Review Article

Overview of sepsis associated acute kidney injury: literature review

Mona Al-Shahrani1*, Sarah Khalil Soofy2, Mouaz Abdullah Mohammad3, Ibrahim Yahya Alfalahi4, Ali Alhussain Alhzam4, Hammad Ahmed Alabdali4, Raghad Abdulrahman Alahmadi5, Rakan Saqer Alutaibi5, Abdullah Mohammed Alluhaidah6, Khalid Seraj Almalki2, Fahad Zaid Alamri7, Mahdi Ali Alhutaylah8

1Department of Nephrology, King Khalid University, Abha, Saudi Arabia
2College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
3College of Medicine, Umm Al-Qura University, Mecca, Saudi Arabia
4College of Medicine in Al-Qunfudhah, Umm Al-Qura University, Mecca, Saudi Arabia
5College of Medicine, Taif University, Taif, Saudi Arabia
6Department of Internal Medicine, Ar Rass General Hospital, Ar Rass, Saudi Arabia
7College of Medicine, Medical university of Silesia, Katowice, Poland
8College of Medicine, Najran University, Najran, Saudi Arabia

Received: 12 December 2020
Revised: 26 December 2020
Accepted: 28 December 2020

*Correspondence:
Dr. Mona Al-Shahrani,
E-mail: mona.alshahrani@medportal.ca

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20210001

ABSTRACT

The incidence of acute kidney injury has been estimated to be around a fifth of the adult patients during their hospital stays. Sepsis is estimated to be the commonest cause for AKI development in critically-ill patients; contributing to the pathology in 20-50% of the cases. We reviewed some aspects of sepsis-associated AKI. Among the risk factors that may contribute to the development of AKI, age, sex, and the presence of comorbidities as diabetes, heart, and liver diseases were reported as significant factors associated with the development of the condition. The pathophysiology of sepsis-induced AKI is still unclear; however, some authors said that it may be related to the hypoperfusion of the renal tissue and subsequently induced ischemia. This theory was supported by animal studies; however, other investigations on humans reported no association between the two events. On the other hand, we believe that sepsis-induced AKI is probably due to the associated severe inflammatory state and hemodynamic instability are the main accusants. The management of this condition requires early diagnosis and early intervention by managing sepsis. Moreover, vasopressors as epinephrines have proved efficient in managing the shock state, even better than renal replacement therapy.

Keywords: Sepsis, Acute kidney injury, Inflammation

INTRODUCTION

The incidence of acute kidney injury (AKI) has been estimated to be around a fifth of the adult patients during their hospital stays. Moreover, it has been estimated that around 50% of critically-ill patients are affected by AKI morbidity.1,2 The prognosis of AKI is usually bad when associated with other comorbidities which is the case with critically-ill hospitalized patients.3-6 Moreover, mortality records from this phenomenon have been estimated at 20-40% rates attributable to the underlying disorder.7,8 In these patients, the etiology behind the development of AKI usually attributes to major surgeries, hypovolemia, iatrogenic nephrotoxicity, and sepsis.7
The incidence rate of developing AKI even greater. A multicenter study conducted by Uchino et al reported that the incidence rate could be up to 47.5% which can lead to a high mortality rate in these patients as 60% of the sepsis-induced AKI patients were dead. Another multi-center Chinese study conducted by Jiang et al reported an incidence rate of 51% in sepsis patients that were admitted to the ICU. The authors also reported that most of these patients developed AKI on the 4th day of hospital stay. On the other hand, previous investigations also showed that AKI can also increase the risk of developing sepsis. Mehta et al reported that after five days of having AKI, 40% of their patients developed sepsis. These high rates indicate the fact that sepsis-induced AKI is a common disorder and are both independently associated, and therefore, interventional approaches should be conducted. For proper intervention, early detection and diagnosis have been reported to be crucial in achieving better diagnostic outcomes and consequently enhancing the prognosis of the disorder.

