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SYSTEMATIC REVIEW

Sean M. Bagshaw
Christoph Langenberg
Michael Haase
Li Wan
Clive N. May
Rinaldo Bellomo

Urinary biomarkers in septic acute kidney injury

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S. M. Bagshaw (✉)
University of Alberta Hospital, Division of Critical Care Medicine,
3C1.16 Walter C. Mackenzie Centre,
8440-112 Street, T6G 2B7 Edmonton, Canada
e-mail: bagshaw@ualberta.ca
Tel.: +1-780-407-6755
Fax: +1-780-407-1228

S. M. Bagshaw · C. Langenberg · M. Haase · L. Wan · R. Bellomo
Austin Hospital, Department of Intensive Care Medicine,
Studley Road, Heidelberg, 3084, VIC, Australia

C. Langenberg · L. Wan · C. N. May
University of Melbourne, Howard Florey Institute,
161 Barry Street, South Carlton, 3053, VIC, Australia

R. Bellomo
Melbourne University, Department of Medicine,
Melbourne, Australia

Abstract *Objective:* To appraise the literature on the value of urinary biomarkers in septic acute kidney injury (AKI). *Design:* Systematic review. *Setting:* Academic medical centre. *Patients and participants:* Human studies of urinary biomarkers. *Interventions:* None. *Measurements and results:* Fourteen articles fulfilled inclusion criteria. Most studies were small, single-centre, and included mixed medical/surgical adult populations. Few focused solely on septic AKI and all had notable limitations. Retrieved articles included data on low-molecular-weight proteins (β_2-microglobulin, α_1-microglobulin, adenosine deaminase binding protein, retinol binding protein, cystatin C, renal tubular epithelial antigen-1), enzymes (N-acetyl-β-glucosaminidase, alanine-aminopeptidase, alkaline phosphatase; lactate dehydrogenase, α/π-glutathione-S-transferase, γ-glutamyl transpeptidase), cytokines [platelet activating factor (PAF), interleukin-18 (IL-18)] and other biomarkers [kidney injury molecule-1, Na/H exchanger isoform-3 (NHE3)]. Increased PAF, IL-18, and NHE3 were detected early in septic AKI and preceded overt kidney failure. Several additional biomarkers were evident early in AKI; however, their diagnostic value in sepsis remains unknown. In one study, IL-18 excretion was higher in septic than in non-septic AKI. IL-18 also predicted deterioration in kidney function, with increased values preceding clinically significant kidney failure by 24–48 h. Detection of cystatin C, α_1-microglobulin, and IL-18 predicted need for renal replacement therapy (RRT). *Conclusions:* Few clinical studies of urinary biomarkers in AKI have included septic patients. However, there is promising evidence that selected biomarkers may aid in the early detection of AKI in sepsis and may have value for predicting subsequent deterioration in kidney function. Additional prospective studies are needed to accurately describe their diagnostic and prognostic value in septic AKI.

Keywords Acute kidney injury · Acute renal failure · Sepsis · Urinary biomarkers · Renal replacement therapy · Interleukin-18

Introduction

Acute kidney injury (AKI) is a common clinical problem in critically ill patients [1, 2]. Sepsis is now recognized as the most important contributing factor for AKI in this population [1]. Epidemiologic studies have reported AKI requiring renal replacement therapy (RRT) in 43–50% of patients with septic shock [3–5]. In addition, mortality in septic AKI remains exceedingly high [6–8].

AKI has traditionally been defined and detected by measuring surrogates of kidney function such as serum creatinine and urea [9]. However, these markers are

insensitive and non-specific for both acute changes to kidney function and kidney injury. They also increase late in the injury process. As a consequence, they may not detect an acute insult or potentially ongoing injury to the kidney.

On the other hand, several novel biomarkers (i.e. antigens, peptides, enzymes, cytokines) have been detected in the urine in AKI and have been characterized as potential early, non-invasive, and more sensitive indicators of AKI [10–12]. Moreover, the pattern of urinary excretion of these biomarkers may potentially aid in understanding the pathophysiology of AKI, allow for localization of injury to specific segments of the nephron, be used to correlate outcome with both the onset and severity of initial injury, and potentially provide added prognostic information.

Accordingly, we systematically reviewed the literature in order to describe the urinary biomarkers detected when the principal stimulus for AKI was sepsis. The primary objectives of our review were: (1) to document those urinary biomarkers that have been detected in septic AKI; (2) to determine the diagnostic value of these biomarkers in septic AKI; and (3) to determine whether these biomarkers have prognostic value in septic AKI.

