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Review Article **Open Access**

Microbial menace to kidney health: A review of the role of infections in acute kidney injury

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Abstract:

Acute kidney injury (AKI) of infectious aetiology is a complex condition that requires a comprehensive microbiological evaluation. This includes sepsis workup, evaluation of urinary tract infection (UTI), assessment for viral, fungal, and bacterial infections, consideration of the patient's microbiome, and vigilance towards antibiotic toxicity. Advanced molecular diagnostic tools such as metagenomic sequencing and rapid point-of-care-testing, may offer future advances in accurate and timely identification of infectious aetiologies in AKI. Careful antibiotic selection, dosing, and duration, taking into account renal function and potential toxicity, are crucial in the era of increasing antibiotic resistance. The information presented in this review were obtained through a thorough literature search using relevant search terms on various databases including PubMed, Embase, and Cochrane Library. The review identified bacterial sepsis and UTI as common infectious syndromes associated with AKI, but also emphasized the need to consider other infectious aetiologies including viral, fungal and parasitic infections in certain clinical scenarios. The review also discussed the potential role of advanced molecular diagnostic tools in identifying infectious aetiologies in AKI and the importance of careful antibiotic selection, dosing, and duration. In conclusion, a comprehensive microbiological evaluation, coupled with the use of advanced diagnostic techniques and antibiotic stewardship, is vital for the effective management of AKI from suspected infectious aetiology, which can aid optimize patient outcomes.

Keywords: Acute kidney injury; infection; sepsis; urinary tract infection; sequelae

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Menace microbienne pour la santé rénale: examen du rôle des infections dans les lésions rénales aiguës

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Résumé:

L'insuffisance rénale aiguë (IRA) d'étiologie infectieuse est une affection complexe qui nécessite une évaluation microbiologique complète. Cela comprend le bilan de sepsis, l'évaluation de l'infection des voies urinaires (IVU), l'évaluation des infections virales, fongiques et bactériennes, la prise en compte du microbiome du patient et la vigilance à l'égard de la toxicité des antibiotiques. Les outils de diagnostic moléculaire avancés, tels que le séquençage métagénomique et les tests rapides au point d'intervention, pourraient offrir de futures avancées dans l'identification précise et rapide des étiologies infectieuses de l'IRA. Une sélection, un dosage et une durée minutieux des antibiotiques, en tenant compte de la fonction rénale et de la toxicité potentielle, sont cruciaux à l'ère de la résistance croissante aux antibiotiques. Les informations présentées dans cette revue ont été obtenues grâce à une recherche documentaire approfondie à l'aide de termes de recherche pertinents dans diverses bases de données, notamment PubMed, Embase et Cochrane Library. L'examen a identifié la septicémie bactérienne et l'infection urinaire comme des syndromes infectieux courants associés à l'IRA, mais a également souligné la nécessité de prendre en compte d'autres étiologies infectieuses, notamment les infections virales, fongiques et parasitaires, dans certains scénarios cliniques. L'examen a également discuté du rôle potentiel des outils de diagnostic moléculaire avancés dans l'identification des étiologies infectieuses de l'AKI et de l'importance d'une sélection, d'un dosage et d'une durée minutieux des antibiotiques. En conclusion, une évaluation microbiologique

complète, associée à l'utilisation de techniques de diagnostic avancées et à la gestion des antibiotiques, est essentielle pour la prise en charge efficace de l'AKI due à une étiologie infectieuse suspectée, ce qui peut contribuer à optimiser les résultats pour les patients.

Mots clés: Lésion rénale aiguë; infection; état septique; infection urinaire; séquelles

Introduction:

Acute kidney injury (AKI) is a complex clinical syndrome that is characterized by a sudden elevation in serum creatinine levels, a reduction in urine output, or a combination with this rapid decline in kidney function leading to the accumulation of metabolic waste products and a range of clinical manifestations and outcomes (1). AKI is however always diagnosed in the context of the patient as it is contextually a clinical diagnosis (2). The World Health Organization (WHO) has identified AKI as a global health priority due to its significant associated morbidity, mortality, and healthcare costs, especially as it is now the 10th leading cause of death globally (3).

