

Pathophysiology of the Infectious Process: From Molecular Mechanisms to Clinical Syndromes

Bon L.I., Maksimovich N.Ye., Znavets P.A., Malenovskaya M.Y

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

***Corresponding Author:** Bon L.I., Candidate of biological science, Assistant professor of pathophysiology department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80 Gorky St, 230009, Grodno, Belarus.

Received Date: 11 September 2026 | Accepted Date: 21 September 2026 | Published Date: 28 September 2026

Citation: Bon L.I., Maksimovich N.Ye., Znavets P.A., Malenovskaya M.Y., (2026). Pathophysiology of the Infectious Process: From Molecular Mechanisms to Clinical Syndromes, *J. Brain and Neurological Disorders*, 9(5): DOI:10.31579/2642-973X/186

Copyright: © 2026, Bon L.I. This is an open-access article distributed under the terms of The Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

The infectious process remains one of the central problems of modern medicine, as infectious diseases consistently rank third in the global structure of morbidity and mortality, surpassed only by cardiovascular pathology and malignant neoplasms

Key Words: infectious process; pathogenicity; virulence; endotoxins; exotoxins; adhesion factors; phagocytosis; cytokines; systemic inflammatory response; fever; hypoxia; sepsis; septic shock

Introduction

The infectious process remains one of the central problems of modern medicine, as infectious diseases consistently rank third in the global structure of morbidity and mortality, surpassed only by cardiovascular pathology and malignant neoplasms [14, 20]. Historical experience demonstrates the devastating power of epidemics: the plague pandemic in the Middle Ages claimed one-third of Europe's population, while smallpox in the 17th-18th centuries affected approximately 10 million people annually [14-26]. It was during this period that the foundations of epidemiology were established - patient isolation, sanitation measures, and the burning of clothing and corpses [14, 36]. Subsequently, the causative agents of major infectious diseases - anthrax, diphtheria, tetanus - were discovered, and the key role of bacterial toxins in the pathogenesis of these diseases was established [2, 17]. The introduction of antitoxic sera became the first triumph of pathogenetic therapy and significantly reduced mortality rates [8-16]. However, the evolution of infectious pathology did not cease: in recent decades, there has been an increasing proportion of diseases caused by opportunistic bacteria, as well as the emergence of fundamentally new pathogens - HIV, prions, and agents of arboviral hemorrhagic fevers [2-5, 11]. All of this renders pathophysiological analysis of the infectious process not merely an academic task but an urgent clinical necessity [1, 17, 20].

The infectious process is understood as a typical pathological process that arises in response to the introduction of microorganisms and represents a complex of interrelated functional, morphological, immunobiological, and biochemical changes underlying specific nosological forms [12, 27]. It is important to recognize that infection is not equivalent to disease: the development of the infectious process is determined by the balance between the aggressive potential of the pathogen and the effectiveness of the host's defense systems [2-17]. This very balance explains the broad

spectrum of clinical manifestations – from asymptomatic bacterial carriage to fulminant forms with fatal outcomes [12, 16, 34].

The Pathogen as an Initiator of the Pathological Process

The human body represents an ideal ecological niche for microorganisms due to the high stability of temperature, electrolyte composition, osmolarity, and pH of the internal environment, as well as the constant availability of nutrients [13-27]. The relationships between macro- and microorganisms can take various forms [18, 21]. In parasitism, the microorganism uses the host as a source of nutrition and habitat, causing harm [27]. In mutualism, both parties benefit - a classic example is the intestinal microflora, which participates in vitamin synthesis and provides colonization resistance [27, 30]. In commensalism, microbes coexist with the host without causing harm, as occurs with the normal microflora of the skin and mucous membranes [3-18].

The causative agents of infectious diseases include five main groups: protozoa, fungi, bacteria, viruses, and prions [5, 36]. Each of these groups determines specific features of pathogenesis [16, 31]. The classical model of the infectious process has been described for bacterial infections, whereas viruses, being "genetic parasites," realize their pathogenic effects through integration into the host cell genome, disruption of protein synthesis, and induction of apoptosis [1, 6, 33]. Prions, in turn, represent a unique class of pathogens consisting exclusively of altered protein molecules and containing no nucleic acids [3-8].

