South Afr J Anaesth Analg. 2022;28(5 Suppl 1):S23-29
https://doi.org/10.36303/SAJAA.2022.28.5.2877

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

FCA REFRESHER COURSE

Pathophysiology of sepsis

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The increasing incidence of sepsis and its related problems, and the associated unacceptably high mortality rates continue despite a wider public awareness of the disease, our improved understanding of the pathophysiology of the disease, continuous refinements in diagnostic technologies and considered therapeutic strategies. This review expounds on the understanding of sepsis pathophysiology, highlighting how this understanding may lead to improved patient care and outcomes.

Keywords: sepsis, high mortality rate, therapeutic strategies, improved patient care

Scope of sepsis

Sepsis is a major problem worldwide, with 47–50 million cases reported annually.[1] At least 11 million deaths occur annually as a result of sepsis, thus accounting for one in five of all deaths worldwide.[1] Sepsis is the number one cause of death in hospitals[2] and of hospital readmissions,[3] and is the leading contributor to healthcare costs.[4] Up to 50% of sepsis survivors suffer from long-term physical and/or psychological effects.[5]

Definitions of sepsis

Throughout history, sepsis has been described in various ways. Hippocrates (c.480–c.370 BC), the Greek physician, considered the 'father' of medicine, described sepsis as *"… the process by which flesh rots, swamps generate foul airs, and wounds fester …"*[6] Centuries later, Louis Pasteur (1822–1895), the French biologist, microbiologist and chemist confirmed the '*germ theory*' and redefined sepsis as "*blood poisoning*".

The concept of sepsis being in large part due to the host response has been noted for many years, with Lewis Thomas noting in 1972 that *"the microorganisms that seem to have it in for us ... turn out ... to be rather more like bystanders ... It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful ... that we are more in danger from them than the invaders".*[7]

The evolution of the definition of sepsis and its related problems are summarised in Table I.

Pathophysiology

The pathophysiology of sepsis is a complex process involving various systems initiated by the impact of a pathogen on the body, and subsequently driven by an excessive host immune

Table I: Sepsis definition and criteria

Definitions	Sepsis-1 (1992)[8]	Sepsis-2 (2001)[9]	Sepsis-3 (2016)[10]	
			Definition	Clinical criteria
Sepsis	Systemic response to infection with two/more SIRS criteria: • $T^0 > 38.3\ ^0C$ or $< 36\ ^0C$ • HR > 90 • RR > 20/min or $P_aCO_2 < 32$ mmHg • WBC > 12 000 or < 4 000 cells/mm^3 or > 10% immature bands	Unchanged *(but noted signs of SIRS to occur in many infectious and non-infectious conditions and therefore not helpful in distinguishing sepsis from other conditions)*	Life-threatening organ dysfunction caused by dysregulated host response to infection	Suspected or documented infection + acute increase ≥ 2 SOFA points
Severe sepsis	Sepsis with organ dysfunction, hypotension, or hypoperfusion including but not limited to lactic acidosis, oliguria or acute alteration in mental status.	Unchanged	Removed	Removed
Septic shock	Sepsis with hypotension, despite adequate fluid resuscitation plus presence of perfusion abnormalities.	Unchanged	Subset of sepsis with underlying circulatory and cellular/metabolic abnormalities profound enough to substantially increase mortality.	Sepsis and vasopressor therapy needed to elevate MAP ≥ 65 mmHg and lactate > 2 mmol/L despite adequate fluid resuscitation.

