surgical complications [11].

Gut microbiota

There are animal experimental studies that demonstrate the alterations caused in the gut microbiome (dysbiosis) by anaesthetic drugs, associated with immune dysfunction, inflammation, and increased susceptibility to infection. Dysbiosis correlates with chronic pain and some post-operative outcomes in humans [12], such as development of postoperative pain, chronic pain [13], inflammatory pain, headache, neuropathic pain, opioid tolerance [14], and postoperative neurocognitive disorders [15] and delirium [16].

The metabolites, neurotransmitters, and neuromodulators produced by the microbiota have the capacity to directly interact with sensory receptors [13], regulating neuroinflammation and peripheral and central sensitization, which in turn mediate the development of chronic pain [14]. These findings support the hypothesis that gut microbiota regulates pain in the peripheral and central nervous system (e.g., the opioid use and gut dysbiosis [17] in cancer patients [18] or the relationship between gut microbiota and immune cells with morphine tolerance [19]).

The influence of the microbiota and its alterations on the pathophysiology of pain should be investigated in depth in order to optimize existing analgesic treatments, minimize the potential adverse effects of anaesthesia, and investigate new therapeutic strategies for the management of chronic pain (e.g., targeting gut microbiota by diet and pharmabiotic interventions) [14]. The same criteria apply to the prevention of perioperative cognitive dysfunctions, whose development seems to be mediated by a systemic inflammatory reaction triggered by surgical trauma that leads to dysfunction of the blood-brain barrier and facilitates the occurrence of neuroinflammation [20].

Cytokine signaling pathways

Anaesthesia can dysregulate cytokine signaling pathways and may contribute to immune dysfunction and inflammation. For example, lidocaine has anti-nociceptive and anti-inflammatory effects mediated by **T**oll-**L**ike **R**eceptor (TLR) [5], **N**uclear **F**actor **k**appa-β (NF-kβ) (which regulate the expression of pro-inflammatory and anti-inflammatory genes), signaling pathways, downstream cytokine effectors **H**igh **M**obility **G**roup **B**ox **1** (HMGB1) and **T**umor **N**ecrosis **F**actor-α (TNF-α) [21].

Isoflurane (but not propofol) protects the myocardium from ischemia/reperfusion injury through remote ischemic preconditioning via the activation of **S**ignal **T**ransducer and **A**ctivation of **T**ranscription 5 (STAT5), which regulates the expression of pro-inflammatory and anti-inflammatory genes [22]. Dexamethasone has distinct pulmonary and systemic effects in critically ill patients with COVID-19, including decreased major histocompatibility complex-II signaling, selecting P ligand signaling, and T cell recruitment by intercellular adhesion molecule and integrin activation [23]. Furthermore, not only anaesthetic drugs can modify cytokine signaling pathways: mechanical ventilation patterns (endogenous **F**ibroblast **G**rowth **F**actor **21** (FGF21) signaling is triggered in response to ventilator-induced lung injury) [24], or genetics (influencing the development of septic shock by regulating STAT3) [25] play a role in cytokine signaling pathways.

Conclusion

The effects of anaesthesia on the immune system are complex and involve modulation of leukocyte activity, cellular and humoral immunity, gut microbiota and cytokine signaling pathways. A better understanding of these processes will help refine perioperative care, reduce postoperative complications, and enhance surgical outcomes and long-term recovery, especially in certain populations more vulnerable to these effects, such as the elderly, critically ill, and immunocompromised patients. Consequently, strategies to minimize these immune alterations are essential to prevent perioperative dysfunction.

The second part of this article reviews the impact of anaesthesia on the inflammatory modulation, stress response and cancer recurrence rates.

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Conflict of interest
None

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