MOLECULAR AND CELLULAR MECHANISMS IN THE PATHOGENESIS OF UROSEPSIS

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Abstract

Urosepsis is one of the most severe complications of urinary tract infections, characterized by systemic inflammatory responses and organ dysfunction, and is associated with high mortality rates in urological practice. The development of urosepsis involves multiple interacting mechanisms, including microbial virulence factors, innate and adaptive immune responses, inflammatory mediators, and endothelial dysfunction. The transition from a localized infection to a systemic pathological process is accompanied by cytokine cascade activation, immune cell dysregulation, microcirculatory disturbances, and metabolic imbalance. These alterations may ultimately result in multiple organ dysfunction syndrome. This study analyzes the principal molecular and cellular mechanisms involved in the development of urosepsis. A comprehensive understanding of urosepsis pathogenesis is essential for improving early diagnosis, prognostic assessment, and targeted therapeutic strategies.

Keywords: urosepsis, sepsis, cytokines, innate immunity, endothelial dysfunction, NF-κB, Toll-like receptors, immune dysregulation, multiple organ dysfunction.

Introduction. Sepsis remains one of the most complex and challenging problems in modern medicine. It is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Urosepsis represents a distinct clinical subtype of sepsis that originates from infections of the urinary tract and accounts for a substantial proportion of septic cases encountered in clinical practice [2].

Several risk factors contribute to the development of urosepsis, including urinary tract obstruction, urolithiasis, invasive urological procedures, urinary catheterization, and infections caused by antibiotic-resistant microorganisms. The clinical severity of the disease depends not only on the pathogenic characteristics of invading microorganisms but also on the magnitude and regulation of the host immune response [3].

Current understanding of sepsis pathogenesis has evolved considerably over recent years. While excessive inflammation was previously regarded as the primary driver of disease progression, contemporary evidence highlights the importance of immune dysregulation, cellular bioenergetic failure, mitochondrial injury, disruption of endothelial barrier integrity, and immunometabolic alterations as critical determinants of clinical outcomes [4,5].

The aim of this study was to analyze the principal molecular and cellular mechanisms underlying the development of urosepsis.

Materials and Methods. This study was designed as a comprehensive analytical review of current evidence concerning the molecular and cellular mechanisms involved in the pathogenesis of urosepsis. Particular emphasis was placed on the interaction between pathogen-associated molecular patterns (PAMPs), innate immune receptors, intracellular signaling pathways, inflammatory mediators, endothelial dysfunction, coagulation abnormalities, mitochondrial injury, and immune dysregulation.

The mechanisms underlying Toll-like receptor (TLR)-mediated signaling, activation of nuclear factor-kappa B (NF-κB), inflammasome formation, cytokine release, neutrophil extracellular trap (NET) generation, oxidative stress, immunometabolic alterations, and multiple organ dysfunction were critically analyzed. The available evidence was synthesized to establish an integrated view of the molecular events responsible for the transition from localized urinary tract infection to systemic inflammatory response and organ failure.

Results. The initiation of urosepsis is characterized by the recognition of microbial structures by pattern-recognition receptors expressed on immune cells. Lipopolysaccharides of Gram-negative bacteria and peptidoglycans of Gram-positive microorganisms activate Toll-like receptors, particularly TLR4 and TLR2, triggering downstream intracellular signaling pathways [3,6].

Activation of the TLR–MyD88–NF-κB axis results in transcription of numerous pro-inflammatory genes and increased production of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8). Simultaneously, activation of the NLRP3 inflammasome promotes maturation and secretion of IL-1β and IL-18, amplifying systemic inflammatory responses [6,7].

Excessive neutrophil activation contributes to pathogen elimination but also promotes collateral tissue injury through the release of reactive oxygen species, proteolytic enzymes, and neutrophil extracellular traps (NETs). Although NET formation represents an important antimicrobial defense mechanism, excessive NET generation facilitates endothelial injury and microvascular thrombosis [8].

Profound alterations in endothelial function occur during disease progression. Inflammatory mediators disrupt endothelial barrier integrity, increase vascular permeability, and impair microcirculatory blood flow. Simultaneous activation of coagulation pathways and suppression of physiological anticoagulant mechanisms contribute to disseminated intravascular coagulation and tissue hypoperfusion [4,9].