SIRS – systemic inflammatory response syndrome, SOFA – sequential organ failure assessment, WBC – white blood cell, RR – respiratory rate, HR – heart rate, T^0 – temperature, MAP – mean arterial pressure

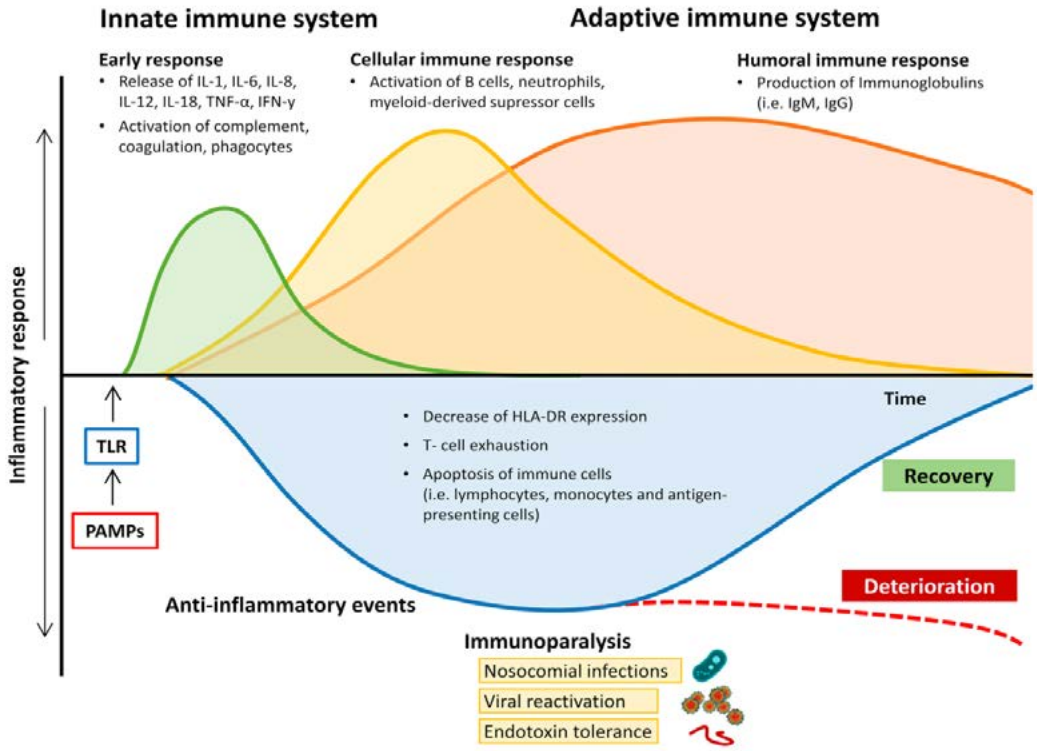

Figure 1: Changes in pro- and anti-inflammatory response of the immune system during sepsis[16]
HLA-DR – human leukocyte antigen-D related, IgM/G – immunoglobulin M/G, I – interleukin, IFN-γ – Interferon γ, PAMP – pathogen-associated molecular patterns, TNF-a – tumour necrosis factor alpha, TLR – toll-like receptor

response triggering cascades of interconnected systems and finally leading to organ failure. This dysregulation of the fine immunological balance between inflammation and anti-inflammation in sepsis contrasts with uncomplicated, localised infections that are usually effectively and efficiently controlled.[11-13]

Not all patients with sepsis present in the same way. A variety of pathogen- and host-related factors will determine the extent of the process and response, and define the clinical and biological phenotypes of sepsis. Pathogen factors include the type of organism (bacteria v. virus v. fungi), the pathogen load, the virulence of the organism and the various products of the organism that trigger a response. Host factors include age, the pre-existing acute illness, other comorbidities, medications, site of infection, time to source control, environment and genetics.[11]

The non-specific innate immune system, using three defence mechanisms (physico-chemical barriers, cellular components, and humoral responses), provides the first line of defence against infection. The physical barriers are epithelial membranes (e.g. skin, mucous membranes of respiratory, gastrointestinal and urogenital tracts) that block pathogen entry. The cellular component of the innate system involves multiple cell types including phagocytic leukocytes, dendritic cells and natural killer cells that recognise and remove pathogens and cell debris. The humoral part of the innate immune response consists of the serine protease cascades of the complement and coagulation systems, as well as naturally occurring antibodies. These three mechanisms act as the host's initial defence against pathogens.

