Anaesthesiology, Perioperative & Critical Care Medicine

OA Critical Care
Open Access

Critical Review

Prediction of acute kidney injury during sepsis: unsolved mystery yet

N Sharawy[1,2,*]

Abstract

Introduction

Acute kidney injury (AKI), the most common part of the multiple organ dysfunction syndrome, is the most frequent cause of death in septic patients admitted to intensive care units. The pathogenesis of sepsis-induced AKI is a controversy area. Whether pre-renal transit AKI or direct tubular injury is the determinant factor for development of permanent renal AKI during sepsis, remain a matter of debt. In addition, the renal hemodynamic changes during sepsis is another unanswered question.

Conclusion

Full understanding of the mechanism of AKI is an essential step for development of ideal biomarker or tool, which is one of the research priority today The aim of this review are to discuss briefly the recent suggested mechanisms of AKI, and to outline the current development in AKI predictive tool and marker during septic shock.

Introduction

Multiple organ dysfunction syndrome is the most frequent cause of death in septic patients admitted to intensive care units. Acute renal failure, recently termed acute kidney injury (AKI), is the most common part of the multiple organ dysfunction syndrome. The great interest for the role of AKI in the ICU is contributed to its association with high mortality, morbidity and economic costs. It develops as a result of the reductions in renal blood flow (RBF), cellular and humoural immune system response to infection, nephrotoxic drugs and cellular injury[1–3].

One important controversy area in the field of AKI is the pathogenesis of AKI. The classification of AKI into pre-renal and renal may be questionable today. The pre-renal state is very transient and mild, but when it becomes severe, prolonged and with already compromised kidney, the pre-renal state can lead to renal AKI. In addition, the fact that acute tubular necrosis (ATN) is the main pathological character of AKI seems to be challenged by the recent findings that renal blood flow may not be reduced, at least in sepsis, and other types of cell damage may occur[4].

The early identification of at-risk patients and prevention of acute kidney injury to reduce mortality rate (50%–70%) associated with acute kidney injury in sepsis is essentially required[5]. However, failure of AKI preventive strategies is contributed to the lack of real-time sensitive and specific renal biomarkers and diagnostic tool, which allow the early detection of AKI. One of the research priority today is to find a tool or marker for an early prediction of AKI, to prevent or attenuate persistent AKI in patients with transient AKI[6].

The aims of this review are to discuss briefly recent advance in understanding the pathological changes in sepsis-induced AKI, and the current investigated tools and biomarkers with their advantages and limitations in field of AKI.

Discussion

Causes and classification of acute kidney injury

AKI could be contributed to pre-renal (functional) or renal [structural, or acute tubular necrosis (ATN)] injuries. While pre-renal AKI is not associated with histopathological renal injury, acute tubular necrosis is associated with reduced renal blood flow. Unlike to pre-renal, renal persists even when the hemodynamic status has been restored[7]. It is usually assumed that decreased renal perfusion is the initial cause for transient AKI and may ultimately lead to acute tubular necrosis when it persists[6].

For clinical investigation, classification scores of AKI were developed. RIFLE classification (risk, injury, failure, loss, end-stage kidney disease) defines three grades of severity and two outcome classes, by using the serum creatinine and urine output[1]. RIFLE was modified recently by the AKI Network (AKIN), which defined AKI as an abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL (≥26.4 μmol/L), a percentage increase in serum creatinine of ≥50% (1.5-fold from baseline) or a reduction in urine output (oliguria of <0.5 mL/kg/h for >6 h)[1].

Urine microscopy is used to differentiate pre-renal azotaemia and renal AKI (e.g. granular casts and renal tubular epithelial cells in acute tubular necrosis). In addition, fractional excretion of sodium (FeNa) could differentiate pre-renal (<1%) and renal (>1%) cause of AKI[8].