Methods

Search strategy

Two individuals (S. M. B. and C. L.) independently identified published articles of urinary biomarkers in septic AKI by use of both electronic and manual search strategies. An initial screen of identified abstracts was performed followed by a full text screen of each article identified. Our search was supplemented by scanning the bibliographies of all recovered articles. This comprehensive search was performed in September 2005 and updated in December 2006.

The databases MEDLINE (1966 through August, 2005), EMBASE (1980 through 2005, Week 38), CINAHL (1982 through 2005, September Week 2) were searched. PubMed was also searched. Articles in any language were considered.

Three comprehensive search themes were derived. The first search theme was compiled by using the term "OR" with the following medical subject headings (MeSH) and textwords: "acute renal failure", "acute kidney failure", "acute tubular necrosis", "kidney dysfunction". The second search theme was put together by using the term "OR" with the following MeSH headings and textwords: "sepsis", "septicemia", "septic shock", "bacteremia", "lipopolysaccharide", "endotoxin", and "gram negative". The final search theme used the term "OR" with the following MeSH headings and textwords: "urinary biomarker", "kidney injury molecule-1", "cystatin C", "sodium-hydrogen exchanger isoform 3 (NHE3)", "neutrophil gelatinase-associated lipocalin (NGAL)", "cytokine", "interleukin-18 (IL-18)", "β_2-microglobulin", "urinary retinol binding protein (RBP)", "enzymuria", and "aminoaciduria". These three search themes were then combined using the Boolean operator "AND".

Study selection

Two individuals independently evaluated all identified articles for eligibility on the basis of four criteria: (1) articles reported original data from a primary publication; (2) articles reported on human subjects; (3) articles made specific mention of urinary biomarkers in AKI; and (4) articles included subjects with sepsis syndrome or septic shock and this represented the principal cause for AKI. Agreement on article inclusion was quantified by the kappa statistic, with disagreements resolved by discussion.

Data extraction and synthesis

Data extracted included: study methods, number of patients and proportion with sepsis, patient population (i.e. adult, critically ill, surgical); details of sepsis, haemodynamic profile, baseline/enrolment kidney function, use of renal replacement therapy (RRT); and mortality outcome. Data were also extracted on specific urinary biomarkers and included: mean/median and peak urinary concentrations detected, timing of detection, operative characteristics when available and the presence of potential confounder factors.

Results

Study selection

The combined computerized and bibliographic search yielded 175 unique citations, of which only 67 were identified as potentially relevant and reviewed further. In all, 14 unique articles fulfilled all inclusion criteria. Agreement was good between reviewers for inclusion. Actual agreement was 91% (chance corrected, kappa 0.81 ± 0.07) and all discrepancies were resolved by consensus.

Study characteristics

Study characteristics are shown in Table 1. Ten (71%) studies were in adults. Four (29%) were focused solely in critically ill patients. Most studies (71%) were performed in mixed medical/surgical patients. Only four studies exclusively enrolled patients with documented or suspected sepsis and in three of these, the focus was on detection of

Table 1 Summary of human studies reporting findings pertaining to urinary biomarkers in septic AKI