The innate immune system is activated when specialised pattern recognition receptors (PRR), e.g. toll-like receptor (TLR) and other receptors on the body's immune cells recognise special microbial structures or small molecular motifs on pathogens called pathogen-associated molecular patterns (PAMPs).[14] Examples of PAMPs include lipopolysaccharides found on cell membranes of gram-negative bacteria, bacterial flagellin, lipoteichoic acid from gram-positive bacteria, fungal antigens and nucleic acid variants such as double-stranded RNA associated with viruses. Each of these PAMPs is specifically recognised by the different subtypes of the host TLRs.[15]

The PAMP-PRR complex triggers activation of multiple signalling cascades in the host immune cells via upregulation of inflammatory gene transcription by stress sensor transcription factors such as NF-κB. The chemokine response occurring locally at the site of sepsis serves to induce migration of white blood cells to the infected tissue. Neutrophils, for example, are activated, which increases their chemotactic migration to the site of infection, rolling along the vascular endothelium, adhesion, and diapedesis between endothelial cells. At the same time, the release of cytokines acting as messenger molecules drives a systemic inflammatory response with resultant endothelial activation.

The inflammatory response and defence system results in damage to host cells with necrotic cell death. This creates cell scrap or damage-associated molecular patterns (DAMPs) which are intracellular material or molecules (such as ATP, mitochondrial DNA, high-mobility group protein B1 and S100 proteins) released