The key property of any pathogen is pathogenicity - a genetically determined, heritable ability to cause disease [11-17]. However, in clinical practice, the physician encounters not pathogenicity per se, but its phenotypic expression - virulence, which characterizes the degree of pathogenicity of a particular strain and depends both on the properties of the microorganism and on the susceptibility of the host [1, 2, 17, 34]. It is virulence that determines why the same pathogen causes a mild,

subclinical form in one patient and a severe, generalized infection in another [2, 16, 34].

The realization of pathogenic potential is ensured by a set of pathogenicity factors [23, 27]. Dissemination factors - hyaluronidase, collagenase, neuraminidase, as well as flagella and undulating membranes - facilitate the penetration of the pathogen into the internal environment of the body and its dissemination [11, 23, 27]. Adhesion and colonization factors are surface molecules of protein or polysaccharide nature that interact with specific receptors on host cells, ensuring attachment and subsequent proliferation of the microorganism [23, 27]. From a clinical standpoint, it is precisely adhesive properties that determine the tropism of the pathogen to specific organs and tissues [30-36].

Equally important are factors that protect the microorganism from the host's immune mechanisms [24, 32]. Capsules of the causative agents of anthrax, gonorrhea, and tuberculosis mechanically impede phagocytosis [22-29]. Catalase, produced by certain strains of staphylococci, destroys hydrogen peroxide, suppressing the digestion of microbes within phagocytes [14, 27, 31]. Proteases hydrolyze immunoglobulin, while coagulase stimulates plasma coagulation around the bacterial colony, creating a protective fibrin barrier [14-21]. These mechanisms explain why some infections acquire a protracted or chronic course despite the presence of an immune response [17, 27].

Toxins as the Central Link in Tissue Damage

The leading role in the pathogenesis of infectious diseases belongs to toxins - substances that exert a direct damaging effect on the cells and tissues of the host organism [2, 11]. To date, more than 50 varieties of bacterial toxins have been described, which by origin are divided into endogenous (endotoxins) and exogenous (exotoxins) [13, 21]. This division has not only theoretical but also important clinical significance, as it determines the strategy of pathogenetic therapy [12, 20].

Endotoxins are lipopolysaccharides that are structural components of the outer membrane of gram-negative bacteria [8, 23]. They are released into the bloodstream upon bacterial cell destruction [4-12]. The biological activity of endotoxin is determined by its hydrophobic component - lipid A [8-15]. The mechanism of action of endotoxin is not specific and develops according to a single scenario regardless of which particular gram-negative pathogen served as its source [1, 23-34]. Upon entering the bloodstream, endotoxin binds to high-density lipoproteins and a specific binding protein, which delivers it to CD14 receptors on the surface of monocytes and macrophages [13, 27]. This triggers a cascade of phagocyte activation with massive release of proinflammatory cytokines - interleukin 1-8, tumor necrosis factor, leukotrienes, platelet-activating factor [2, 17, 33]. It is this cytokine storm that underlies the systemic manifestations of endotoxemia: fever, tachycardia, complement activation, microcirculatory disturbances, and coagulopathy [2, 20]. Clinically, this manifests as systemic inflammatory response syndrome, which upon progression may transition to endotoxic shock [12-16, 20]. Currently, critical stages of this process have been identified, intervention at which can suppress target cell activation and block the pathogenic effect of endotoxins [21-26].

Exotoxins, in contrast to endotoxins, are secreted by microorganisms during their vital activity and possess high specificity of action [12, 23]. Based on the site of action, they are subdivided into membranotoxins, which increase permeability or cause destruction of the cytollemma, and toxins affecting intracellular structures [19-23]. Membranotoxins include pore-forming proteins, enzymes with direct membrane-damaging action (neuraminidase, phospholipases), and substances with detergent effects [12-23]. Toxins acting on intracellular targets have a modular structure comprising receptor and catalytic domains [16, 23]. Interaction with the cell proceeds through four stages: receptor binding, internalization, translocation into the cytosol, and realization of the catalytic effect [3, 19-23]. The clinical significance of this mechanism can hardly be overestimated: it is precisely due to the high specificity of exotoxins that

strictly defined syndromes develop - botulism with flaccid paralysis, tetanus with generalized convulsions, diphtheria with myocardial and nervous system involvement [12, 23]. This same property underlies serum therapy: antitoxins neutralize exotoxin, preventing its binding to target cell receptors [16-23].