Reference	Biomarker(s) measured	Study type	No. with sepsis/no. of patients (%)*	Study population	Surgical	Detail of sepsis[a]	Haemodynamic profile	Vasopressors	Control group	Mortality
Zager [24]	HRTE-1	Prospective	9/27 (33)	Adults; not all critically ill	Mixed	NA	NA	NA	No	NA
Cabrera [18]	β_2-M	Prospective	35/35 (100)	Adults; not all critically ill	Medical	Gram (-) sepsis	NA	NA	No	54%
Ehrich [25]	NAG, AAP	Prospective	23/382 (6)	Paediatric; not critically ill	Mixed	NA	NA	NA	No	NA
Tessin [26]	NAG, AAP	Prospective	62/62 (100)	Neonatal; critically ill	Medical	NA	NA	NA	Yes	NA
Chew [13]	ALP, NAG	Prospective	19/50 (38)	Adults; not critically ill	Mixed	NA	NA	NA	No	36%
Gordjani [19]	β_2-M, α_1-M, ABP	Prospective	33/33 (100)	Neonates; not critically ill	Medical	Suspected only	NA	NA	Yes	NA
Mehta [17]	β_2-M	Prospective	8/46 (17)	Neonatal; critically ill	Mixed	NA	NA	NA	Yes	NA
Mariano [28]	PAF, IL-1, IL-6, IL-8, TNF-α	Case-series	12/12 (100)	Adults; critically ill	Mixed	Septic shock	Shock	Yes	Yes	50%
Han [15]	KIM-1	Prospective	4/23 (17)	Adults; not critically ill	Mixed	NA	NA	NA	Yes	NA
du Cheyron [22]	NHE3	Prospective	12/54 (22)	Adults; critically ill	Mixed	NA	NA	NA	Yes	AKI 27.8% No AKI 21.4%
Westhuyzen [16]	γ-GT, ALP, NAG, LDH, α/π-GST	Prospective	12/26 (46)	Adults; critically ill	Mixed	Pulmonary/intra-abdominal	Shock	Yes	Yes	NA
Herget-Rosenthal [14]	β_2-M, α_1-M, RBP, Cystatin C, γ-GT, LDH, α-GST, NAG	Prospective	19/73 (26)	Adults; most critically ill	NA	NA	NA	NA	Yes	RRT 84.6% No RRT 12.8%
Parikh [31]	IL-18	Prospective	6/22 (27)	Adults; not all critically ill	Mixed	NA	NA	NA	Yes	NA
Parikh [33]	IL-18	Prospective	83/138 (60)	Adults; critically ill	Mixed	Pulmonary	MAP 97–102	Yes	Yes	AKI 63.5% No AKI 25.6%

Abbreviations: *NA*, not available or not specified; *HRTE-1*, renal tubular epithelial antigen-1; *β_2-M*, β_2-microglobulin; *α_1-M*, α_1-microglobulin; *NAG*, N-acetyl-β-glucosaminidase; *AAP*, alanine aminopeptidase; *ALP*, alkaline phosphatase; *ABP*, adenosine deaminase binding protein; *PAF*, platelet activating factor; *MODS*, multiple organ dysfunction syndrome; *KIM-1*, kidney injury molecule-1; *NHE3*, Na/H exchanger isoform 3; *MAP*, mean arterial pressure; *RRT*, renal replacement therapy

[a] Sepsis: either suspected or proven

aminoglycoside toxicity. Most studies were small, single-centre, prospective, observational and included a control group for comparison (Table 1). Few studies provided data on patient haemodynamics, use of vasopressors, or mortality.

Measures of kidney function

Details of kidney function across studies are displayed in Table 2. The occurrence of AKI varied between studies, and few provided complete data on estimated glomerular filtration rate, serum creatinine, or urine output. Only two studies (14%) reported on the proportion of patients that received RRT.

Limitations of included studies

Inferences on the value of urinary biomarkers in septic AKI described in this review may be limited due to: (1) not all patients described across reports had sepsis; (2) not all patients described across reports had AKI; (3) several studies had potential confounding factors (Table 3); (4) several reports had potential weaknesses in study design (i.e. single centre and/or tertiary referral centre, small sample size, no control group); and (5) several reports were prone to selection bias due to study inclusion/exclusion criteria. For example, studies excluded patients based on radiographic evidence of small bilateral kidneys, those with biochemically defined pre-renal failure (i.e. FeNa $< 1\%$), those not fulfilling sufficient criteria to be classified as having acute tubular necrosis (ATN) or those requiring RRT within 48 h [13–15].

Urinary biomarkers

The urinary biomarkers described in septic AKI are outlined in Tables 4 and 5. As a general rule, the detection of urinary biomarkers was considered a surrogate for evidence of structural injury to renal tubular epithelial cells occurring before and/or during overt acute renal failure (ARF), specifically ATN. In selected instances, biomarker detection occurred prior to clinically evident increases in serum creatinine and/or urea [16–19].