However, serum creatinine, the urine microscopic changes and FeNa changes are usually seen relatively

*Corresponding author
Email: nivinsharawi@gmail.com

[1]Department of Anaesthesia, Dalhousie University, Sir Charles Tupper Medical building, Room 6H-1, 5850 College street, Halifax, Nova Scotia B3H 2Y9, Canada
[2]Kasr EL Eni, Faculty of Medicine, Cairo University, Cairo, Egypt

FOR CITATION PURPOSES: *Sharawy N.* Prediction of acute Kidney injury during sepsis: Unsolved mystery yet. OA Critical Care 2013 Oct 01;1(2):14.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Critical Care
Open Access

Critical Review

late, and thus are not sensitive for early detection of AKI[1]. In addition, there is no evidence that urine tests can discriminate pre-renal azotaemia from renal AKI (ATN), particularly in septic patients[8]. Since the time and type (pre-renal/renal) of AKI are important for development of preventive strategies, there is an urgent need for new predictive tool or biomarker based on the full clear understanding of the pathological changes associated with sepsis induced AKI.

Pathophysiological changes of acute kidney injury: Figure 1

The pathophysiology of AKI in sepsis is complex and includes haemodynamic changes, renal parenchyma inflammatory changes and obstruction of tubules with necrotic cells and debris[9].

Haemodynamic changes within kidney during sepsis remain not clearly understood. For several decades it was thought that hypotension associated with sepsis results in a decrease in RBF, compensatory increase in renal vascular resistance (RVR) to maintain glomerular filtration rate (GFR) and decline in capillary perfusion. This can lead to epithelial injury (swelling, cast formation, cell sloughing) that can disrupt tubular–glomerular feedback regulation of GFR and cause reduction in GFR[10].

While long-standing presumption that AKI associated with sepsis is mainly, if not completely due to an increase in RVR and decrease in RBF, some experimental studies reported that septic AKI may be associated with renal vasodilation and increased RBF[10,11]. This observation was further supported by small clinical cohort study that reported that RBF was either preserved or increased in septic patients[9,12]. In addition, Langenberg et al.[13] found that in addition to generalised vasodilation and the increased cardiac output, there was renal vasodilation accompanied by a prominent increase in RBF. He found also that the increase in RBF was associated with a significant decrease in creatinine clearance and a four-fold increase in serum creatinine. Chvojka et al.[14] found a significant renal microvascular and metabolic stress in hyperdynamic septic shock without apparent renal vasoconstriction or changes in oxygen consumption and renal histology, and he suggested that renal venous congestion could contribute to the pathogenesis of septic AKI. These recent findings strongly suggest that sepsis-induced AKI is a hyperemic injury, and that dilatation of both afferent and efferent arterioles (with efferent dilatation is greater than afferent dilatation) could lead to decreased glomerular capillary pressure and filtration[9].

Another important factor that could lead to reduction in GFR is sepsis-associated proximal tubule injury, which results in inadequate sodium re-absorption and reduced GFR through tubulo-glomerular feedback mechanism[15]. The proximal tubule injury could be due to endothelium injuries and activation of leukocyte both of which will result in amplification of renal arteriole vasoconstriction. This could be due to imbalance between vasoconstrictor substances [such as of endothelin-1, angiotensin II, thromboxane A2, prostaglandin H2, leukotrienes C4 and D4, and adenosine as well as sympathetic nerve stimulation] and other vasodilator substances that are produced by the endothelium [such as nitric oxide]. In addition, vasoconstriction is augmented by the vasoactive cytokines, generated due to increased leukocyte-endothelial adhesion[16–22] [such as TNFα, IL1, IL-6, IL-12, IL-15, IL-18 and IL-32]. Vasoconstriction, endothelial-leukocyte interactions and activation of the coagulation system result in regional compromise of the microcirculation especially in the outer medulla, due to the anatomical character of the capillaries in the outer medulla that makes them very vulnerable to occlusion[15].