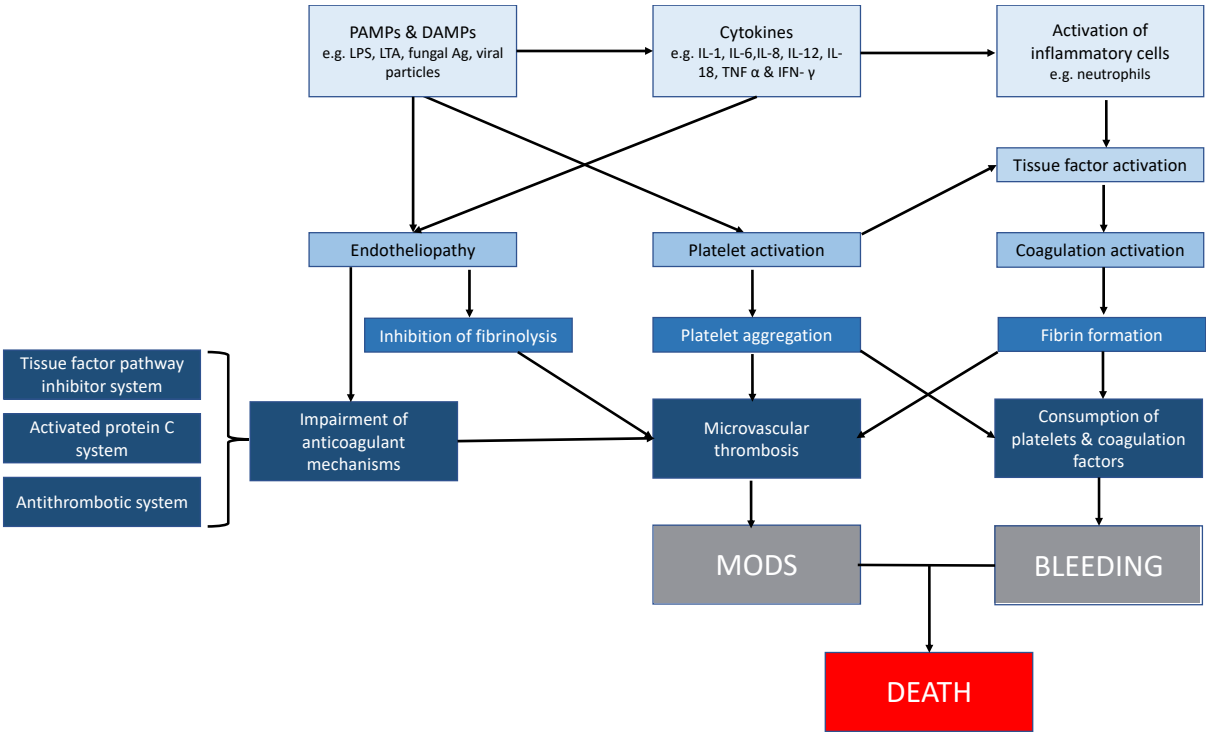

Figure 2: Dysregulation of haemostasis in sepsis leading to sepsis-induced coagulopathy (Adapted from Rossio et al.[25])
PAMPs – pathogen-associated molecular patterns, DAMPs – damage-associated molecular patterns, LPS – lipopolysaccharide, LTA – lipoteichoic acid, Ag – antigen, IL – interleukin, TNF – tumour necrosis factor, IFN – interferon

from dead or damaged host cells.[11,15,17] These DAMPs further stimulate the immune system creating a vicious circle.

The aim of the innate response is the eradication of the PAMPs and DAMPs. If the innate immune system is not able to destroy the pathogen, its cytokine signature then plays a role as activator and controller of the adaptive immune system that takes over (Figure 1). The slower, more specific adaptive immune system is made up of T-lymphocytes, B-lymphocytes and antibodies.

The initial cytokine response of the innate system is pro-inflammatory with the expression of inflammatory mediators such as IL-1, IL-6, IL-8, IL-12, IL-18, TNF α, IFN- γ, and MIF. This is then followed by an anti-inflammatory response that includes IL-10, IL-4, IL-13, and TGF-β.[18] In pathological states, the timing, magnitude, and coordination of the pro- and anti-inflammatory processes are disturbed, leading to a dysregulated immune response that initiates four important processes:[11]

Loss of barrier function

Neutrophils become adherent to endothelial cells and release a range of mediators including reactive oxygen species (ROS), prostaglandins and coagulation proteases into the space between endothelial cells. The endothelium is thus activated, gaps between the cells are increased with an increase in permeability and resultant capillary leak and interstitial oedema as fluid and other molecules are extravasated.[18] This redistribution of fluid from vascular to extravascular space contributes to the hypovolaemia of sepsis that occurs with obvious causative fluid losses, e.g. diarrhoea and vomiting and increased insensitive losses from fever and tachypnoea.

The activated neutrophils also release DNA-histone complexes and proteins that form net-like structures called neutrophil extracellular traps (NETs).[19,20] NETs play a key role in the neutrophil innate immune response, but may also contribute to endotheliopathy and dysregulation of coagulation. Endothelial cell shrinkage and death worsen this loss of endothelial barrier function. As the inflammatory response is systemic, the endothelial dysfunction or endotheliopathy occurs in all organs. In the brain, for example, the breakdown of the blood–brain barrier (BBB) allows the entry of peripheral immune cells into the brain, which triggers the activation of glial cells and neuroinflammation.[21] Gut barrier dysfunction in sepsis is also a problem with sepsis-mediated alteration of the gut-blood barrier and increase in the intestinal permeability, which may correlate with the phenomena of bacterial translocation and lymphatic activation.[22]

Vasodilatation[23]

Vasodilatation, a key feature of sepsis, is particularly excessive in septic shock and is thus the major cause of hypotension. There is a loss of vascular smooth muscle reactivity and a decreased responsiveness to natural vasoconstrictors. Activation of the renin-angiotensin system and a deficiency of vasopressin exacerbate the vasodilatation. The vascular effect is mediated mainly by two mechanisms: increased nitric oxide (NO) via Ca-independent NO synthase induction by endotoxin interaction with vascular endothelial cells, and prostacyclin synthesis and release by endothelial cells in response to endotoxin and inflammatory cytokines. Adrenomedullin, a pleiotropic vasodilating hormone, and the activation of transient receptor

potential vanilloid type 4 (TRPV4) channels are also thought to play a role.