Clinical and Pathogenetic Aspects of Infection

The development of the infectious process is determined by three groups of factors: portal of entry, routes of pathogen dissemination, and the state of antineffective resistance [12, 17]. The portal of entry - the site of microbial penetration into the host - can determine not only the possibility of infection development but also its clinical form [10-17]. This principle has direct clinical significance [8-17]. For example, introduction of streptococcus through the tonsillar mucosa leads to angina, through the skin - to erysipelas or pyoderma, through the uterine mucosa - to endometritis [10-21]. Thus, the same pathogen through different portals of entry causes different nosological forms [4, 20, 36].

The infectious dose - the minimum number of viable pathogens required for disease development - correlates with the severity of the course [12, 17]. For opportunistic bacteria, this parameter becomes critical: a low dose may not cause disease in an immunocompetent patient but may provoke a severe infection in an immunocompromised individual [17-34].

Following penetration, the pathogen disseminates through the intercellular space (with the participation of hyaluronidase), lymphogenously, hematogenously, or through serous cavity fluid and the spinal canal [14-23]. Most pathogens exhibit tropism for specific tissues, determined by the presence of complementary receptors on target cells [13, 27]. This tropism explains the clinical features of diseases: hepatitis viruses affect the liver, neurotropic viruses affect the nervous system, and pneumococci affect the lungs [16, 23].

Even upon entry of the pathogen into the body, the infectious process may not develop [12, 17]. This is precisely why infection is not equivalent to disease [9-17]. In the case of effective functioning of defense systems, asymptomatic bacterial carriage is possible, in which systemic responses, including immune ones, are not detected [16-27]. This principle has important practical significance for understanding epidemiology and the management of carriers [14-24].

Pathogenetic Links and Their Clinical Manifestations

A key role in the mechanism of infectious process development is played by the interaction of the pathogen with phagocytes [21-30]. In the classic variant, phagocytes engulf and destroy microorganisms, which clinically manifests as subsidence of the inflammatory reaction and recovery [27, 35]. However, the causative agents of some infections exhibit resistance to the effector mechanisms of phagocytes and are even capable of multiplying within them [11, 27-30]. Herpesviruses, Rickettsia prowazekii, Mycobacterium tuberculosis and Mycobacterium leprae, Legionella, Leishmania, Trypanosoma, and Toxoplasma use phagocytes as a "Trojan horse," leading to chronicity of infection, prolonged persistence of the pathogen, and formation of secondary foci [23-30]. From a clinical standpoint, this explains the recurrent course of herpetic infection, chronic forms of tuberculosis, and protracted leishmaniasis [16, 27].

The infectious process as a typical pathological process includes several general links [12-20]. Fever, which is the most frequent component of infectious diseases, develops as a result of leukocyte stimulation by primary pyrogens, followed by the release of secondary pyrogens - cytokines that act on the thermoregulatory center of the hypothalamus [12-20]. Clinically, this manifests as a characteristic temperature curve, which in different infections has its own specificity [12, 16-21]. Inflammation at the site of pathogen introduction serves a dual function: it limits the spread of infection and its toxins, but at the same time causes tissue damage through inflammatory mediators, which may exacerbate

metabolic disorders, hemodynamic disturbances, and trophic impairments [20-26].

Hypoxia is a constant companion of severe infections [13, 19]. Respiratory hypoxia occurs when the respiratory center is depressed by toxins (e.g., in botulism), circulatory hypoxia - in microcirculatory disorders (in sepsis), hemic hypoxia - in malaria due to erythrocyte hemolysis, and tissue hypoxia - in uncoupling of oxidation and phosphorylation under the influence of endotoxins of *Salmonella* and *Shigella* [16-20, 31]. Clinical manifestations of hypoxia - cyanosis, dyspnea, impaired consciousness - correlate with the severity of the condition and require timely correction [33, 36].

Metabolic disturbances at the initial stages are catabolic in nature: proteolysis, lipolysis, and glycogen breakdown are activated, with the development of hyperglycemia [9-16]. During the convalescent period, catabolic reactions are replaced by anabolic ones [12, 20]. The specificity of the nosological form determines the predominant impairment of a particular type of metabolism: in intestinal infections, disturbances of water-electrolyte balance dominate; in viral hepatitis - protein metabolism disorders; in sepsis - all types of metabolism simultaneously [12, 14, 27].