Low-molecular-weight proteinuria

β_2-Microglobulin (β_2-M) is an endogenous 12-kDa protein that forms part of the class I major histocompatibility complex. β_2-M is freely filtered at the glomerulus and subsequently reabsorbed and catabolized by proximal renal tubular cells. It is not normally detected in the urine. Urinary β_2-M excretion was described in four studies

Table 2 Details of baseline renal function and need for renal replacement therapy in studies reporting on urinary biomarkers in sepsis

Reference	Biomarker(s) measured	ARF (%)	Estimated GFR (ml/min)	Estimated Scr[a] (μmol/l)	Proportion with oliguria (%)[b]	Baseline urine output (ml/h)[c]	Proportion with need for RRT (%)
Zager [24]	HRTE-1	100	NA	NA	18 (67)	NA	NA
Cabrera [18]	β_2-M	60	18	301	40	45–46	NA
Ehrich [25]	NAG, AAP	17	NA	66	NA	NA	NA
Tessin [26]	NAG, AAP	NA	NA	NA	NA	NA	NA
Chew [13]	ALP, NAG	100	NA	274–292	NA	NA	NA
Gordjani [19]	β_2-M, α_1-M, ABP	0	16.9–24.7	NA	NA	NA	NA
Mehta [17]	β_2-M	14	NA	NA	NA	NA	NA
Mariano [28]	PAF, IL-1, IL-6, IL-8, TNF-α	100	NA	<177	NA	<17	NA
Han [15]	KIM-1	58	NA	336	NA	NA	NA
du Cheyron [22]	NHE3	100	NA	186–292	NA	22–44	NA
Westhuyzen [16]	γ-GT, ALP, NAG, LDH, α/π-GST	15	38	100	NA	NA	0
Herget-Rosenthal [14]	β_2-M, α_1-M, cystatin C, RBP, γ-GT, LDH, α-GST, NAG	100	NA	159–194	NA	67–75	36
Parikh [31]	IL-18	100	NA	124–530	NA	NA	NA
Parikh [33]	IL-18	38	NA	75–80	NA	79–104	NA

Abbreviations: *HRTE-1*, renal tubular epithelial antigen-1; *β_2-M*, β_2-microglobulin; *α_1-M*, α_1-microglobulin; *NAG*, N-acetyl-β-glucosaminidase; *AAP*, alanine aminopeptidase; *ALP*, alkaline phosphatase; *ABP*, adenosine deaminase binding protein; *PAF*, platelet activating factor; *MODS*, multiple organ dysfunction syndrome; *KIM-1*, kidney injury molecule-1; *NHE3*, Na/H exchanger isoform 3; *NA*, not available or not specified

[a] Serum creatinine: to convert from μmol/l to mg/dl divide by 88.4; [b] Oliguria variably defined across studies; [c] Estimated based on either inclusion criteria or available data provided

Table 3 Summary of the potential confounding factors for the assessment of urinary biomarkers in septic AKI

Confounding factor	Number of studies (%)	References
Aminoglycosides	11 (79)	[13, 14, 16–19, 22, 24–26, 31]
Radiocontrast medium	5 (36)	[13–15, 22, 24]
Use of diuretics	4 (29)	[18, 22, 24, 28]
Chronic kidney disease	3 (21)	[15, 18, 25]
Rhabdomyolysis	3 (21)	[14, 18, 24]
Cirrhosis	2 (14)	[18, 31]
Acute glomerulonephritis	2 (14)	[13, 25]
Renal transplantation	2 (14)	[15, 25]
Other nephrotoxin	2 (14)	[25, 31]

(29%) [14, 17–19]. In three of these studies, it was used for detection of tubular damage attributed to aminoglycosides rather than sepsis [17–19]. However, in one study, 90% of critically ill neonates had significant increases in urinary detection of β_2-M, while only 17% exhibited evidence of abnormal serum creatinine values [17]. Moreover, the highest detected β_2-M levels were in septic neonates. However, Cabrera et al. found no difference in β_2-M levels between septic and non-septic patients when tubular injury was arbitrarily defined by β_2-M values $> 3{,}000\,\mu g/l$ [18]. In a small observational study, Herget-Rosenthal et al. found that urinary β_2-M performed poorly at predicting need for RRT [area under receiver operating characteristic curve (AuROC) 0.51] [14].

α_1-Microglobulin (α_1-M) is a 31-kDa protein produced by the liver and associated with immunoglobulin A. Similar to β_2-M, α_1-M is freely filtered at the glomerulus and is completely reabsorbed when tubular function is normal. Only two studies (14%) including septic patients assessed urinary α_1-M excretion [14, 19]. In one study of neonatal sepsis treated with aminoglycosides, α_1-M was found to be significantly increased at > 3 days [19]. Herget-Rosenthal et al. found that early detection of increased urinary α_1-M was an excellent discriminator for future need of RRT (AuROC 0.86) [14].