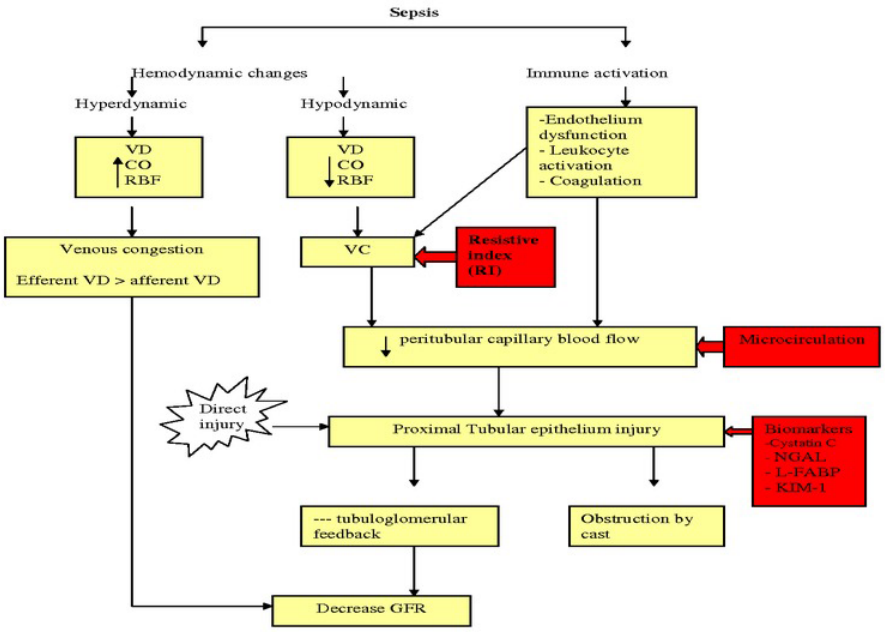

Figure 1: The recently developed tools and biomarkers according to the suggested mechanisms for acute kidney injury during sepsis. VD, vasodilation; CO, cardiac output; RBF, renal blood flow; VC, vasoconstriction; GFR, glomerular filtration rate; NGAL, neutrophil gelatinase associated lipocalin; L-FABP, L-type fatty acid-binding protein; KIM-1, Kidney injury moleclue-1.

FOR CITATION PURPOSES: *Sharawy N.* Prediction of acute Kidney injury during sepsis: Unsolved mystery yet. OA Critical Care 2013 Oct 01;1(2):14.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Critical Care
Open Access

Critical Review

In addition, previous studies demonstrated that a decrease in total RBF alone cannot entirely account for the reduction in GFR and that the heterogeneity of the blood flow distribution between cortex (glomeruli) and the medulla (tubule) with regional shift of blood to medulla could be of greater importance during an episode of AKI[14,15].

Since the three critical determinant issues in AKI are renal hemodynamics, peritubular microcirculatory dysfunction and renal tubular injury, they were used as basic background for the development and validation of different tools and biomarkers.

Current available tools and Biomarkers for AKI prediction: Figure 1

1. *Doppler-based renal arterial resistive index (RI)*

Ultrasonography (US) is used routinely to assess renal morphology. In addition, renal Doppler US helps to assess large arterial or venous abnormalities and evaluate changes in intra-renal perfusion due to diseases of the renal parenchyma. Recently it was found that Doppler ultrasonography with arterial RI calculation can be useful as an early indicator of the vascular resistance changes and in the determination of the optimal systemic hemodynamicsrequired for renal perfusion[8].

This easily calculated parameter is defined as RI = [(peak systolic velocity – end diastolic velocity)/ peak systolic velocity]. It theoretically ranges from 0 to 1and it is normally lower than 0.7 with age differences[6].

RI is a non-invasive Doppler-measured parameter that is directly correlated with intra-renal arterial resistance. Several factors could determine the RI such as arterial compliance (i.e. renal interstitial and intra-abdominal pressures), age and central hemodynamic parameters[7]. Therefore, renal circulatory response to sepsis estimated by RI could not be reliable for detection of the renal hemodynamic changes. Recent clinical studies reported that RI was useful in differentiating between parenchymatous renal failure and pre-renal azotemia[7]. Lerolle et al.[16] group found that, in septic shock patients, a high RI was predictive of AKI[7]. In addition, Darmon et al.[17] found that RI was significantly higher in patients with persistent AKI compared to those without AKI and those with transient AKI. However, IR value should be carefully interpreted before concluding that there is renal injury, since low renal perfusion pressure and low oxygen could result in high RI without AKI[11].

The ability of RI to monitor renal perfusion remains questionable. However, the early detection and reversing of AKI during sepsis using renal RI deserves further investigation to understand the exact clinical meanings of these variations[6].

Currently, new techniques are under development to assess renal perfusion such as contrast-enhanced US that allows an accurate quantification of regional and global RBF through injection of specific contrast agents that create a signal of high echogenicity, thus allowing macro- and microvascular structure visualisation. However, only few data are currently available to assess the interest of this technique in the clinical setting[6].