Disorders of Organ and System Functions

When protective mechanisms are insufficient, the infection generalizes, and pronounced functional disturbances of various systems develop [2, 16-20]. Changes in the nervous system pass through a stage of activation (stress response, mobilization of resistance) and, as intoxication progresses, give way to depression [16-31]. Clinically, this manifests from excitation, anxiety, and hyperesthesia in the early stages to lethargy, somnolence, and coma in severe infections [29-36]. In a number of infections, such as botulism, neurotrophic function is impaired with the development of characteristic paralyses [20, 26, 33].

Activation of the immune system is aimed at the formation of immunity; however, during the infectious process, immunopathological reactions may also develop [1, 17, 27]. Type III hypersensitivity reactions according to Gell and Coombs occur upon massive release of antigens resulting from the death of microorganisms in a sensitized host [16-27]. A clinical example is glomerulonephritis complicating streptococcal infection [25, 36]. Immune autoaggression reactions develop upon modification of host antigens by microbial factors, similarity of host and pathogen antigens, or integration of viral DNA into the host genome [11]. Immunodeficiencies in infections are usually transient, with the exception of HIV infection, where the virus directly attacks immune system cells, blocking the formation of an immune response [16, 23, 34].

Cardiovascular system involvement manifests as arrhythmias, coronary insufficiency, heart failure, and microcirculatory disturbances, caused by the action of microbial toxins, ionic and water imbalance, and changes in blood rheological properties [2-20]. Clinically, this presents as tachycardia, hypotension, and peripheral circulatory impairment [12-19].

External respiration function is initially enhanced as a compensatory reaction, then may be depressed due to toxin-mediated suppression of the respiratory center or pathogen-induced damage to pulmonary tissue [13, 27]. Impairments of liver, kidney, and gastrointestinal tract function are determined by the nature of the pathogen: hepatotropic viruses cause hepatitis, enterotropic bacteria cause diarrhea, and nephrotropic pathogens cause renal parenchymal damage [5, 14, 22].

Staging and Clinical Outcomes

One of the pathognomonic features of infectious diseases is staging of the course [12, 16]. The incubation period - from the moment of infection to the appearance of first symptoms - may last from several hours (acute intestinal infections) to several years (HIV, prion diseases) [3-5, 16]. During this period, pathogen multiplication occurs in target organs and adaptive mechanisms are mobilized [12-16]. Clinically, the patient

appears healthy, which complicates early diagnosis and creates epidemiological risks [2, 14-16].

The prodromal period is characterized by nonspecific symptoms: malaise, headache, fever, myalgia, arthralgia [9-16]. These manifestations result from decreased general resistance and increasing toxemia [11, 16]. The absence of specific signs makes differential diagnosis during this period extremely difficult [12, 30]. The period of peak manifestations is distinguished by the appearance of symptoms typical of the given disease, allowing nosological diagnosis [13, 26]. The duration of this period varies depending on the pathogen and the state of the host [12-22].

The outcomes of the infectious process are diverse [1-9]. Complete recovery with elimination of the pathogen and formation of stable immunity is the most common outcome of acute infections [1, 2, 11]. Clinical recovery occurs significantly earlier than the complete restoration of structural and functional impairments: for example, the period of liver function recovery after viral hepatitis ranges from 6 months to one year, whereas the disease itself lasts 1-1.5 months [18, 26, 32]. Incomplete recovery is characterized by the persistence of residual effects [22, 35]. Development of complications may be specific (directly related to pathogenesis, e.g., intestinal perforation in typhoid fever) or nonspecific (caused by activation of secondary infection or superinfection) [16, 23]. Bacterial carriage formation is clinically asymptomatic but has significant epidemiological importance [14, 16, 17].

Special Groups of Pathogens

Prion diseases are slowly progressive brain lesions caused by infectious proteins [3-6]. Prions are a unique class of pathogens consisting solely of altered protein molecules and containing no nucleic acids [3, 7]. Pathogenesis is associated with the transformation of normal prion protein into a pathological isoform, leading to neuronal vacuolization and the formation of spongiform changes [3, 18]. The incubation period may last decades [3, 19]. Clinically, the diseases manifest as progressive dementia, extrapyramidal disorders, cerebellar disturbances, and myoclonus [3, 9, 13]. The most well-known forms are Creutzfeldt-Jakob disease, kuru, fatal familial insomnia, and Gerstmann-Sträussler-Scheinker syndrome [6-20]. No etiotropic treatment exists, making these diseases fatal [4-11]. Complications - pneumonia, bedsores, sepsis - worsen the prognosis [3, 11, 16].