The pathophysiology of sepsis-associated AKI has been controversial and vague for a long time. However, recent approaches have provided useful information in the field which may have made it closer to a better understanding. Studies showed that reduced renal perfusion and ischemia may contribute to the lesion, and are even considered the primary factors behind the development of AKI. However, this theory was not always validated as discussed before, and new evidence shows that inflammation and subsequent cell apoptosis are also contributing agents. These reports are logical as tissue inflammation and microvascular complications have been associated with sepsis-associated end-organ failure. Tissue inflammation induced by sepsis might contribute to the pathophysiology of AKI.
involve the release of many cytokines and acute phase reactants that may contribute to the pathology. For instance, nitric oxide, and reactive oxygen species have been described to be playing a role in end-arterial thrombosis and endothelial damage.\textsuperscript{38-41} An in vitro study conducted by Langenberg et al showed that sepsis-associated AKI induced a state of inflammation with patchy changes, but with a limited renal tubular injury.\textsuperscript{36} Moreover, the authors found that animals with sepsis-associated AKI showed higher RBF rates. On the other hand, previous studies on humans showed that RBF was much reduced and therefore, it was thought to be the main contributing factor.\textsuperscript{42,44} These different findings between animal and human studies indicate the need for further comparative studies and also necessitates the need for more histological examination of the affected kidneys for better examination and diagnosis.

**REPORTED MARKERS IN SEPSIS-ASSOCIATED AKI**

Previous studies showed that many markers have been associated with the development of AKI that is attributable to sepsis. These markers have been divided into; metabolomics, standard and serum biomarkers, urinary markers, experimentally associated markers and microRNAs (mRNAs).\textsuperscript{45} In general, the diagnosis of AKI is based on the presence of elevated levels of serum urea and creatinine, in addition to the urine output of the patients. Kashaki et al have also reported the presence of other markers that are associated with AKI diagnosis.\textsuperscript{46} These include cystatin C, neutrophile gelatinase-associated lipocalin (NGAL), kidney injury molecule -1 (KIM-1), urinary insulin like growth factor binding protein-7 (IGFBP-7), interleukin 18 (IL-18), interleukin 18 (IL-18), urinary tissue inhibitor of metalloproteinase 2 (TIMP-2), urine angiotensinogen, calprotectin, and liver fatty acid-binding protein.\textsuperscript{46} The presence of these biomarkers may help in the early detection of renal injury, and consequently, the early initiation of therapeutic modalities for better prevention of complications and chronicity. Among the previously mentioned biomarkers, Klein et al conducted a meta-analysis to find the most significant risk biomarkers associated with AKI.\textsuperscript{47} The authors reported that in 15,928 patients with critical AKI injuries, the most significant biomarkers were serum NGAL, cystatin C, and urinary TIMP-2 and IGFBP-7. Although these markers have been proven to be associated with AKI and might be considered as sensitive agents for early detection of the lesion, the diagnosis, and initiation of therapy are not dependant on them, but also other clinical and laboratory markers. The creatinine clearance test has been the most sensitive factor for diagnosis of AKI and initiation of therapy. Therefore, these biomarkers should be reconsidered with other clinical and laboratory features when applied clinically.\textsuperscript{48} Previous animal model studies have also shown that sepsis-associated AKI is related to the presence of metabolomic markers. These include N-acetylglutamine, lactate, alanine, myoinositol, pyruvate, glutamine, glucose, valine, ascorbic acid, N-acetyl-aspartate aminoacidic acid, and betaine in addition to other markers that has been found to be correlated with NGAL, and serum creatinine.\textsuperscript{49} Additional various findings have been also associated with the different forms of AKI. These include mesangial cells, podocytes, tubular cells, endothelial cells, fibroblasts, macrophages. Besides, HSP70, HSP27, HSP47, HSP90, HSP60, and HSP32 have been also expressed.\textsuperscript{50} A previous investigation showed that HSP 72 was also significantly elevated in the first three days of AKI in 30.4% of their population.\textsuperscript{51} Additionally, miRNAs have been also reported to be associated with tissue inflammation and apoptosis in AKI. These include; miR-9, miR-15a, miR-16, miR-146 a/b, miR-223, miR-155, miR-203, miR-126, and miR-199a.\textsuperscript{52,53} These agents are supposed to play important roles against tissue inflammation and proliferation, however, they may lead to serious side effects as vascular complications, and cellular apoptosis.\textsuperscript{50}