In recent years, the role of infectious agents in causing AKI has been increasingly recognized, leading to a growing interest in the microbiological aetiology of this condition especially for sepsis associated AKI (SA-AKI) which has extremely high mortality (4-7). The UTI-associated AKI (UTI-AKI) is another increasingly described syndrome with a multifactorial pathogenesis (8). There are numerous methods to categorize AKI. However, the conventional approach involves classifying AKI based on urine output and changes in creatinine levels, which can be further categorized as prerenal, intrinsic renal, or postrenal (1). Syndromic classification is increasingly becoming more popular as physicians find it more clinically relevant. The syndromic classification captures the underlying pathophysiology and include the nephrotoxic, hepatorenal, and cardiorenal AKIs (1,9-11).

To successfully manage AKI, it is essential to accurately diagnose the underlying cause, including potential microbiological factors. This usually requires a thorough clinical assessment, relevant laboratory tests (such as blood and urine cultures), and imaging to identify potential sources of infection or inflammation (12). Precise diagnosis can guide targeted therapeutic strategies, such as administering appropriate antibiotics for bacterial infections or treating underlying factors for inflammation or injury. Therefore, it's important to have a good understanding of the possible microbiological and infectious causes of AKI for effective clinical management.

Given the significant impact of infectious agents on kidney health and patient outcomes, understanding the microbiological aetiology of AKI is crucial. Here, we provide an overview of the microbiological aetiology of AKI, with a focus on the role of infectious agents. This study reviewed the epidemiology of AKI caused by infectious agents, highlighting the different pathogens responsible for this condition and their modes of transmission. Additionally, the study delves into the pathogenesis of AKI caused by various infectious agents, including the mechanisms by which they can cause kidney damage and the factors that contribute to disease severity. The study concludes by discussing the various diagnostic techniques used to determine the cause of AKI and also covers the treatment and management approaches for AKI resulting from infectious cases.

Methododology:

A comprehensive literature search was conducted using various databases, including PubMed, Embase, and Cochrane Library, to identify relevant articles related to the microbiological evaluation of AKI with suspected infectious aetiology. The search was conducted using MESH terms such as "acute kidney injury," "AKI", "sepsis-associated AKI", "urinary tract infections associated AKI", "viral infections associated AKI", "bacterial infections associated AKI", "fungal infections associated AKI", and "microbiome in AKI". The search was limited to English language articles published from January 1980 to April 2023.

Relevant articles were identified through a systematic process that included screening of article titles, abstracts, and full texts. Additional articles were identified through manual searching of reference lists of relevant articles. Inclusion criteria for the review were articles that discussed the microbiological aspects of AKI with suspected infectious aetiology including sepsis-related AKI, UTI-related AKI, viral, fungal, and bacterial infections. Articles that discussed the diagnosis, treatment, and antibiotic stewardship in AKI with suspected infectious aetiology were also included. Data extraction and synthesis were performed independently by two reviewers. Any discrepancy was resolved through discussion and consensus.

Results and Discussion:

Infectious syndromes as aetiology of AKI

1. Urinary tract infections and AKI

Urinary tract infection (UTI) refers to primarily bacterial infection occurring any-

where from the urethral meatus to the perinephric fascia and kidneys (13). They are a relatively significant cause of AKI and can lead to significant morbidity and mortality if left untreated. In general, UTIs are more common in women than in men, with up to 60% of women experiencing a UTI at some point in their lifetime (14,15). To initiate UTI, the bacteria typically ascend the urethra into the bladder and can cause cystitis, pyelonephritis, or both. In severe cases, the bacteria can enter the bloodstream and cause sepsis, which is a significant risk factor for AKI.

The UTI-associated AKI (UTI-AKI) is increasingly being recognized as an important syndrome with associated high morbidity and mortality. The pathogenesis of UTI-AKI is multifactorial and involves both direct and indirect mechanisms. The direct mechanisms include bacterial invasion of the renal parenchyma, leading to pyelonephritis, interstitial nephritis, and/or glomerulonephritis. The indirect mechanisms include sepsis-induced hypotension, intrarenal vasoconstriction, and/or tubular obstruction by cellular debris or crystals (8). Immune-mediated injury, or the activation of pro-inflammatory cytokines also contributes to kidney injury (8,16).