Viruses, being obligate intracellular parasites, induce a wide spectrum of cytopathic effects: cell lysis, apoptosis, membrane changes, and suppression of cellular protein synthesis [6-17]. Clinical variants of the course range from acute (influenza, measles) to latent (herpes) and chronic (hepatitis B, C) infections [1-17]. The oncogenic potential of viruses (papillomaviruses, Epstein-Barr virus) has direct clinical significance in the development of malignant neoplasms [1, 6, 17].

Rickettsiae, occupying an intermediate position between bacteria and viruses, are intracellular parasites transmitted through arthropod bites [15, 27]. They contain both DNA and RNA, possess a cell wall, but do not multiply outside the cell [11, 27]. Clinically, rickettsioses manifest with acute onset, high fever, intoxication, and characteristic rash, caused by systemic endothelial damage [13, 25].

Bacterial infections are distinguished by a diversity of damage mechanisms [12, 23]. Toxins (tetanus, botulinum, diphtheria, cholera) play a central role in pathogenesis, determining specific clinical syndromes [12, 16, 23]. Bacteria also produce tissue-destroying enzymes and form biofilms that protect against antibiotics and immune responses [17, 23, 33]. Clinically, this manifests as delayed response to therapy and chronicity of the process [16-23].

Parasitic infections affect the host through depletion of nutritional resources, modulation of the immune response, and alteration of the microbiota, creating a favorable background for the development of

secondary infections and exacerbation of chronic non-infectious diseases [17-30].

Host Defense Mechanisms

The outcome of the infectious process is determined by the balance between the pathogen's aggressiveness factors and the host's defense systems [2, 17, 32]. Nonspecific defense constitutes the first barrier [22, 31]. The skin with its stratum corneum, low pH, and bactericidal sweat components, as well as mucous membranes with lysozyme, secretory immunoglobulin, and glycoproteins, form the first line of defense [13, 27]. Normal microflora provides colonization resistance [17-30]. Gastric juice with low pH creates a bactericidal barrier, making the stomach nearly sterile [21, 27].

Phagocytosis is one of the main mechanisms of nonspecific defense [12, 27]. Neutrophils and macrophages engulf and destroy microorganisms using oxygen-dependent (myeloperoxidase, catalase, reactive oxygen species) and oxygen-independent (lysozyme, lactoferrin, cationic proteins, acidosis, hydrolases) mechanisms [22-30]. Humoral factors-lysozyme, lactoferrin, transferrin, lysis, complement, and interferons – complement cellular mechanisms [26, 33].

Specific immunity is activated upon recognition of pathogen antigens [17, 27]. Humoral response dominates against extracellular bacteria and toxins, while cellular response dominates against intracellular parasites [14, 23]. Antitoxins neutralize exotoxins, preventing their binding to target cell receptors [16, 23, 27]. Local immunity (secretory IgA) plays a crucial role in infections entering through mucous membranes [17, 36]. Immunological memory provides long-term protection - from lifelong in measles and smallpox to short-term in dysentery [16, 27].

Principles of Therapy and Clinical Significance of Sepsis

Treatment of infectious diseases is based on three principles [12, 17]. Etiotropic therapy is directed against the pathogen and includes antibacterial, antiviral, antifungal, and antiprotozoal agents [3-12, 34]. Pathogenetic therapy blocks the mechanisms of infectious process development: detoxification (antitoxic sera, hemodialysis, plasmapheresis), anti-inflammatory therapy, immunocorrection, normalization of organ function, and correction of homeostasis [17, 27]. Symptomatic therapy alleviates the patient's condition [6-16, 28].