Adenosine deaminase binding protein (ABP) is a 120-kDa glycoprotein found in the brush border of proximal renal tubular cells. Increased ABP detection in the urine is considered indicative of AKI; however, most studies have only described ABP in non-septic patients with ischaemic, nephrotoxic or post-transplant AKI [20, 21]. ABP was described in only one study of neonatal sepsis [19]. Urinary excretion of ABP was found to be a superior and earlier marker of AKI than both β_2-M and α_1-M [19].

Retinol binding protein (RBP) is a 21-kDa protein synthesized primarily in the liver and bound in serum with pre-albumin and vitamin A. RBP is freely filtered and reabsorbed by proximal tubular cells. Detection of urinary RBP is considered indicative of tubular damage. Urinary RBP was described in two studies (14%) that included septic patients [14, 22]. Du Cheyron et al. found that urinary RBP was significantly increased in AKI compared with non-AKI controls; however, levels of RBP were unable to discriminate pre-renal AKI and ATN [22]. Increased urinary RBP was intermediately discriminatory for need of RRT (AuROC 0.80) [14].

Cystatin C is an endogenous cysteine proteinase inhibitor synthesized at a relatively constant rate and released into plasma by all nucleated cells in the body. It is freely filtered at the glomerulus, not secreted or reabsorbed, and nearly completely catabolized by proximal renal tubular cells and thus not normally detected in the urine [23]. Herget-Rosenthal et al. found that urinary cystatin C was predictive for need of RRT (AuROC 0.92), performing better than several other urinary biomarkers (i.e. β_2-M, RBP, γ-GT, LDH, α-GST, NAG) [14].

Proximal renal tubular epithelial antigen (HRTE-1) is a proximal tubular brush border peptide that is sloughed into the tubular lumen and detected in the urine following kidney injury [24]. While Zager et al. described an increase in urinary HRTE-1 excretion in ATN that was not evident in pre-renal AKI, only nine patients in this study were septic. Consequently, no inferences were possible for septic versus non-septic AKI.

Enzymuria

Numerous urinary enzymes have been studied as early and non-invasive biologic indicators of AKI [11, 12]. We found five studies (35%) that described the detection of urinary enzymes and included septic patients [13, 14, 16, 25, 26]. Two were in neonatal/paediatric populations that focused on aminoglycoside toxicity rather than sepsis and had limited value [25, 26]. Several urinary enzymes were detected, including alanine aminopeptidase (AAP), alkaline phosphatase (ALP), N-acetyl-β-glucosaminidase (NAG), lactate dehydrogenase (LDH), α-glutathione S-transferase (α-GST), π-glutathione S-transferase (π-GST), and γ-glutamyl transpeptidase (γ-GT). These enzymes are released from various sites in the nephron (i.e. proximal tubule, loop of Henle, distal tubule) and may reflect different patterns of subcellular injury (i.e. lysosomal, cytoplasmic, brush border membrane).

Chew et al. described the urinary detection of ALP and NAG in a cohort of 50 non-critically ill patients with ARF, of which 38% had probable sepsis as a contributing

Table 4 Summary of urinary biomarkers from studies including patients with septic AKI