**THERAPEUTIC AND INTERVENTIONAL APPROACHES IN SEPSIS-ASSOCIATED AKI**

Kellum et al said that preventing sepsis-associated AKI from developing in nearly impossible as most patients would have developed during hospitalization at presentation.\textsuperscript{54} Therefore, it is recommended that sepsis treatment should be inaugurated as early as possible using suitable antibiotics that can enhance the prognosis of the condition and intervene against the development of sepsis-associated severe complications including AKI. Bagshaw et al showed that delaying the treatment of sepsis with antibiotics significantly increased the risk of developing early AKI.\textsuperscript{55} On the other hand, other conditions should be considered when choosing the appropriate treatment for sepsis. For instance, nephrotoxic agents, like vancomycin, aminoglycosides, amphotericin B, and radiopaque substances, should be avoided or used with caution to prevent the deterioration of the kidney functions. Accordingly, the limited use of these agents should be approached with caution and with continuous monitoring. Renal replacement therapy (RRT), and vasopressins have been also described in the literature as preventive measures that main intervene against the bad prognosis of the kidney lesions. Rhodes et al recommended the use of norepinephrine for the management of septic shock, and therefore, reduce the complications as AKI.\textsuperscript{56} On the other hand, previous investigations showed that dopamine should not be used as a renoprotective modality in septic shock patients due to the remarkable adverse effects it can produce, unlike norepinephrine which possesses less frequent side events.\textsuperscript{56-59} Moreover, Gordon et al in a clinical trial concluded that using vasopressin therapy significantly lowered the need to conduct RRT.\textsuperscript{60} Using pharmacological modalities is usually preferred over invasive procedures which frequently lead to the development of serious side effects and may aggravate the condition. Moreover, the timing of conducting RRT has been controversial among studies in the literature.
Some observational studies showed that early conduction of the modality can decrease the severity of AKI while other randomized trails showed that no association was found. Therefore, it has been concluded that adequate conservative and symptomatic treatment can dispose of the need to conduct RRT modalities.

After the treatment of sepsis by suitable antibiotics, physicians should immediately start treating AKI and other conditions that may affect the prognosis. Early treatment modalities include caring for fluids and volume status of the patient that is sufficient enough to achieve adequate perfusion of the kidney, for it to heal. Moreover, this step should be done carefully to avoid hypervolemia and the development of other severe, and unnecessary complications. This can happen following the previous AKI-induced plasma protein loss, and increased capillary permeability which attributes for the accumulation of fluids in the body and developing complications. Specifically, in the renal parenchyma, fluid overload can increase the venous pressure reducing renal perfusion and glomerular filtration rate, which may lead to further accumulation of fluids from AKI-induced renin secretion and salt and water retention. Therefore, it has been agreed that the appropriate use of fluid resuscitation with continuous monitoring of the patient’s hemodynamics should be approached carefully for obtaining better outcomes. Saline and crystalloid solutions have shown favorable outcomes, while gelatine and hydroxyethyl starches have been associated with increased risk of sepsis-induced AKI. Other reported pharmacological modalities include the use of alkaline phosphatase which is a human-recombinant subject designed to mimic an endogenous enzyme that may play a role in protecting the kidneys against the manifestations of sepsis. Moreover, angiotensinogen II has been reported to increase the glomerular filtration rate and enhance the nourishment of both kidneys.