2. Microcirculation and AKI

Changes in the microcirculation, due to increase capillary permeability, cells adhesion, endothelium dysfunction and an increase in intra-abdominal pressure, can occur in septic patients with a hyperdynamic circulatory state, in the absence of renal hypoperfusion or renal ischaemia[8,18]. Chvojka et al. observed[14] that the renal microcirculation changes during sepsis induced AKI could be total or at least partially independent of the renal macrocirculation. In particular, Wang group[19] have found that capillary leakage is the early measured microvascular change (2 hrs after sepsis), even before any measured reduction in RBF and peritubular capillary perfusion, and suggested that renal microcirculatory failure and direct tubular injury, even after correction of systemic hemodynamics, contribute significantly to sepsis-induced AKI in humans. Recently, it was reported that the severity of microvascular dysfunction correlates with septic patients' outcomes[20,21].

For several decades the disturbance of the microcirculation was indirectly assessed, depending on the alterations of some systemic biochemical markers of dysoxia such as arterial blood lactate concentration, base excess and the oxygen saturation of the superior vena cava or of the pulmonary artery. In recent years, the development of the orthogonal polarisation spectral (OPS) and Side stream Dark Field (SDF) imaging techniques have allowed the direct visualisation of the sublingual microvasculature by means of a beam of polarised light directed over the investigated area.

Whether or not the sublingual microcirculatory abnormalities during septic shock reflect alterations in other microvascular beds remain unclear. Boerma et al.[22] reported that there is no correlation between sublingual microcirculation and intestinal microcirculation in early stage of sepsis. However, at late stages of sepsis the correlation is restored, due to final common pathway that is involved in microcirculatory failure. To our best of knowledge, no clinical study for evaluation of the role of sublingual microcirculation as an early predictive tool of acute renal injury during sepsis was done. Berlot et al.[23] found a substantial improvement of the sublingual microvascular blood flow after the initiation of the coupled plasma filtration and adsorption (CPFA), method of renal replacement therapy, which was slightly

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Critical Care
Open Access

Critical Review

decreased after CPFA discontinuation. Further investigation is needed to evaluate the role of sublingual microcirculation in early detection and differentiation of pre-renal/renal AKI.

3. Biomarkers for the early detection of AKI

The need for sensitive, simple and time-applicable biomarker to predict AKI development after renal insult is urgent. Serum creatinine (SCr) and urea are used routinely for the diagnosis of AKI. However, these parameters are not accurate for the diagnosis of AKI. In addition, high distribution volume, liver function abnormalities and malnutrition observed in septic patients could contribute to the delayed elevation of SCr(7). The concentration of serum creatinine may not change until 50% of kidney function has already been lost[24].

(A) Cystatin C. Recently, it was found that Cystatin C, a low-molecular-weight protein produced by all nucleated cells and freely filtered by the glomeruli and then fully reabsorbed and degraded in the proximal tubular cells, could detect a decline in the GFR earlier and more accurately than SCr values[7]. CysC is suggested to be a good biomarker because of its constant rate of production, almost filtered by glomeruli (99%), has no significant protein binding and not secreted by renal tubule[25].

In addition, elevated urinary cystatin (UCys) was predictive of presence of the ATN[7]. It was reported that patients with serum CysC levels < 0.8 mg/L are less likely to develop AKI after renal insult, and those with levels > 2.04 mg/L are at increased risk of developing AKI. However, the predictive value of urinary CysC excretion should be interpreted with caution in pre-renal AKI, who were responsive to fluid challenge[25].

(B) Neutrophil gelatinase-associated lipocalin (NGAL). NGAL is a protein that is expressed at very low concentrations in the kidney, lungs, and gastrointestinal tract, and highly up-regulated in injured epithelial cells and it is secreted into the urine by the thick ascending limb of Henle and collecting ducts of the kidney. NGAL is recently identified and extensively investigated as a most promising early marker of AKI[24, 26–29]. Urinary NGAL not only effective in detection of AKI but also its degree of expression might distinguish among AKI, pre-renal azotemia and chronic kidney disease, and it is detectable before the accumulation of serum creatinine[28]. However, a wide range of predictive values of NGAL for AKI have been reported across observational cohort studies[27,30]. In addition, a clear cut off NGAL concentration for the detection of AKI has not yet been reported[31]. Wheeler et al.[24] suggested that serum NGAL concentration may also be a marker of MODS, even in the absence of AKI, similar to C-reactive protein, procalcitonin, or interleukin (IL)-6.