Biomarker	Nephron segment	Subcellular origin	C_N	C_U	C_{MAX}	Detection time
Low-molecular-weight proteins						
α_1-Microglobulin (α_1-M)	Proximal tubule	Plasma	Undetected	34.5 g**	45.1 g**	NA
β_2-Microglobulin (β_2-M)	Proximal tubule	Plasma	16–760 μg/l	12,100 μg/l	100,540 μg/l	NA
Retinol binding protein (RBP)	Proximal tubule	Plasma	250 μg/l	1,209–2,270 μg/l	2,700 μg/l	24 h
Adenosine deaminase binding protein (ABP)	Proximal tubule	Brush border	NA	NA	NA	24 h
Cystatin C	Proximal tubule	Plasma	Undetected	1.7 g**	4.1 g**	NA
Tubular enzymes						
Proximal renal tubular epithelial antigen (HRTE-1)	Proximal tubule	Brush border	0.1–1.0 μg/ml	0.6–1.67 μg/ml	12 μg/ml	NA
α-Glutathione S-transferase (α-GST)	Proximal tubule	Cytoplasm	7.0 μg/l	40.6 μg/l	140 μg/l	12 h
π-Glutathione S-transferase (π-GST)	Distal tubule	Cytoplasm	6.0 μg/l	51 μg/l	143 μg/l	12 h
γ-Glutamyl transpeptidase (γ-GT)	Proximal tubule	Brush border	33 mmol/l	113 mmol/l	232 mmol/l	12 h
Alanine aminopeptidase (AAP)	Proximal tubule	Brush border	Undetected	453 μmol*	NA	12 h
Lactate dehydrogenase (LDH)	Proximal/distal tubule	Cytoplasm	17 mmol/l	38 mmol/l	58 mmol/l	12 h
N-acetyl-β-glucosaminidase (NAG)	Proximal/distal tubule	Lysosomes	0.07–5.6 U/g*	13.7–48.6 U/g*	875.5 U/g*	12 h
Alkaline phosphatase (ALP)	Proximal/distal tubule	Brush border	0.08–3.02 U/g*	2.2–3.2 U/g*	156.2 U/g*	12 h
Cytokines						
Interleukin-18 (IL-18)	Proximal tubule	Proximal tubule/plasma	16 pg/mg*	63–644 pg/mg*	2,500 pg/mg*	NA
Interleukin-8 (IL-8)	Glomerulus	Plasma	5.9 pg/mg*	788.6 pg/mg*	788.6 pg/mg*	24 h
Interleukin-6 (IL-6)	Glomerulus	Plasma	2.7 pg/mg*	143.7 pg/mg*	143.7 pg/mg*	24 h
Interleukin-1 (IL-1)	Glomerulus	Plasma	2.9 pg/mg*	50.0 pg/mg*	168.1 pg/mg*	24 h
Platelet activating factor (PAF)	Glomerulus	Plasma	20.5 pg/mg*	404.3 pg/mg*	412.7 pg/mg*	24 h
Tumour necrosis factor-α (TNF-α)	Glomerulus	Plasma	2.5 pg/mg*	49.4 pg/mg*	125.7 pg/mg*	24 h
Kidney injury molecule-1 (KIM-1)	Proximal tubule	Apical membrane	Undetected	0.76 ng/ml	2.99 ng/ml	12 h
Na/H exchanger isoform 3 (NHE3)	Proximal tubule/LOH	Apical membrane	Undetected	0.12–0.78§	1.52§	24 h

Abbreviations: C_N, normal concentration; C_U, mean/median concentration; C_{MAX}, maximal reported concentration; *Time*, mean/median time from insult to an increased detection in urine; *LOH*, loop of Henle; *NA*, not available or not specified

* Standardized to unit biomarker/mg creatinine expressed in urine by litre of urine

** Standardized to unit biomarker/mol creatinine expressed in urine by litre of urine

§ Arbitrary band density units standardized to urinary creatinine

Table 5 Summary of associations of selected urinary biomarkers and traditional biochemical and clinical outcomes from included studies of patients with septic AKI

Biomarker	Associated with ΔSCr[a]	Distinguish PRA and ATN	Detect sub-clinical or predict AKI	Associated with need for RRT	Associated with mortality
Low-molecular-weight proteins					
α_1-Microglobulin (α_1-M)	Yes	NA	Yes	Yes	NA
β_2-Microglobulin (β_2-M)	Yes	Yes	Yes	No	NA
Retinol binding protein (RBP)	Yes	NA	NA	Yes	NA
Adenosine deaminase binding protein (ABP)	Yes	NA	Yes	NA	NA
Cystatin C	Yes	NA	NA	Yes	NA
Tubular enzymes					
Proximal renal tubular epithelial antigen (HRTE-1)	Yes	Yes	NA	NA	NA
α-Glutathione S-transferase (α-GST)	Yes	NA	Yes	Yes	NA
π-Glutathione S-transferase (π-GST)	Yes	NA	Yes	NA	NA
γ-Glutamyl transpeptidase (γ-GT)	Yes	NA	Yes	Yes	NA
Alanine aminopeptidase (AAP)	Yes	NA	NA	NA	NA
Lactate dehydrogenase (LDH)	Yes	NA	No	No	NA
N-acetyl-β-glucosaminidase (NAG)	Yes	Yes	Yes	Yes	Yes
Alkaline phosphatase (ALP)	Yes	Yes	Yes	Yes	Yes
Cytokines					
Interleukin-18 (IL-18)	Yes	NA	Yes	Yes	Yes
Interleukin-8 (IL-8)	Yes	NA	NA	NA	NA
Interleukin-6 (IL-6)	Yes	NA	NA	NA	NA
Interleukin-1 (IL-1)	Yes	NA	NA	NA	NA
Platelet activating factor (PAF)	Yes	NA	NA	NA	NA
Tumour necrosis factor-α (TNF-α)	Yes	NA	NA	NA	NA
Kidney injury molecule-1 (KIM-1)	Yes	Yes	NA	NA	NA
Na/H exchanger isoform 3 (NHE3)	Yes	Yes	NA	NA	NA