Mitochondrial dysfunction represents a critical event in organ injury. Increased oxidative stress, calcium dysregulation, and inflammatory signaling impair oxidative phosphorylation, resulting in reduced ATP production and cellular bioenergetic failure. These alterations contribute directly to the development of multiple organ dysfunction syndrome [5].

As the disease progresses, a compensatory anti-inflammatory response emerges. Extensive lymphocyte apoptosis, decreased monocyte HLA-DR expression, impaired antigen presentation, and T-cell exhaustion collectively lead to immunosuppression. This immunological shift increases susceptibility to secondary infections and is associated with adverse clinical outcomes [10].

Discussion. The pathogenesis of urosepsis cannot be explained solely by uncontrolled inflammation. Current evidence indicates that disease progression results from a dynamic interaction between hyperinflammatory responses, endothelial dysfunction, coagulation abnormalities, metabolic disturbances, and subsequent immune suppression [4,5,7,9]. This perspective has substantially changed the traditional understanding of sepsis as a purely inflammatory disorder.

Activation of the TLR–NF-κB signaling pathway serves as a central mechanism linking pathogen recognition with cytokine production [6,7]. However, excessive activation of this pathway contributes to the development of a cytokine storm, endothelial injury, and microcirculatory failure [4,7,9]. The dual role of inflammatory signaling highlights the complexity of therapeutic interventions aimed at modulating immune responses during sepsis.

Recent findings suggest that mitochondrial dysfunction and immunometabolic reprogramming play pivotal roles in determining disease severity [5,7].Impaired oxidative phosphorylation, altered glucose metabolism, and excessive reactive oxygen species production compromise cellular adaptation to systemic stress. Consequently, organ dysfunction may persist even after adequate control of the primary infection.

The transition from hyperinflammation to immunosuppression remains one of the most challenging aspects of sepsis biology. Although suppression of excessive inflammation may reduce tissue damage, prolonged immune paralysis increases vulnerability to opportunistic and nosocomial infections. Therefore, future therapeutic approaches should focus on individualized immune profiling and precision-based immunomodulatory strategies rather than uniform anti-inflammatory interventions.

These observations support the concept that urosepsis should be regarded as a complex immunometabolic syndrome involving interconnected molecular networks rather than a simple consequence of bacterial dissemination.

Conclusion. The development of urosepsis involves complex molecular and cellular processes associated with microbial virulence, activation of innate immunity, cytokine cascades, endothelial dysfunction, and disturbances in cellular energy metabolism.

NF-κB signaling, oxidative stress, microcirculatory abnormalities, and mitochondrial dysfunction constitute the principal molecular mechanisms responsible for organ injury during urosepsis. Furthermore, immunosuppression that develops during the later stages of the disease has a substantial impact on clinical outcomes and prognosis.

Identification of molecular biomarkers, individualized assessment of immune responses, and refinement of targeted therapeutic strategies represent promising approaches for reducing mortality and morbidity associated with urosepsis.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810.
2. Bonkat G, Bartoletti R, Bruyère F, Cai T, Geerlings SE, Köves B, et al. EAU Guidelines on Urological Infections. Arnhem: European Association of Urology; 2025.

3. Wagenlehner FME, Pilatz A, Weidner W, Naber KG. Urosepsis: Overview of the diagnostic and treatment challenges. Microbiol Spectr. 2021;9(2).
4. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Intensive Care Med. 2021;47(11):1181-1247.
5. Pool R, Gomez H, Kellum JA. Mechanisms of organ dysfunction in sepsis. Crit Care Clin. 2020;36(2):181-193.
6. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol Rev. 2016;274(1):330-353.
7. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis and potential therapeutic targets. Nat Rev Immunol. 2021;21(11):685-700.
8. McDonald B, Kubes P. Neutrophils and intravascular immunity in sepsis. Trends Immunol. 2019;40(8):683-693.
9. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, Ospina-Tascón GA, et al. The endothelium in sepsis. Shock. 2016;45(3):259-270.
10. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primers. 2016;2:16045.