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# AMR, Sepsis and AKI: Global Risk and Biomarker Mitigation

**Editorial by** : Chris Groke, PharmD, BCPS, BCIDP
Medical Science Liaison, bioMérieux

*Quickly assessing the risk of acute kidney injury (AKI) and treating incidents is essential to minimizing kidney damage and potentially restoring kidney function. During this process, healthcare professionals must balance treating the underlying infection, monitoring the effects of nephrotoxic medications, and adhering to antimicrobial stewardship practices. With the threat of antimicrobial resistance (AMR) continuing to rise, treating cases of sepsis and bacterial infections that can lead to AKI requires more careful monitoring than ever.*

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Incidents of AKI may show virtually no outward signs or symptoms, and can therefore easily be overshadowed by the primary disease state. For example, myocardial infarction (MI) may present with chest pain; and sepsis often presents with temperature extremes, hypotension, and tachycardia. Although AKI is just as common as MI, it can actually be more deadly, especially when both are present in the same patient.[1] Due to hemodynamic compromise in congestive heart failure or sepsis, the kidneys are negatively affected due to collateral damage caused by inadequate perfusion. AKI occurs in 57% of patients during their first day in the ICU and in 42% of critically ill sepsis patients.[2,3] Researchers estimate that as many as 10-20% of all hospitalized patients develop AKI during their stay.[1]

Providers must balance complex and often competing factors to treat AKI while being mindful of AMR and addressing the root cause of the kidney injury. Inappropriate antimicrobial use can put individual patients at risk of adverse effects while increasing the burden and economic costs of AMR at institutional and population levels. Yet, in striving to follow sepsis guidelines, many institutions use a combination of broad-spectrum nephrotoxic antibiotics (e.g., piperacillin/tazobactam and vancomycin) to treat septic patients within 1 hour of the diagnosis.[4] While the growing threat of AMR is a large public health issue on its own, increased bacterial resistance also puts more people at risk for developing sepsis. Sepsis, along with COVID-19, heart conditions, and other infectious diseases, are key causes of AKI.[5] A recent analysis of cases from 1990 to 2017 estimated that 48.9 million cases of sepsis are recorded worldwide per year.[4] Additionally, 11 million sepsis-related deaths were reported per year, representing 19.7% of all global deaths.[6]

Although there is no treatment for directly reversing AKI, the prudent use of biomarkers to assess for AKI and mitigate risk is an important consideration in patient care and in restoring kidney function.[7] These biomarkers can be used to evaluate various kidney functions such as cellular damage and glomerular filtration rate. Tissue inhibitor of metalloproteinase-2 (TIMP-2) and the insulin-like growth factor binding protein-7 (IGFBP-7) are examples of kidney-specific biomarkers that can be used to help assess the risk of kidney stress before significant damage occurs.[8]

**Crucial Biomarkers of Interest for AKI/Sepsis Monitoring and their Biological Indications**[9]

| Biomarkers | Significance |
|---|---|
| TIMP-2*, IGFBP-7*, ALP, GGT, GST, NAG, L-FABP | Increased presence can indicate increased organ stress |
| NGAL, KIM-1, Clusterin, IL-18, Netrin-1 | Upregulation can indicate AKI (acute kidney injury) or CKD (chronic kidney damage) |
| TFF3 | Downregulation can indicate renal tubular injury |
| Albumin, Cystatin C, Beta-2 Microglobulin, L-FABP | Presence can indicate filter-impaired tubular absorption |

***NOTE:** The combination of urinary tissue inhibitor of metalloproteinase (TIMP-2) and insulin-like growth factor binding protein (IGFBP-7) is currently the only FDA approved biomarker(s) to assess acute kidney injury risk.

**Abbreviations**

ALP: alkaline phosphatase
GGT: gamma glutaryl transferase
GST: glutathione S-transferase
IGFBP-7: insulin-like growth factor binding protein-7
IL-18: interleukin-18
KIM-1: kidney injury molecule-1
L-FABP: liver-type fatty acid-binding protein
NAG: N-acetyl-beta-d-glucosaminidase
NGAL: neutrophil gelatinase associated lipocalin
TIMP-2: tissue inhibitor of metalloproteinase-2
TFF3: trefoil factor 3

Biomarker testing should be considered a priority after major surgery, within 72 hours of ICU admissions or when hemodynamic instability or sepsis are indicated.[5] A positive test prompts management of nephrotoxic drugs and fluids to potentially mitigate the severe consequences associated with AKI. By employing precision medicine concepts through a combination of biomarkers and syndromic testing, healthcare providers are more empowered now than ever to appropriately mitigate the risks of AMR, sepsis and AKI when managing patients.

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