Sepsis is a severe generalized form of the infectious process with multiplication of the pathogen in the blood [12, 20, 31]. Septic shock, complicating sepsis, is characterized by persistent hypotension not responsive to fluid resuscitation and leads to multiple organ dysfunction syndrome [12-20]. Mortality in septic shock reaches 25-50% [17, 29]. Clinically, sepsis is diagnosed in the presence of infection and two or more criteria of systemic inflammatory response syndrome: temperature above 38°C or below 36°C, tachycardia above 90 beats per minute, tachypnea above 20 per minute or PaCO₂ below 32 mm Hg, leukocytosis above 12×10⁹/L or leukopenia below 4×10⁹/L [12-28]. Septic shock is diagnosed in the presence of persistent hypotension (systolic pressure below 90 mm Hg, mean arterial pressure below 70 mm Hg, or a decrease of more than 40 mm Hg from baseline) [12, 20, 33].

Conclusion

The infectious process represents a complex multicomponent interaction between the pathogen and the host, the outcome of which is determined by the balance between the pathogenic properties of the microorganism and the effectiveness of host defense systems [10, 21-27]. Understanding general pathophysiological patterns – from molecular mechanisms of toxin action to systemic reactions of the body – is a fundamental basis for clinical diagnosis, rational etiologic and pathogenetic therapy, and the development of new approaches to the prevention of infectious diseases [6-20]. The evolution of pathogens and the growth of antimicrobial resistance require continuous deepening of knowledge in this field,

making pathophysiological analysis of the infectious process not merely a theoretical but an urgent practical task of modern medicine [18-33].

References

1. Bahl A, Pandey S, Rakshit R, Kant S, Tripathi D., (2025), Infection-induced trained immunity: a twist in paradigm of innate host defense and generation of immunological memory. *Infect Immun.* 93(1).
2. Yilmaz S, Ateş S, Uçar S, Cömert A., (2026), Molecular Mechanisms Involved in the Pathophysiology of Sepsis: Role of Signaling Pathways. *J Biochem Mol Toxicol.*
3. Sigurdson CJ, Bartz JC, Glatzel M., (2019), Cellular and molecular mechanisms of prion disease. *Annu Rev Pathol.* 14:497-516.
4. Sigurdson CJ, Bartz JC, Glatzel M., (2019), Cellular and molecular mechanisms of prion disease. *Annu Rev Pathol.* 14:497-516.
5. Prusiner SB., (2013), Biology and genetics of prions causing neurodegeneration. *Annu Rev Genet.* 47:601-623.
6. Collinge J., (2016), Mammalian prions and their wider relevance in neurodegenerative diseases. *Nature.* 539(7628):217-226.
7. Soto C, Satani N., (2011), The intricate mechanisms of neurodegeneration in prion diseases. *Trends Mol Med.* 17(1):14-24.
8. Singh J, Udgaonkar JB., (2015), Molecular mechanism of the misfolding and oligomerization of the prion protein: current understanding and its implications. *Biochemistry.* 54(29):4431-4442.
9. Mondal B, Reddy G., (2020), A transient intermediate populated in prion folding leads to domain swapping. *Biochemistry.* 59(1):114-124.
10. Caughey B, Baron GS, Chesebro B, Jeffrey M., (2009), Getting a grip on prions: oligomers, amyloids, and pathological membrane interactions. *Annu Rev Biochem.* 78:177-204.
11. David J Bonda, Sunil Manjila, Prachi Mehndiratta, Fahd Khan, Benjamin R Miller, et al., (2016), Human prion diseases: surgical lessons learned from iatrogenic prion transmission. *Neurosurg Focus.*
12. Mervyn Singer, Clifford S Deutschman, Christopher Warren Seymour, Manu Shankar-Hari, Djillali Annane, et al., (2016), The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 315(8):801-810.
13. Manu Shankar-Hari, Gary S Phillips, Mitchell L Levy, Christopher W Seymour, Vincent X Liu, et al., (2016), Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 315(8):775-787.
14. Kristina E Rudd, Sarah Charlotte Johnson, Kareha M Agesa, Katya Anne Shackelford, Derrick Tsoi, et al., (2020), Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet.* 395(10219):200-211.
15. Habibollah Arefian, Steffen Heublein, André Scherag, Frank Martin Brunkhorst, Mustafa Z Younis, et al., (2017), Hospital-related cost of sepsis: a systematic review. *J Infect.* 74(2):107-117.
16. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL., (2016), Sepsis and septic shock. *Nat Rev Dis Primers.* 2:16045.
17. van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG., (2017), The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol.* 17(7):407-420.