CONCLUSION

In this review, we summarized some of the aspects of sepsis-associated AKI including the demographics, risk factors, pathophysiology, prevention, and treatment. We recommend that further studies should be conducted for better management of the condition as the risk of mortality might be high. Moreover, early management of sepsis should be approached by clinicians to prevent any complications as AKI. Moreover, many markers have been found as good and early indicators of AKI, however, these can be used solely due to the presence of more sensitive agents as creatinine clearance. Additionally, previous studies showed that conservative treatment might be more effective than RRT in attaining better clinical outcomes and avoiding side effects.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL. Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482-93.
2. Macedo E, Garcia-Garcia G, Mehta RL, Rocco MV. International Society of Nephrology 0 by 25 Project: Lessons Learned. Ann Nutr Metab. 2019;74(suppl 3):45-50.
3. Uchino S, Kellum JA, Bellomo R. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813-8.
4. Bagshaw SM, Uchino S, Bellomo R. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol. 2007;2(3):431-9.
5. Bouchard J, Acharya A, Cerda J. A prospective international multicenter study of AKI in the intensive care unit. Clin J Am Soc Nephrol. 2015;10(8):1324-31.
6. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23.
7. Uchino S, Kellum JA, Bellomo R. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813-8.
8. Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkonen M, Karlsson S, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med. 2013;39(3):420-8.
9. Mehta RL, Bouchard J, Soroko SB. Sepsis as a cause and consequence of acute kidney injury: Program to Improve Care in Acute Renal Disease. Intensive Care Med. 2011;37(2):241-8.
10. Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML. Incidence and outcomes of acute kidney injury in intensive care units: A Veterans administration study. Crit Care Med. 2009;37(9):2552-8.
11. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis?. Nat Rev Nephrol. 2011;7(4):209-17.
12. Prowle JR, Ishikawa K, May CN, Bellomo R. Renal blood flow during acute renal failure in man. Blood Purificat. 2009;28(3):216-25.
13. Langenberg C, Wan L, Egi M, May CN, Bellomo R. Renal blood flow in experimental septic acute renal failure. Kidney Int. 2006;69(11):1996-2002.
14. Murugan R, Karajala-Subramanyam V, Lee M. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. Kidney Int. 2010;77(6):527-535.
15. Takasu O, Gaut JP, Watanabe E, To K, Fagley RE, Sato B, et al. Mechanisms of cardiac and renal
dysfunction in patients dying of sepsis. Am J Respir Crit Care Med. 2013;187(5):509-17.
16. Hotchkiss RS, Swanson PE, Freeman BD. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med. 1999;27(7):1230-51.
17. De Backer D, Creteur J, Preiser J-C, Dubois M-J, Vincent J-L. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med. 2002;166(1):98-104.
18. Wang Z, Holthoff JH, Seely KA. Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. Am J Pathol. 2012;180(2):505-16.
19. Seely KA, Holthoff JH, Burns ST, Wang Z, Thakali KM, Golden N, et al. Hemodynamic changes in the kidney in a pediatric rat model of sepsis-induced acute kidney injury. Am J Physiol Renal Physiol. 2011;301(1):F209-17.
20. de Mendonça A, Vincent JL, Suter PM. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000;26(7):915-21.
21. Chertow GM, Soroko SH, Paganini EP. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. Kidney Int. 2006;70(6):1120-6.
22. Thakar CV, Liangos O, Yared J-P. ARF after open-heart surgery: Influence of gender and race. Am J Kidney Dis. 2003;41(4):742-51.
23. Pannu N, James M, Hemmelgarn BR. Modification of outcomes after acute kidney injury by the presence of CKD. Am J Kidney Dis. 2011;58(2):206-13.
24. Bagshaw SM, Laupland KB, Doig CJ. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care. 2005;9(6):R700-9.
25. Chawla LS, Bellomo R, Bhiorac A. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol. 2017;13(4):241-57.
26. Wiedermann CJ, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. Intensive Care Med. 2010;36(10):1657-65.
27. Lima RSA, Marques CN, Silva Júnior GB. Comparison between early and delayed acute kidney injury secondary to infectious disease in the intensive care unit. Int Urol Nephrol. 2008;40(3):731-9.
28. Jiang L, Zhi Y, Luo X. Epidemiology of acute kidney injury in intensive care units in Beijing: the multi-center BAKIT study. BMC Nephrol. 2019;20(1):468.