Activation of coagulation[24,25]

Coagulation and inflammation are intricately linked in sepsis with the resultant dysregulation of haemostasis (Figure 2). This sepsis-induced coagulopathy, defined as the systemic activation in coagulation with suppressed fibrinolysis that leads to organ dysfunction in combination with systemic inflammation, occurs in 29% of critically ill patients with sepsis.[26] Normally, the three key anticoagulant pathways (tissue factor pathway inhibitor system, activated protein C system and antithrombotic system) work in concert to ensure that procoagulant systems are balanced. In sepsis, the PAMPs, DAMPs and cytokines cause endothelial cell dysfunction thereby impairing these anticoagulant mechanisms and also inhibit fibrinolysis. Tissue factor expression activates coagulation and leads to fibrin formation. Platelets are also activated and thus aggregate. The net effect of all these processes is the formation of microvascular thrombi. This is an important mechanism contributing to multi-organ failure. Additionally, as platelets and coagulation factors are consumed, the propensity for bleeding increases.[27]

Mitochondrial dysfunction[28]

Sepsis-induced mitochondrial damage or dysfunction leads to insufficient energy production and oxidative stress, thereby disturbing cellular metabolism. Various mechanisms of mitochondrial dysfunction are proposed:[29]

- tissue hypoxia, i.e. insufficient oxygen at the mitochondrial level to drive oxidative phosphorylation of ADP to ATP
- generation of ROS causes direct damage to mitochondrial proteins and lipid membrane
- hormonal alterations in sepsis impact mitochondrial function and efficiency
- genes transcribing mitochondrial proteins are downregulated early in the inflammatory response

The inhibition and damage of mitochondria, and the decreased turnover of new mitochondrial protein leads to bioenergetic failure. This evokes apoptosis in both organ cells and immune cells and leads to immunological dissonance and multiple organ failure.

The net effect of all these processes is tissue hypoperfusion with decreased tissue oxygenation leading to organ dysfunction as the final pathway. As a systemic process, these effects are seen across the body in various organs. Additionally the effects can be viewed at the levels of the organism, systems, and organs. These effects further extend to the cellular and organelle levels, and ultimately at the level of genes.

To balance the potentially harmful pro-inflammatory pathways, the immune system activates several anti-inflammatory pathways via neuroendocrine, humoral and cellular systems.[11,12] The number and function of immune cells is reduced and pro-inflammatory gene transcription is inhibited. The immunosuppression follows shortly after the onset of inflammation and is postulated to be mediated by PD-1 (programmed cell death-1), expressed on activated T cells, natural killer cells and B cells.[30] The exhaustion of T cells results in immunosuppression. The host is thus predisposed to immunoparesis with the development of secondary nosocomial infections or other opportunistic infections such as latent viral reactivation.

It is important to note that the various processes do not necessarily occur sequentially and will co-exist during various stages of sepsis. This complex, variable and often prolonged host response is a delicate interplay between pro- and anti-inflammatory mechanisms where both may be beneficial in helping clear the infection and accelerate tissue recovery, whilst at the same time posing inherent risks to the host in terms of organ injury and secondary infections.

The differentiation of sepsis phenotypes according to the underlying pathogen was used for many years. This depended on whether the causative organisms were bacteria, viruses, fungi or protozoa with each believed to generate varying responses. Bacteria, for example, lead to direct damage via their toxins, such as LPS with gram-negative bacteria, whilst with viruses, inter alia, macrophages stimulate interferon production. More recently, novel groups of clinical phenotypes for sepsis have been described.[31] Four groups (α, β, γ and δ) were described. The α phenotype was the commonest with lowest vasopressor administration, whilst the δ phenotype was least common but had more liver dysfunction and septic shock.

This understanding of the pathophysiology may have potential treatment implications for each of these four groups.