(C) Liver-type fatty acid–binding protein (L-FABP). L-FABP is a member of the FABPs that is expressed in the proximal tubules and the level of urinary L-FABP reflects the extent of tubulo-interstitial damage. Only urinary L-FABP correlates with the progression of chronic kidney disease[32]. In addition, renal proximal tubular epithelial cells (L-FABP-producing cells) are targets for LPS during sepsis/septic shock[33]. Nakamura et al.[34] reported that urinary L-FABP levels were significantly higher in patients with septic shock than in healthy subjects and suggested that renal ischemia extending to the proximal tubule tends to overload fatty acids in the cytoplasm, and thereby damage tubules.

(D)Kidney injury moleclue-1(KIM-1). Urinary KIM-1 is a recent identified cell membrane glycoprotein that is strongly up-regulated in proximal tubular epithelial cells during various states that are characterised by epithelial cell dedifferentiation, such as ischemia, toxic renal injury and renal cell carcinoma. Some clinical studies have shown that KIM-1 is a sensitive and specific marker for the early detection of AKI after cardiopulmonary bypass surgery[35]. To our best of knowledge, no studies have investigated the value of KIM1 in early prediction or differentiation of pre-renal/renal AKI induced by sepsis and septic shock.

Conclusion

Sepsis-induced AKI represent an economic burden and serious problem, due to associated high mortality and morbidity. However, AKI could be reversible and prevention of permanent renal damage will represent a great advance in the clinical arena. Therefore, understanding of sepsis-induced pathological changes is critical issue for development of biomarker or tool that could predict AKI.

References

1. Dennen P, Douglas IS, Anderson R. Acute kidney injury in the intensive care unit: an update and primer for the intensivist. Crit Care Med. 2010 Jan;38(1): 261–75.
2. Ronco C, Brendolan A, Lonnemann G, Bellomo R, Piccinni P, Digito A, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. Crit Care Med. 2002 Jun;30(6):1250–5.
3. Dirkes S. Sepsis and inflammation: impact on acute kidney injury. Nephrol Nurs J. 2013 Mar–Apr;40(2):125–32; quiz 133.
4. Kellum JA, Ronco C, Vincent JL. Unveiling current controversies in acute kidney injury. Contrib Nephrol. 2011;174:1–3.
5. Bagshaw SM, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G, et al. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med. 2009 May;35(5):871–81.

FOR CITATION PURPOSES: *Sharawy N.* Prediction of acute Kidney injury during sepsis: Unsolved mystery yet. OA Critical Care 2013 Oct 01;1(2):14.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Critical Care
Open Access