The most common pathogens associated with UTI are Gram-negative bacteria (17). Of these, *Escherichia coli* is the most commonly implicated and accounts for up to 80% of community-acquired infections (18-21). Other Gram-negative bacteria such as *Klebsiella pneumoniae, Proteus mirabilis,* and *Pseudomonas aeruginosa*, are also common causes of UTI. Gram positive organisms such as *Enterococcus faecalis* and *Staphylococcus saprophyticus* can also cause UTI, especially in older adults and sexually active women. These bacteria express virulence factors, which promote inflammation and tissue damage. These include lipopolysaccharide, adhesins, and toxins. Acute kidney injury can occur as a complication of UTI in some cases. The mechanism of AKI due to UTI is complex and can involve several factors enumerated below.

Infection-related inflammation:

Urinary tract infection, particularly pyelonephritis which is an upper UTI, can cause inflammation of the kidneys. Inflammatory processes triggered by the infection can lead to damage to the kidney tissue, including the renal tubules. Inflammation can also result in increased permeability of blood vessels in the kidney, leading to leakage of fluid and proteins into the kidney tissue and impairing normal kidney function (22). Predisposing factors to development of UTI-AKI include advancing age, diabetes mellitus, upper UTI, afebrile status, and impaired baseline renal function (23). Advanced age is a known risk factor for UTI-associated AKI, as elderly patients may have reduced physiological reserves and increased vulnerability to infections. Diabetes mellitus predisposes patients to UTI-related AKI due to compromised immune function and impaired renal perfusion (23).

Furthermore, upper UTIs, which involve the kidneys pose a higher risk of AKI compared to lower UTIs (22). Additionally, afebrile UTI patients may not exhibit typical signs of infection, leading to delayed diagnosis and treatment, which can increase the risk of AKI. Lastly, patients with impaired baseline renal function such as those with pre-existing chronic kidney disease, may be more susceptible to UTI-related AKI due to reduced renal reserve (13). Therefore, vigilance and close monitoring is required in management of UTI especially in immunocompromised patients to avoid progression, thus preventing further renal damage and improving patient outcomes.

Obstruction:

UTI can cause obstruction in the urinary tract, which can lead to backflow of urine and increased pressure in the kidneys. This can disrupt normal kidney function and impair blood flow to the kidneys, leading to AKI. Obstruction can be caused by factors such as urinary stones, blood clots, or swelling of the urinary tract due to infection (24).

Toxins produced by bacteria*:*

Some bacteria that cause UTIs can produce toxins which can directly damage the kidney tissue. For example, certain strains of *E. coli*, which are a common cause of UTIs, can produce Shiga toxin that can cause kidney injury (25,26).

Immune response:

AKI may also be brought on by the immunological response to UTIs (27). The immune system may generate inflammatory mediators in reaction to the infection, which can harm kidney tissue and decrease kidney function (27-29).

Host factors:

Individual patient factors, such as age, overall health status, and pre-existing kidney disease, can also influence the development of AKI in the setting of UTI. Patients with pre-existing kidney disease or other risk factors for AKI may be more susceptible to kidney injury due to UTI (1).

It is important to note that not all UTIs will result in AKI, and the risk of AKI due to UTI varies depending on multiple factors. Prompt diagnosis and appropriate treatment of UTIs are important to prevent complications such as AKI. Treatment of UTI-related AKI involves the use of antibiotics to eradicate the bacterial infection and supportive measures such as hydration and electrolyte manage-

ment (1). In severe cases, renal replacement therapy may be necessary (1). Prevention of UTIs can be achieved through good hygiene practices, adequate fluid intake, and prophylactic antibiotic therapy in high-risk individuals.

2. Sepsis-associated AKI

The Surviving Sepsis Campaign 2016 International guidelines define sepsis as a life-threatening organ dysfunction caused by dysregulated host response to infection, spreads throughout the body (30). Sepsis is a leading cause of AKI in critically ill patients (31). The most commonly implicated bacterial species implicated in sepsis include *E. coli, K. pneumoniae,* and *P. aeruginosa* (32-34). Viral, fungal, and parasitic causes of sepsis are relatively uncommon (34). Respiratory, gastrointestinal, genitourinary, and skin or soft tissue infections are the most common foci of sepsis, accounting for more than 80% of cases (30,34). Urinary tract infections more commonly lead to culture positive sepsis. The pathogenesis of UTI-AKI is thought to differ from non-UTI-AKI but is also complex and multifactorial (35).

