JAMA Diagnostic Test Interpretation

Serum Creatinine in the Critically Ill Patient With Sepsis

Matthieu Legrand, MD, PhD; John A. Kellum, MD

A 73-year-old man underwent esophageal resection for cancer. He had a history of hypertension that was treated with an angiotensin receptor blocker. Preoperative estimated glomerular filtration rate (GFR) was 98 mL/min/1.73 m^2. On the second postoperative day, body temperature was 38.6°C. Chest x-ray revealed bilateral lung consolidations consistent with pneumonia. Blood pressure decreased from 145/72 mm Hg to 96/53 mm Hg with a heart rate of 105/min. The patient was admitted to the intensive care unit (ICU) with acute respiratory failure and was placed on mechanical ventilation. In the ICU, urine output was 50 mL over 3 hours. On day 3, he received 4.5 L of Ringer lactate over 12 hours. Laboratory values are shown in the **Table**.

Table. Patient's Laboratory Results

Laboratory Test	Preoperative Values	Postoperative Values						Reference Range
		Day 1, 8 AM	Day 2, 11 PM[a]	Day 3, 3 AM	Day 3, 2 PM	Day 3, 7 PM	Day 5, 6 AM	
Serum creatinine, mg/dL	0.81	0.85	1.03	1.1	1.4	1.6	2.5	0.5-1.2
Blood urea nitrogen, mg/dL	8.1	9.6	11.9	14.7	16.4	17.9	26.0	10-20
Hemoglobin, g/dL	13.6	11.9	11.1	10.4	10.5	10.5	9.5	14-17

SI conversion factors: to convert blood urea nitrogen to mmol/L, multiply by 0.357; serum creatinine to µmol/L, multiply by 88.4.

[a] Time of admission to the intensive care unit.

HOW DO YOU INTERPRET THE TEST RESULTS FROM DAY 3 POSTOPERATIVELY AT 3 AM?

A. The change in serum creatinine is within the coefficient of variation.

B. The patient has acute kidney injury most likely related to sepsis.

C. The patient has prerenal azotemia.

D. There are insufficient data to conclude that a decrease in glomerular filtration rate has occurred.

Answer

B. The patient has acute kidney injury most likely related to sepsis.

Tests Characteristics

Serum creatinine is a marker of GFR. Serum creatinine level depends on creatinine production and elimination. Elimination mostly depends on GFR but tubular secretion is also important, especially in patients with markedly reduced kidney function. While muscle injury (ie, rhabdomyolysis) might increase creatine release, sepsis may decrease creatinine production such that serum creatinine may not increase despite a decrease in GFR. Serum creatinine increases slowly after acute kidney injury (AKI). Creatinine distributes in a large volume, approximating 60% to 70% of total body weight. The increase in serum creatinine is further delayed by administration of large amounts of fluid and positive fluid balance.[1] For example, when patients with sepsis receive a large amount of fluids, AKI might be underrecognized.[2] Reaching a steady state of serum creatinine level requires that all compartments in which creatinine distributes are at equilibrium between production and elimination. Current international consensus criteria for AKI include a relative increase in serum creatinine (≥50% from baseline within 7 days) or an absolute increase in serum creatinine (≥0.3 mg/dL within a 48-hour period).[3] Mean Medicare reimbursement for serum creatinine testing is $5 to $6.

Application of the Test Results for This Patient

On postoperative day 3 at 3AM, serum creatinine was only marginally increased despite AKI. Increased volume of distribution would be expected to lead to a decrease in serum creatinine level if the GFR was stable. The slight increase in serum creatinine, in this specific clinical context, led to early identification of AKI. Low urine output is also characteristic in AKI diagnosis (<0.5 mL/kg/h for more than 6 hours) and may precede the increase of serum creatinine. However, AKI can develop without oliguria, and 6-hour urine output monitoring is not always available, as in this case. The patient later met criteria for AKI stage 3 (ie, 3-fold increase in serum creatinine above baseline or ≥4 mg/dL). Early identification of AKI, however, allows for rapid identification of sepsis severity,[4] which may facilitate earlier initiation of optimal care and avoidance of nephrotoxins (ie, vancomycin).[5] It is important to recognize that AKI can develop in patients with sepsis, despite absence of arterial hypotension or shock.[6]

What Are Alternative Diagnostic Testing Approaches?