Sepsis-induced cardiac dysfunction

Sepsis-induced cardiac dysfunction is a severe complication in ICU patients with sepsis, with the prevalence ranging from 10–70%.[32] Three mechanisms are proposed: direct cardiac depression, impaired myocardial circulation, and impaired cardiac mitochondrial function.[33] Cardiomyocytes secrete pro-inflammatory cytokines that initiate a local inflammatory response and recruit inflammatory cells. The cell surface adhesion molecules expressed act on actin filaments to reduce contractile efficiency. Additional molecules produced reduce calcium flux. These cardiomyocyte inflammatory changes lead to decreased cardiomyocyte contractility through reduced calcium transients and interference with excitation–contraction coupling.[34] Patients with septic cardiomyopathy present with altered global haemodynamic parameters affecting both the right and left sides of the heart. Septic cardiomyopathy carries a significantly increased mortality of up to 50%.[35]

Why is understanding the pathophysiology of sepsis important?

Various decision-making challenges are encountered when managing patients with sepsis, especially those that are critically

Table II: Overview of pharmacokinetic alterations in sepsis, with examples of potential clinical effects[43]

Pharmacokinetic process	Alteration in sepsis	Potential clinical effect
Absorption	• Decreased for most routes • Potentially increased transdermal absorption	• Potential for subtherapeutic effects of all enterally administered medications • Potential increased absorption of transdermal preparations (fentanyl)
Distribution	• Lipophilic medications – decreased V_D • Hydrophilic medication – increased V_D • Hyperalbuminaemia – increased free drug concentration of acidic protein bound drugs • Increase α_1 acid glycoprotein – decreased freed rug concentration of basic protein-bound drugs • Acidaemia – decreased V_D of weak bases	• Increased plasma concentration of intravenous anaesthetic agents, opioids and sedative leading to adverse effects (e.g. cardiovascular depression) • Potential for subtherapeutic levels of commonly used hydrophilic antimicrobial agents such as beta-lactams and aminoglycosides • Midazolam may have a more rapid onset because of decreased protein binding in hypoalbuminaemia • Decreased clinical effect of opioids because of increased binding by the α_1 acute phase reactant acid glycoprotein
Metabolism	• Generally decreased	• Prolonged clinical effect and risk of toxicity
Excretion	• Generally decreased	• Prolonged clinical effect and risk of toxicity

ill. Deciding whether sepsis is present, whether and how to treat, and whether there is an appropriate response to therapy are often difficult. Understanding the pathophysiology of sepsis will allow for better diagnostic, therapeutic and prognostic approaches through the development of better and earlier diagnostic tools, more effective strategies to practise personalised and precision medicine with better treatment decisions, and clearer directions for future research.[16,36]

A clearer elucidation of the pathophysiology of sepsis has identified numerous biomarkers playing key roles in the various sepsis processes. Biomarkers are naturally occurring molecules, genes, or characteristics by which a particular pathological or physiological process, or disease can be identified. In sepsis, biomarkers offer utility for diagnosis, prognosis, early disease recognition, risk stratification, appropriate treatment, and trial enrichment for patients with sepsis or suspected sepsis.[37,38] The use of procalcitonin, for example, only emerged as the pathophysiology of sepsis became clearer. It had many properties making it ideal as a biomarker: upregulation of production during the acute phase of sepsis, rapid achievement of peak levels after bacterial insult, correlation of values with intensity of stimulation, short half-life, and drop in levels rapidly after end of insult. Procalcitonin has been associated with lower antibiotic use, ability to rule out bacterial infectious processes, and identification of patients eligible for early antibiotic de-escalation.[39] A variety of other biomarkers, including presepsin, sTREM-1 and copeptin, have been developed and are finding favour in practice.

Although culture growth currently remains the gold standard for fungal and bacterial detection, the development of next-generation sequencing (NGS) using culture-independent PCR-based methods to detect cell-free microbial DNA holds much promise. NGS is becoming more widely available and has the advantage of faster detection within hours. Transcriptomics is an early sepsis detection method not based on pathogen detection that searches for special gene expression signatures of circulating WBCs. It is based on NGS technology but RNA is sequenced instead of DNA, with this transcripted RNA reflecting the host gene expression.