Sepsis results in widespread release of cytokines and other inflammatory mediators, which ultimately results in extensive inflammation and damage to various organs, including the kidneys where tubular cell injury and necrosis results in decline in glomerular filtration rate and ultimately lead to AKI (31,35-37). Previous assumption has been that hypotension causing hypoperfusion of kidneys was the major cause of AKI in sepsis, however, recently it has been proven that microvascular dysfunction with release of inflammatory mediators, cytokines, microparticles with adaptation of tubular cells, is the major contributor of sepsis induced AKI (31). It has also been suggested that patients with UTI-AKI may respond differently to interventions and have outcomes different from patients with non-UTI-AKI (1).

The severity of AKI in sepsis can vary, but it is often associated with a high mortality rate. In addition, sepsis-related AKI has been linked to an increased risk of developing chronic kidney disease (CKD) and end-stage renal disease (ESRD) (1,35). Therefore, early recognition and treatment of sepsis are critical in preventing the development of AKI and its associated complications. The management of sepsis-related AKI involves addressing the underlying infection, optimizing hemodynamic status, and providing supportive care, such as renal replacement therapy when necessary (30,31). Antibiotic therapy is the cornerstone of sepsis management and should be initiated as soon as possible after diagnosis (30,34).

3. Viral infections and AKI

Viral infections have been identified as potential causes of acute kidney injury AKI. The viruses that have been associated with AKI include adenovirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C viruses, and human immunodeficiency virus (HIV) (38-42). Direct viral invasion of kidney cells is one mechanism by which certain viruses can cause AKI. For example, viruses like cytomegalovirus (CMV) and adenovirus can directly invade renal tissue, leading to inflammation, necrosis, and dysfunction of the kidneys (41,43). This can result in direct damage to the renal cells and structures, leading to AKI. Immune-mediated injury is another mechanism by which viral infections can lead to AKI. Viral infections can trigger an immune response that results in inflammation and immune-mediated injury to the kidneys (44,45). This can occur through the formation of immune complexes during the viral infection that deposit in the kidneys, leading to glomerulonephritis.

Haemodynamic instability is another significant factor in the development of AKI during viral infections. Severe viral infections can cause hemodynamic instability such as hypotension, sepsis, or shock, which can reduce blood flow to the kidneys and result in ischemic injury (46). Reduced blood flow can impair the normal functioning of the kidneys and contribute to the development of AKI. Systemic inflammation is also a key mechanism by which viral infections can cause AKI. Viral infections can trigger a systemic inflammatory response that can directly or indirectly damage renal tissue (47,48). This can occur through the release of inflammatory mediators and cytokines during the viral infection, leading to inflammation and injury to the kidneys (38).

Rhabdomyolysis is another mechanism by which viral infections can contribute to AKI. Certain viral infections can cause muscle breakdown, resulting in the release of myoglobin into the bloodstream. Myoglobin can then accumulate in the kidneys, leading to myoglobin-induced kidney injury and potentially contributing to the development of AKI (49). Thrombotic microangiopathy is also a mechanism by which certain viral infections can cause AKI (50). Viral infections, such as human immunodeficiency virus (HIV), can cause widespread clotting of small blood vessels, impairing renal blood flow and leading to AKI (50,51).

Identifying the viral aetiology of AKI requires a thorough evaluation, including a detailed patient history, physical examination, and laboratory investigations. Serological testing for viral antibodies, viral nucleic acid test-

ing (such as polymerase chain reaction), and viral antigen detection are commonly used methods for identifying the viral cause of AKI. In some cases, renal biopsy may be necessary to confirm the viral aetiology of AKI (52,53). Viral infections can thus cause AKI through various mechanisms, including direct cytopathic effects, immune complex deposition, and drug toxicity. Although rare, AKI should be considered in patients with viral infections, especially those who are immunocompromised or have other risk factors for AKI.

4. Fungal infections and AKI

Fungal infections are increasingly recognized as a potential cause of acute kidney injury (AKI), particularly in immunocompromised individuals (54). Fungal infections can cause AKI through various mechanisms, including direct invasion of renal tissue, immune-mediated injury, thrombotic microangiopathy, and obstructive manifestations. Direct invasion of renal tissue by fungi can result in tissue damage and inflammation, leading to AKI (54). Fungal species such as *Candida*, *Aspergillus* and *Cryptococcus* can invade the renal tissue, leading to inflammation, necrosis, and dysfunction of the kidneys (55,56). This can result in direct damage to renal cells and structures, leading to AKI.