Cystatin C may be less affected by muscle mass and metabolism than creatinine, but it is not more sensitive to detect AKI than serum creatinine. Alternative biomarkers (eg, neutrophil gelatinase–associated lipocalin, insulin-like growth factor binding protein 7, and tissue inhibitor of metalloproteinases-2) can detect kidney damage

and indicate impending AKI but do not directly measure GFR[7] and should not replace serum creatinine. Urine analysis is important for some forms of AKI (eg, glomerular nephritis) but lacks sensitivity and specificity. Measuring creatinine clearance estimates GFR but requires a steady-state serum creatinine, urine creatinine, and precise urine volume measurement. Formulas have been proposed for correcting serum creatinine for fluid overload.[8] In this case, correcting serum creatinine based on a positive fluid balance of 4.5 L and an estimated volume of distribution of 45 L (ie, 60% of 75 kg) indicated a corrected serum creatinine of 1.22 mg/dL at 3 AM on day 3.

Patient Outcome

The patient was diagnosed with postoperative pneumonia complicated by sepsis and AKI. The patient's condition improved and he was discharged 23 days after admission to the ICU. At discharge, his serum creatinine was 0.7 mg/dL. Recovery can be overestimated because of muscle mass loss during an ICU stay and persistent positive fluid balance.[9] Measured creatinine clearance was 72 mL/min/1.73 m^2 over a 24-hour urine volume collection, reflecting partial recovery from AKI because the GFR had not reverted to baseline levels.[10]

ARTICLE INFORMATION

Author Affiliations: AP-HP, GH Saint Louis-Lariboisière, Department of Anesthesiology and Critical Care and Burn Unit, Paris, France (Legrand); University Paris Diderot, Université Sorbonne Paris Cité, France (Legrand); UMR INSERM 942, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France, (Legrand); F-CRIN, INICRCT Network, Paris, France (Legrand); Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Kellum).

Corresponding Author: Matthieu Legrand, MD, PhD, Department of Anesthesiology and Critical Care and Burn Unit, Saint Louis Hospital, 1 Avenue Claude Vellefaux, 75010, Paris; France (matthieu.legrand@aphp.fr).

Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Published Online: November 16, 2018. doi:10.1001/jama.2018.16627

Conflict of Interest Disclosures: Dr Legrand reports receipt of research grants from Sphingotec, consulting fees from Novartis, and lecture fees from Fresenius. Dr Kellum reports receipt of grant support from Bioporto and Astute Medical; and consulting fees from Astute Medical.

Additional Contributions: We thank the patient for sharing his experience and for granting permission to publish it.

REFERENCES

1. Pickering JW, Ralib AM, Endre ZH. Combining creatinine and volume kinetics identifies missed cases of acute kidney injury following cardiac arrest. *Crit Care*. 2013;17(1):R7. doi:10.1186/cc11931

2. Liu KD, Thompson BT, Ancukiewicz M, et al; National Institutes of Health National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med*. 2011;39(12):2665-2671. doi:10.1097/CCM.0b013e318228234b

3. Acute Kidney Injury Work Group. Kidney disease: improving global outcome: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2(1):1-138.

4. Kellum JA, Chawla LS, Keener C, et al; ProCESS and ProGReSS-AKI Investigators. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. *Am J Respir Crit Care Med*. 2016;193(3):281-287. doi:10.1164/rccm.201505-0995OC

5. Legrand M, Payen D. Case scenario: hemodynamic management of postoperative acute kidney injury. *Anesthesiology*. 2013;118(6):1446-1454. doi:10.1097/ALN.0b013e3182923e8a

6. Murugan R, Karajala-Subramanyam V, Lee M, et al; Genetic and Inflammatory Markers of Sepsis (GenIMS) Investigators. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int*. 2010;77(6):527-535. doi:10.1038/ki.2009.502

7. Kellum JA, Prowle JR. Paradigms of acute kidney injury in the intensive care setting. *Nat Rev Nephrol*. 2018;14(4):217-230. doi:10.1038/nrneph.2017.184

8. Macedo E, Bouchard J, Soroko SH, et al; Program to Improve Care in Acute Renal Disease Study. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care*. 2010;14(3):R82. doi:10.1186/cc9004

9. Prowle JR, Kolic I, Purdell-Lewis J, Taylor R, Pearse RM, Kirwan CJ. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. *Clin J Am Soc Nephrol*. 2014;9(6):1015-1023. doi:10.2215/CJN.11141113

10. Chawla LS, Bellomo R, Bihorac A, et al; Acute Disease Quality Initiative Workgroup 16. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13(4):241-257. doi:10.1038/nrneph.2017.2