Anaesthesia and sepsis

Anaesthesiologists are likely to face patients with sepsis initially presenting to the operating room prior to ICU or patients already in ICU needing surgical interventions for sepsis. A thorough understanding of the sepsis process and its implications is vital in ensuring appropriate clinical management. Many reviews cover key aspects in this regard.[40-42]

An important consideration in the anaesthetic management of patients with sepsis and septic shock is the pharmacokinetic alterations with respect to absorption, distribution, metabolism and excretion of the various anaesthetic drugs. These effects are compounded by the multiple organ dysfunctions that are found in these patients.[43]

Most anaesthetic agents may directly or indirectly suppress the immune response via complex and varied mechanisms including apoptosis of lymphocytes, impairment of neutrophil phagocytosis, modulation of the neural immune-regulatory circuit and activation of cholinergic anti-inflammatory pathways modulating adrenocortical functions.[44] A summary of the effects of individual anaesthetic drugs on the inflammatory pathways is shown in Table III.

Current evidence is contradictory, with clinical relevance remaining unclear. Consequently, no single mode of anaesthesia can be preferred for its effect on the inflammatory response in the patient with sepsis whose first stop is often the operating theatre. As anaesthesiologists, we are a crucial part of the continuum of care of the septic surgical and critically ill patients

Conclusion

While the key aspects of the management of sepsis and septic shock remain appropriate microbiological screening, early source control, prompt administration of antimicrobial agents and haemodynamic management with vasopressors and fluids,

Table III: Summary of effects of anaesthetic drugs on the inflammatory pathways[44]

Agent	Proposed mechanisms
Ketamine	Inhibition of transcription factor activator protein-1 and NF-κB, Dose-dependent ↓ in mortality + ↓ TNF-α and IL-6 in septic rats
Midazolam	Binds to peripheral receptors on macrophages and modulates metabolic oxidative responsiveness Inhibits human neutrophil function + activation of mast cells induced by TNF-α Suppresses expression of IL-6 mRNA in human blood mononuclear cells Administration to LPS-stimulated macrophages, suppresses respiratory burst of ROS, + inhibits NF-κB activation
Propofol	Impairs monocyte and neutrophil functions of innate immune system, including respiratory burst, chemotaxis, phagocytosis & polarisation
Opioids in general	Central neuro-endocrine/neuro-paracrine and peripheral mechanisms by mu-opioid receptors on immune cells
Morphine	Dose-dependent impairment of monocyte and neutrophil function, NK cell-mediated cytotoxicity, lymphocyte and macrophage proliferation and cytokine release Promotes apoptosis by direct activation of enzymes involved Inhibits leukocyte function by increasing intracellular concentrations of NO and cyclic AMP, + by inhibiting nuclear NF-κB via NO-dependent mechanisms
Inhalations agents in general	Inhibitory effects on neutrophil function, decrease lymphocyte proliferation, suppress cytokine release from peripheral blood mononuclear cells
Sevoflurane	Attenuates activation of NF-κB + expression of mediators via TLRs Protects against vascular endothelium dysfunction through activation of eNOS/NO pathway + NF-κB inhibition
Isoflurane	↓ leukocyte counts, ↓ levels of systemic pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β), ↓ macrophage activation
Local anaesthetics	Affect PMNs directly + macrophage and monocyte function

more recently, additional novel diagnostic and therapeutic intervention has surfaced as the complex pathophysiology of sepsis has slowly been unravelled. The shift in focus from the pathogens to the host response has been a vital part of this as the complex interplay between various processes is better described. The dysregulation of the balance between the pro- and anti-inflammatory responses is at the core of the immunological basis of sepsis, and together with the endotheliopathy that causes a loss of barrier function, vasodilatation, sepsis-induced coagulopathy, and mitochondrial dysfunction all serve to highlight the heterogeneity of the common but serious problem of sepsis. Understanding these intricate processes of the pathophysiology of sepsis helps demystify the disease and will allow for better diagnostic, therapeutic and prognostic approaches through the development of more effective and efficient diagnostic tools, more effective treatment strategies and clearer directions for future research.

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