29. Mehta RL, Bouchard J, Soroko SB. Sepsis as a cause and consequence of acute kidney injury: Program to Improve Care in Acute Renal Disease. Intensive care Med. 2011;37(2):241-8.
30. Rewa O, Bagshaw SM. Acute kidney injury-epidemiology, outcomes and economics. Nat Rev Nephrol. 2014;10(4):193-207.
31. Hobson C, Ozrazgat-Baslangi T, Kuxhausen A. Cost and Mortality Associated With Postoperative Acute Kidney Injury. Ann Surg. 2015;261(6):1207-14.
32. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(1):3365-70.
33. Gómez H, Kellum JA. Sepsis-induced acute kidney injury, Curr Opin Crit Care. 2016;22(6):546-53.
34. Pool R, Gomez H, Kellum JA. Mechanisms of organ dysfunction in sepsis. Crit Care Clin. 2018;34(1):63-80.
35. Gots J, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016;353:i1585.
36. Langenberg C, Gobe G, Hood S, May CN, Bellomo R. Renal histopathology during experimental septic acute kidney injury and recovery. Crit Care Med. 2014;42(1):e58-67.
37. Maiden MJ, Otto S, Brealey JK. Structure and Function of the Kidney in SepticShock. A Prospective Controlled Experimental Study. Am J Resp Crit Care Med. 2016;194(6):692-700.
38. Post EH, Kellum JA, Bellomo R, Vincent J-L. Renal perfusion in sepsis: from macro- to microcirculation. Kidney Int. 2017;91(1):45-60.
39. Chelazzi C, Villa G, Mancinelli P, De Gaudio AR, Adembri C. Glycocalyx and sepsis-induced alterations in vascular permeability. Crit Care. 2015;19(26).
40. Tsukahara Y, Morisaki T, Kojima M, Uchiyama A, Tanaka M. iNOS expression by activated neutrophils from patients with sepsis. ANZ J Surg. 2001;71(1):15-20.
41. Guerci P, Ergin B, Ince C. The macro- and microcirculation of the kidney, Best Pract Res Clin Anaesthesiol. 2017;31(3):315-29.
42. Prowle JR, Ishikawa K, May CN, Bellomo R. Renal plasma flow and glomerular filtration rate during acute kidney injury in man. Ren Fail. 2010;32(3):349-55.
43. Redfors B, Bragadottir G, Sellgren J, Swärd K, Ricksten S-E. Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. Intensive care Med. 2011;37(1):60-7.
44. Prowle JR, Molan MP, Hornsey E, Bellomo R. Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: a pilot investigation. Crit Care Med. 2012;40(6):1768-1776.
45. Petejova N, Martinek A, Zadrzaj J. Acute Kidney Injury in Septic Patients Treated by Selected Nephrotoxic Antibiotic Agents-Pathophysiology and Biomarkers-A Review. Int J Mol Sci. 2020;21(19):7115.
46. Kianoush K, Wisit C, Claudio R. Biomarkers of acute kidney injury: the pathway from discovery to
47. Klein SJ, Brandtner AK, Lehner GF. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2018;44(3):323-36.
48. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). Best Practice Res Clin Anaesthesiol. 2017;31(3):331-44.
49. Izquierdo-Garcia JL, Nin N, Cardinal-Fernandez P. Identification of novel metabolomic biomarkers in an experimental model of septic acute kidney injury. Am J Physiol Renal Physiol. 2019;316(1):F54-62.
50. Chebotareva N, Bobkova I, Shilov E. Heat shock proteins and kidney disease: perspectives of HSP therapy. Cell Stress Chaperones. 2017;22(3):319-43.
51. Morales-Buenrostro LE, Salas-Nolasco OI, Barrera-Chimal J. Hsp72 Is a Novel biomarker to predict acute kidney injury in critically ill patients. PLOS ONE. 2014;9(10):e109407.
52. Giza DE, Fuentes-Mattei E, Bullock MD. Cellular and viral microRNAs in sepsis: mechanisms of action and clinical applications. Cell Death Differ. 2016;23(12):1906-1918.
53. Fan P-C, Chen C-C, Chen Y-C, Chang Y-S, Chu P-H. MicroRNAs in acute kidney injury. Human Genomics. 2016;10(1):29.
54. Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, et al. The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock. Am J Respir Crit Care Med. 2016;193(3):281-7.
55. Bagshaw SM, Lapinsky S, Dial S. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med. 2009;35(5):871-81.
56. Rhodes A, Evans LE, Alhazzani W. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.
57. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779-89.
58. De Backer D, Aldecoa C, Njimi H, Vincent J-L. Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. Crit Care Med. 2012;40(3):725-30.
59. Gordon AC, Russell JA, Walley KR. The effects of vasopressin on acute kidney injury in septic shock. Intensive Care Med. 2010;36(1):83-91.
60. Gordon AC, Mason AJ, Thirunavukkarasu N. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the vanishing randomized clinical trial. JAMA. 2016;316(5):509-18.

Cite this article as: Al-Shahrani M, Soofy SK, Mohammad MA, Alfalali IY, Alhazmi AA, Alabdali HA, et al. Overview of sepsis associated acute kidney injury: literature review. Int J Community Med Public Health 2021;8:849-54.