

# BPI fold-containing family a member 2 as a biomarker of acute kidney injury – close but no (clinical) cigar?

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*Comment on:* Kota SK, Pernicone E, Leaf DE, *et al.* BPI fold-containing family a member 2/parotid secretory protein is an early biomarker of AKI. *J Am Soc Nephrol* 2017;28:3473-8.

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Acute kidney injury (AKI) affects up to 50% of critically ill patients and is independently associated with both short and long-term mortality (1). Early identification of AKI is the main impulse for AKI biomarker research. Biomarkers are complementary to functional tests and, in addition, may be used to optimize AKI staging, to direct intervention, and to predict prognosis. Over the last decade, various AKI biomarkers have emerged: neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1, monocyte chemoattractant peptide-1, N-acetyl- $\beta$ -D-glucosaminidase, interleukin-18, liver-type fatty acid-binding protein, netrin-1, endogenous ouabain, selenium-binding protein 1, and the cell cycle arrest initiating proteins tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) (2).

Kota *et al.* furnish ample and well-documented molecular, genetic, and clinical proof to adopt BPI fold-containing family A member 2 (BPIFA2) as a novel sensitive AKI biomarker. They assessed the utility of BPIFA2 in different mouse models of AKI (ischemia reperfusion, drug-induced, and endotoxemic AKI) and in patients with AKI of diverse origin (acute tubular necrosis, renal failure post-cardiac surgery, hepatorenal syndrome, and contrast nephropathy) (3). BPIFA2 expression was induced early in both murine and human kidneys and BPIFA2 protein became readily

detectable in urine and plasma following AKI. Such dynamic and kidney-specific expression pattern led the authors to propose BPIFA2 as an attractive biomarker for early diagnosis and monitoring of AKI.

Apart from molecular typing and categorizing, BPIFA2 has not been extensively studied. BPIFA2 (or parotid secretory protein) is one of the mammalian lipid-binding bactericidal/permeability-increasing protein (BPI) fold-containing glycoproteins formerly known as palate, lung and nasal epithelium clone (PLUNC) proteins. There are currently six BPIFA families. The BPIFA2 family is by far the most diverse and complex entity, with two lineage-specific duplications and low pairwise identities between the remaining members (4). Sharing structure similarity, BPIFA peptides are functionally related to BPI. BPI is a 456-residue cationic protein stored in leukocytes with potent anti-endotoxin activity and highly selective bactericidal effects on Gram-negative bacteria (5,6). PLUNC proteins, in general, are involved in local antibacterial responses in the upper and proximal respiratory tract of air-breathing mammals. However, unlike the BPI fold-containing BPIFA1 protein which has well-determined immunoregulatory, antibacterial, and host-protective capabilities (7), information on similar or comparable BPIFA2 actions is extremely scarce (8).

Biomarkers of AKI are theoretically useful in any type of AKI. In clinical practice, however, sensitive

biomarkers are of crucial importance for early detection and monitoring of sepsis-induced AKI. Sepsis is characterized by a dysregulated immune-inflammatory host response to infection resulting in life-threatening organ failure (9). Up to 50% of patients with severe sepsis and septic shock develop AKI (10). Whether BPIFA2 would be a good marker of sepsis-induced AKI is insufficiently supported by the study of Kota *et al.* models of renal ischemia are not relevant to the pathophysiology of septic AKI (11). In the absence of global hypoperfusion, septic AKI more likely has a functional (glomerular) rather than an injurious (tubular) origin (12). The complexity and mutual interaction of molecular mechanisms underlying septic AKI furthermore clouds insight into BPIFA2 behaviour. Moreover, the presence of AKI *in se* mediates a systemic inflammatory response that causes remote damage in heart, lung, brain, spleen, liver, and gut (13). The BPI superfamily probably plays an active, yet undetermined, role in this process. Of note is that, despite its thoroughly documented anti-inflammatory and antimicrobial potential, BPI has not gained major biomarker importance (14). In a large cohort of patients with suspected infection, BPI performed poorly as predictor of severe sepsis (15).

Kota *et al.* demonstrated that BPIFA2 allowed adequate detection of kidney “stress” or “damage” in patients with established AKI (3). It remains to be proven whether BPIFA2 may adequately predict AKI development or severity. Such potential has been clinically demonstrated for the (TIMP-2)·(IGFBP-7) biomarker panel. In critically ill patients, urinary (TIMP-2)·(IGFBP-7) highly predicted evolution to moderate and severe AKI. (TIMP-2)·(IGFBP-7) was significantly superior to all previously described markers of AKI and improved risk stratification when added to a nine-parameter clinical model (16). A single urinary (TIMP-2) (IGFBP-7) test also accurately predicted early development and severity of AKI in high-risk postoperative (17), post cardiac surgery (18), and septic (19) patients.

An increasing number of critically ill patients suffering AKI, and in particular those with septic AKI, will receive renal replacement therapy. Continuous techniques have progressively supplanted intermittent dialysis. Substances are expected to be removed by continuous hemodiafiltration when their molecular weight (MW) lies below the 30–35 kDa MW cut-off point of “classic” dialysis membranes (20). In addition, removal may be boosted when highly adsorptive dialysis membranes are employed (21). This has been shown for inflammatory peptides (monomeric

C-reactive protein and procalcitonin) and cytokines (22,23) as well as AKI biomarkers (e.g., NGAL) (24). The BPIFA2 forms identified in circulation have a MW of 15 and 18 kDa (3) and thus must stand the “test of continuous renal epuration” before being implemented as a valuable diagnostic and prognostic marker.

Biomarkers are increasingly embraced as important adjuvant tools for refining diagnosis, optimizing treatment, and predicting prognosis of AKI. AKI biomarker research advances by giant leaps. BPIFA2 certainly represents one more promising marker arising from the molecular pipeline. However, its validity in critically ill postoperative and septic patients who present with varying degrees of inflammation and concomitant evolving organ dysfunction or failure remains to be proven.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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