Abbreviations: Δ *SCr*, change in serum creatinine; *PRA*, pre-renal azotaemia; *ATN*, acute tubular necrosis; *AKI*, acute kidney injury; *RRT*, renal replacement therapy; *NA*, not available or assessed

[a] Association with ΔSCr represents elevated levels of urinary biomarker in the context of acute increases in SCr and not necessarily evidence of a linear association, correlation or dose-response

factor [13]. Both higher urinary ALP and NAG at the time of diagnosis and higher peak NAG, despite similar serum creatinine values, were associated with a poor prognosis, defined as death or RRT dependence at hospital discharge [13]. Regrettably, no data were available on the time to peak urinary measures or on values in the septic subgroup. Interestingly, urinary ALP and NAG failed to discriminate pre-renal ARF from ATN when classified by traditional biochemical criteria.

Westhuyzen et al. described the detection of several urinary enzymes (γ-GT, ALP, NAG, LDH, α/π-GST) in a small cohort of critically ill patients [16]. All urinary enzymes (except LHD) were significantly higher at ICU admission in those who developed ARF (defined as an increase of at least 50% in baseline serum creatinine to a value ≥ 150 μmol/l) than in controls and preceded evidence of ARF by serum creatinine criteria by a median 36 h. All urinary enzymes (except LHD) had excellent discrimination (AuROC > 0.80) for predicting ARF and were superior in this respect to serum creatinine and calculated creatinine clearance (AuROC 0.79). Regrettably, in this study there were only four patients who developed ARF, only one of whom was septic; thus, inferences are limited.

Recently, Herget-Rosenthal assessed whether patterns of the urinary low-molecular-weight protein and enzyme excretion could predict the need for RRT in 73 non-critically ill patients with ATN (defined by traditional biochemical criteria), of which 26% had sepsis [14]. RRT was required in 36% after a median 4 days. Of the enzymes measured, NAG had the greatest discrimination for need for RRT (AuROC 0.81), yet performed less well than cystatin C and α_1-M. The remaining urinary enzymes were less predictive of need for RRT.

Cytokines

Platelet activating factor (PAF) is a phospholipid mediator of inflammation that has been shown to participate in the pathophysiology of septic AKI [27]. Mariano et al. described significant early elevations in urinary PAF in 12 critically ill patients with septic shock and AKI [28]. Furthermore, urinary PAF correlated with other serum and urine inflammatory cytokines, specifically serum IL-6, serum IL-8 and urine IL-6. Serum PAF was also found to correlate with serum creatinine concentration. This study suggests that PAF may contribute to the pathophysiology of septic AKI and that urinary PAF may predict the clinical course and correlate with severity of AKI. In this study, the urinary concentration of cytokines IL-1β or TNF-α added little information.

Interleukin-18 (IL-18) has been shown to be a potent mediator of ischaemia-induced AKI in experimental models [29, 30]. Early detection of urinary IL-18 has been shown to predict delayed graft failure after kidney transplantation and late increases (48–72 h) in serum creatinine after cardiac surgery with cardiopulmonary bypass [31, 32]. Parikh et al. found that urinary IL-18 levels were significantly elevated in patients with ATN compared with patients with pre-renal azotaemia, urinary tract infection, or chronic kidney disease or with healthy controls [31]. This study found that a cut-off urinary IL-18 to serum creatinine ratio of 500 pg/mg creatinine had sensitivity and specificity of 85% and 88% for the diagnosis of ATN, respectively. Unfortunately, of the 22 patients with ARF (pre-renal and ATN), only 27% had sepsis, and the timing of measurement of urinary IL-18 was not specified. However, despite similar serum creatinine concentrations in septic and non-septic AKI patients (281 ± 114 μmol/l vs. 291 ± 142 μmol/l, $p = 0.86$), urinary IL-18 was significantly higher in those with a diagnosis of sepsis (1010 ± 763 pg/mg creatinine vs. 411 ± 382 pg/mg creatinine, $p = 0.02$). More recently, in a nested case–control study of mostly septic critically ill patients with acute respiratory distress syndrome (ARDS), an elevated urinary IL-18 value preceded clinical evidence of overt ARF by 24–48 h [33]. Moreover, an increased urinary IL-18 to creatinine ratio > 100 pg/mg creatinine had a 6.5-fold increase in odds of AKI within 24 h (odds ratio 6.5, 95% confidence interval 2.1–20.4). Finally, a high urinary IL-18 at the time of enrolment was also an independent predictor of mortality.