Critical Review

6. Schnell D, Darmon M. Renal Doppler to assess renal perfusion in the critically ill: a reappraisal. Intensive Care Med. 2012 Nov;38(11):1751–60.
7. Schnell D, Deruddre S, Harrois A, Pottecher J, Cosson C, Adoui N, et al. Renal resistive index better predicts the occurrence of acute kidney injury than cystatin C. Shock. 2012 Dec;38(6):592–7.
8. Bougle A, Duranteau J. Pathophysiology of sepsis-induced acute kidney injury: the role of global renal blood flow and renal vascular resistance. Contrib Nephrol. 2011;174:89–97.
9. Zarjou A, Agarwal A. Sepsis and acute kidney injury. J Am Soc Nephrol. 2011 Jun;22(6):999–1006.
10. Holthoff JH, Wang Z, Seely KA, Gokden N, Mayeux PR. Resveratrol improves renal microcirculation, protects the tubular epithelium, and prolongs survival in a mouse model of sepsis-induced acute kidney injury. Kidney Int. 2011 Feb;81(4):370–8.
11. Dewitte A, Coquin J, Meyssignac B, Joannes-Boyau O, Fleureau C, Roze H, et al. Doppler resistive index to reflect regulation of renal vascular tone during sepsis and acute kidney injury. Crit Care. 2012 Sep;16(5):R165.
12. Bradley VE, Shier MR, Lucas CE, Rosenberg IK. Renal hemodynamic response to furosemide in septic and injured patients. Surgery. 1976 May;79(5):549–54.
13. Langenberg C, Wan L, Egi M, May CN, Bellomo R. Renal blood flow in experimental septic acute renal failure. Kidney Int. 2006 Jun;69(11):1996–2002.
14. Chvojka J, Sykora R, Krouzecky A, Radej J, Varnerova V, Karvunidis T, et al. Renal haemodynamic, microcirculatory, metabolic and histopathological responses to peritonitis-induced septic shock in pigs. Crit Care. 2008;12(6):R164.
15. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011 Nov;121(11):4210–21.
16. Lerolle N, Guerot E, Faisy C, Bornstain C, Diehl JL, Fagon JY. Renal failure in septic shock: predictive value of Doppler-based renal arterial resistive index. Intensive Care Med. 2006 Oct;32(10):1553–9.
17. Darmon M, Schortgen F, Vargas F, Liazydi A, Schlemmer B, Brun-Buisson C, et al. Diagnostic accuracy of Doppler renal resistive index for reversibility of acute kidney injury in critically ill patients. Intensive Care Med. 2011 Jan;37(1): 68–76.
18. Langenberg C, Bellomo R, May C, Wan L, Egi M, Morgera S. Renal blood flow in sepsis. Crit Care. 2005 Aug;9(4): R363–74.
19. Wang Z, Holthoff JH, Seely KA, Pathak E, Spencer HJ 3rd, Gokden N, et al. Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. Am J Pathol. 2012 Feb;180(2):505–16.
20. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med. 2004 Sep;32(9):1825–31.
21. Vincent JL, De Backer D. Microvascular dysfunction as a cause of organ dysfunction in severe sepsis. Crit Care. 2005;9(Suppl 4):S9–12.
22. Boerma EC, van der Voort PH, Spronk PE, Ince C. Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis. Crit Care Med. 2007 Apr;35(4):1055–60.
23. Berlot G, Bianco N, Tomasini A, Vassallo MC, Bianco F. Changes in microvascular blood flow during coupled plasma filtration and adsorption. Anaesth Intensive Care. 2011 Jul;39(4):687–9.
24. Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, et al. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Crit Care Med. 2008 Apr;36(4):1297–303.
25. Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis. 2011 Sep;58(3):356–65.
26. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, et al. Endocytic delivery of lipocalin–siderophore–iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest. 2005 Mar;115(3):610–21.
27. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005 Apr;365(9466):1231–8.
28. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med. 2008 Jun 3;148(11):810–9.
29. Zappitelli M, Washburn KK, Arikan AA, Loftis L, Ma Q, Devarajan P, et al. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Crit Care. 2007;11(4):R84.
30. Haase-Fielitz A, Bellomo R, Devarajan P, Bennett M, Story D, Matalanis G, et al. The predictive performance of plasma neutrophil gelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. Nephrol Dial Transplant. 2009 Nov;24(11):3349–54.
31. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009 Dec;54(6):1012–24.
32. Kamijo A, Kimura K, Sugaya T, Yamanouchi M, Hikawa A, Hirano N, et al. Urinary fatty acid-binding protein as a new clinical marker of the progression of chronic renal disease. J Lab Clin Med. 2004 Jan;143(1):23–30.
33. Bussolati B, David S, Cambi V, Tobias PS, Camussi G. Urinary soluble CD14 mediates human proximal tubular epithelial cell injury induced by LPS. Int J Mol Med. 2002 Oct;10(4):441–9.
34. Nakamura T, Sugaya T, Koide H. Urinary liver-type fatty acid-binding protein in septic shock: effect of polymyxin B-immobilizedfiberhemoperfusion. Shock. 2009 May;31(5):454–9.
35. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, et al. Urinary N-acetyl-beta-(d)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am SocNephrol. 2007 Mar;18(3): 904–12.

FOR CITATION PURPOSES: *Sharawy N.* Prediction of acute Kidney injury during sepsis: Unsolved mystery yet. OA Critical Care 2013 Oct 01;1(2):14.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.