Immune-mediated injury is another mechanism by which fungal infections can lead to AKI (57). Fungal infections can trigger an immune response that results in inflammation and immune-mediated injury to the kidneys. This can occur through the formation of immune complexes or hypersensitivity reactions during the fungal infection, leading to glomerulonephritis or interstitial nephritis, which can contribute to the development of AKI (54,57).

Thrombotic microangiopathy is another mechanism by which fungal infections can cause AKI. Fungal infections, such as invasive aspergillosis, can cause widespread clotting of small blood vessels, impairing renal blood flow and leading to AKI (58-60). The formation of microclots in the renal vasculature can cause thrombotic microangiopathy, a condition characterized by microvascular thrombosis, platelet aggregation, and endothelial injury (61, 62). Obstructive manifestations of fungal infections can also lead to AKI (61,63). Fungal infections can cause obstruction in the urinary tract, leading to obstructive uropathy and subsequent renal dysfunction. Fungal elements can form mycotic balls or fungal balls in the renal pelvis, ureters, or bladder, leading to obstruction and impaired urine flow, which can result in AKI.

Diagnosing fungal infections as the cause of AKI requires a high index of suspicion and careful evaluation. A thorough patient history, physical examination, and laboratory investigations, including blood cultures, fungal serology, and imaging studies, may be necessary to identify the fungal aetiology of AKI. In some cases, renal biopsy may be required to confirm the presence of fungal elements in renal tissue.

Management of fungal-associated AKI involves prompt removal of any indwelling urinary catheters or other foreign bodies, as well as the initiation of appropriate antifungal therapy (12,64). In cases of obstructive uropathy, urgent decompression of the collecting system with placement of a nephrostomy tube may be necessary to preserve renal function. In severe cases, renal replacement therapy may be required until the patient's underlying infection is controlled and renal function recovers. Understanding the mechanisms by which fungal infections can cause AKI, including direct invasion, immune-mediated injury, thrombotic microangiopathy, and obstructive manifestations, is crucial for accurate diagnosis and management of AKI associated with fungal infections.

Role of microbiome in AKI

The human microbiome, which consists of trillions of microorganisms residing in and on the body, has been recognized as a crucial factor in human health and disease (65,66). Emerging evidence suggests that alterations in the microbiome can impact the development and progression of AKI. The microbiome can play a role in AKI through several mechanisms. First, dysbiosis, or an imbalance in the composition and function of the microbiome, can lead to the production of harmful metabolites or toxins that can directly damage renal tissue and impair renal function (67). For example, gut dysbiosis can result in increased production of trimethylamine-N-oxide (TMAO), a metabolite associated with cardiovascular and renal dysfunction, which can contribute to the development of AKI (68,69).

The microbiome can also influence the host immune response, leading to immune-mediated injury in the kidneys. Dysbiosis can trigger an abnormal immune response, leading to systemic inflammation and immune-mediated injury to renal tissue. This can result in inflammation, tissue damage, and impaired renal function, contributing to the development and progression of AKI (70,71). The microbiome can affect the systemic and renal hemodynamics (65,72). Microbial metabolites, such as short-chain fatty acids, can modulate renal blood flow, vascular tone, and blood pressure, which can have direct effects on renal function (73). Alterations in the microbiome can disrupt these regulatory mechanisms, leading to haemodynamic instability and contributing to AKI. Dysbiosis can affect the microbiome's capacity to control the imm-

une response and modify the host's reaction to sepsis (74). In septic individuals, this may lead to organ failure, systemic inflammation, and AKI .

An active area of research is figuring out how the microbiota affects AKI, and interventions targeting the microbiome may hold promise as potential therapeutic strategies for AKI. Strategies such as probiotics, prebiotics, faecal microbiota transplantation, and dietary interventions are being explored to modulate the microbiome and potentially mitigate the risk or severity of AKI.

Approach to management of patients with microbial-associated AKI

In the context of AKI with suspected infectious aetiology, a systematic and comprehensive microbiological workup is imperative for appropriate diagnosis and management. This includes a step-wise approach that encompasses sepsis workup, evaluation of UTI (complicated and uncomplicated), assessment for viral, fungal, and bacterial infections, consideration of the patient's microbiome and vigilance towards antibiotic toxicity.