18. Wiersinga WJ, van der Poll T., (2022), Immunopathophysiology of human sepsis. *EBioMedicine*. 86:104363.
19. Gourd NM, Nikitas N., (2020), Multiple organ dysfunction syndrome. *J Intensive Care Med*. 35(12):1564-1575.
20. Huang M, Cai S, Su J., (2019), The pathogenesis of sepsis and potential therapeutic targets. *Int J Mol Sci*. 20(21):5376.
21. Tijana Srdić, Siniša Đurašević, Iva Lakić, Aleksandra Ružičić, Predrag Vujović, et al., (2024), From molecular mechanisms to clinical therapy: understanding sepsis-induced multiple organ dysfunction. *Int J Mol Sci*. 25(14):7770.
22. Liu Z, Ting Y, Li M, Li Y, Tan Y, Long Y., (2024), From immune dysregulation to organ dysfunction: understanding the enigma of sepsis
23. Liu J, Kang R, Tang D., (2024), Lipopolysaccharide delivery systems in innate immunity. *Trends Immunol*. 45(4):274-287.
24. Li J, Zhu CS, He L, Qiang X, Chen W, Wang H., (2023), A two-decade journey in identifying high mobility group box 1 (HMGB1) and procathepsin L (pCTS-L) as potential therapeutic targets for sepsis. *Expert Opin Ther Targets*. 27(7):575-591.
25. Chao Deng, Lin Zhao, Zhi Yang, Jia-Jia Shang, Chang-Yu Wang, et al., (2022), Targeting HMGB1 for the treatment of sepsis and sepsis-induced organ injury. *Acta Pharmacol Sin*. 43(3):520-528.
26. Millar MW, Fazal F, Rahman A., (2022), Therapeutic targeting of NF-κB in acute lung injury: a double-edged sword. *Cells*. 11(20):3317.
27. Shanze Chen, Abdullah F U H Saeed, Quan Liu, Qiong Jiang, Haizhao Xu, et al., (2023), Macrophages in immunoregulation and therapeutics. *Signal Transduct Target Ther*. 8(1):207.
28. Clere-Jehl R, Mariotte A, Meziani F, Bahram S, Georgel P, Helms J., (2020), JAK-STAT targeting offers novel therapeutic opportunities in sepsis. *Trends Mol Med*. 26(11):987-1002.
29. Hu X, Li J, Fu M, Zhao X, Wang W., (2021), The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduct Target Ther*. 6(1):402.
30. Qiu P, Liu Y, Zhang J., (2019), Review: the role and mechanisms of macrophage autophagy in sepsis. *Inflammation*. 42(1):6-19.
31. Prauchner CA., (2017), Oxidative stress in sepsis: pathophysiological implications justifying antioxidant co-therapy. *Burns*. 43(3):471-485.
32. Nagar H, Piao S, Kim CS., (2018), Role of mitochondrial oxidative stress in sepsis. *Acute Crit Care*. 33(2):65-72.
33. Hang Pan, Wenhan Huang, Zhongjie Wang, Feifeng Ren, Lei Luo, et al., (2021), The ACE2-Ang-(1-7)-Mas axis modulates M1/M2 macrophage polarization to relieve CLP-induced inflammation via TLR4-mediated NF-κB and MAPK pathways. *J Inflamm Res*. 14:2045-2060.
34. Michels EHA, Butler JM, Reijnders TDY, et al., (2022), Association between age and the host response in critically ill patients with sepsis. *Crit Care*. 26(1):385.
35. Melegari G, Arturi F, Gazzotti F, Villani M, Bertellini E, Barbieri A., (2025), Sepsis biomarkers: what surgeons need to know. *Anesth Res*. 2(4):23.
36. He RR, Yue GL, Dong ML, Wang JQ, Cheng C., (2024), Sepsis biomarkers: advancements and clinical applications - a narrative review. *Int J Mol Sci*. 25(16):9010.



This work is licensed under Creative Commons Attribution 4.0 License

To Submit Your Article, Click Here:

Submit Manuscript

DOI:10.31579/2642-973X/186

Ready to submit your research? Choose Auctores and benefit from:

- fast, convenient online submission
- rigorous peer review by experienced research in your field
- rapid publication on acceptance
- authors retain copyrights
- unique DOI for all articles
- immediate, unrestricted online access

At Auctores, research is always in progress.

Learn more <https://auctoresonline.com/journals/brain-and-neurological-disorders>