Sepsis workup:

Suspected sepsis requires expedited blood cultures to identify the causative microorganism(s) and guide timely initiation of appropriate antibiotic therapy (31). Multiple blood cultures from different sites should be obtained prior to initiating antibiotics, if feasible, to maximize the likelihood of positive culture results. Concurrent laboratory tests such as complete blood count, coagulation studies, and inflammatory markers aid in determining the severity and progression of sepsis.

UTI work up:

A urine culture with sensitivity testing should be performed in all suspected cases of UTIs with AKI. Quantitative urine cultures are preferred for accurate results (75,76). Urine culture identifies the specific microorganisms responsible and facilitates tailored antibiotic selection. In complicated UTIs, additional imaging studies such as computerized tomographic (CT) or ultrasound scan may be necessary to evaluate for urinary tract abnormalities or abscesses.

Viral, fungal, and bacterial workup:

In certain clinical scenarios, viral, fungal, and bacterial infections may need to be considered. For instance, in immunocompromised patients, viral infections such as CMV or polyomavirus may be suspected. Risk factors such as recent antibiotic use or indwelling urinary catheters may prompt consideration of fungal infections caused by *Candida*. Extended-spectrum beta-lactamase (ESBL) testing may be warranted in cases of suspected antibiotic-resistant bacterial infections.

Other factors worth considering:

Antimicrobial therapy, in addition to other supportive therapies, may be required to effectively manage AKI. Renal replacement therapy (RRT) is a common intervention used in cases of severe AKI or when conservative management fails to improve renal function. RRT includes haemodialysis, peritoneal dialysis, and continuous renal replacement therapy. Other supportive therapies may include electrolyte replacement, blood pressure management, and nutritional support.

Prevention:

In addition to contributing to emergence of antibiotic-resistant bacteria that can cause serious infections that can result in AKI, antibiotic abuse and misuse can also cause renal impairment. However, when used appropriately, antibiotics can prevent development of AKI (77,78). AKI-causing diseases such as hepatitis and COVID-19 can be prevented by vaccinations. For proper kidney function to be maintained, adequate water intake is essential as AKI can develop as a result of dehydration, especially in persons who are already at higher risk due to underlying medical disorders.

Early recognition and management of infections that can lead to AKI are critical in preventing the progression of the disease. Timely diagnosis and appropriate treatment of infections can help reduce the risk of complications and improve outcomes in people with AKI. It is important to note that the comprehensive management of AKI requires a multidisciplinary approach, involving physicians, nurses, pharmacists, and other healthcare professionals. The management of AKI should be guided by the underlying cause, severity of the condition, and the patient's clinical status.

Conclusion and future direction:

There is still much to learn about the pathophysiology of AKI caused by infectious pathogens, despite progress in diagnosis and treatment. To find novel biomarkers that can help in the early identification and diagnosis of AKI brought on by infectious pathogens, more study is required. Additionally, more research is required to examine the possible application of novel therapeutics, such as immunomodulatory drugs and stem cell therapies, for the prevention and treatment of AKI.

Furthermore, for the development of targeted therapeutics that can successfully treat and prevent this disorder, it will be essential to comprehend the interaction between infectious pathogens and the immune system in the pathogenesis of AKI. To address this significant public health concern and enhance

outcomes for patients with AKI brought on by infectious agents, doctors, researchers, and public health officials must work together. The emerging understanding of how the microbiome influences the risk and severity of AKI is another significant advance. Modulation of the microbiome may be a viable strategy for preventing and treating AKI.

Despite recent advances, much remains to be done to improve the prevention, diagnosis, and management of AKI caused by infectious agents. Future research should focus on developing new strategies for preventing infections, identifying novel biomarkers for early detection and monitoring of AKI, and exploring the role of the microbiome in AKI pathogenesis. By addressing these challenges, we can hope to reduce the burden of AKI and improve outcomes for affected patients.

Contributions of authors:

AB conceived the review idea, designed the outline, wrote the aspects of abstract and conclusion, and reviewed the manuscript; MN searched the literature for relevant publications, wrote the aspects of introduction, methodology, infectious syndromes, patient approach, and future directions. Both authors approved the final manuscript.

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