Additional Biomarkers

Kidney injury molecule-1 (KIM-1) is a type 1 transmembrane glycoprotein that is markedly up-regulated in proximal renal tubular cells in response to ischaemic or nephrotoxic AKI [34–36]. The ectodomain segment of KIM-1 is shed from proximal cells and detected in the urine by immunoassay [15]. KIM-1 levels are higher for ATN defined by abnormal sediment compared with other AKI (2.0 ng/ml vs. 0.22 ng/ml). Increased urinary detection of KIM-1 was found superior to urinary ALP and γ-GT for the diagnosis of ATN [15]. Moreover, kidney biopsies from patients with ATN show significantly greater KIM-1 tissue expression than other acute and chronic kidney diseases. However, no biopsy specimens were taken from septic patients. Moreover, of those with ischaemic ATN, only four had sepsis, and there was no significant difference in KIM-1 levels between the septic and non-septic patients.

Urinary Na^+/H^+ exchanger isoform 3 (NHE3) is the most abundant sodium transporter in the renal tubule and is responsible for the reabsorption of large quantities of filtered sodium from the urine. NHE3 is not normally detectable in the urine; however, abnormal elevations have been described in critically ill patients with AKI [22]. Du Cheyron et al. found urinary NHE3 was higher in those with ATN than with pre-renal ARF (6.1 vs. 0.92,

$p < 0.0001$) and undetectable in controls or those with other causes of intrinsic ARF (i.e. glomerulonephritis or vasculitis). In addition, NHE3 was shown to be superior to RBP in discriminating pre-renal AKI and ATN and correlated positively with serum creatinine concentration. Urinary NHE3 was serially followed in two patients admitted to ICU with septic shock and normal initial kidney function who later developed AKI. At baseline, urinary NHE3 was undetected in these two patients; however, both later showed acute increases in the urine membrane fractions of NHE3 that corresponded with clinical evidence of AKI. Moreover, the NHE3 became undetectable again upon recovery of kidney function.

Novel biomarkers not described in septic AKI

There are several additional novel urinary biomarkers that have been characterized in AKI, including neutrophil gelatinase-associated lipocalin (NGAL) [37–39]; cysteine-rich protein 61 (Cyr61) [40]; perforin and granzyme B [41]; CXCR3-binding chemokines [42]; urinary endothelin; and urinary SSAT [43]. Regrettably, however, most of these biomarkers have been characterized in ischaemic or nephrotoxic AKI, following kidney transplant, or have been restricted to experimental studies and have yet to be evaluated in AKI associated with sepsis.

Discussion

We performed a systematic review of all human studies describing urinary biomarkers to assess their diagnostic and prognostic value in septic AKI. We found there are numerous biomarkers that have been characterized for the early and non-invasive detection of AKI. However, relatively few clinical studies have documented their urinary excretion in septic AKI. Moreover, several recently characterized urinary biomarkers have yet to be described in patients with septic AKI. We also found that studies included in our review showed marked heterogeneity, specifically in terms of patient populations, severity of illness, study inclusion/exclusion criteria, proportion with sepsis, and the presence of potential confounding factors. Due to these features, inferences regarding the diagnostic and prognostic value of urinary biomarkers in septic AKI are limited and problematic.

On the other hand, we found that urinary IL-18 excretion was higher in septic than in non-septic AKI patients; increased urinary excretion of IL-18 was a predictor for subsequent deterioration in kidney function preceding clinically significant AKI by 24–48 h. These observations suggest that IL-18 may represent a useful early marker of AKI. We also found evidence that selected biomarkers (i.e. PAF, IL-18, NHE3) may aid in the detection of early kidney injury in sepsis prior to the development of overt kidney failure characterized by elevated serum creatinine and/or urea. Several additional low-molecular-weight proteins (i.e. β_2-M, α_1-M, ABP) and enzymes (i.e. γ-GT, ALP, NAG, α/π-GST) may be evident early in the urine of patients with AKI and precede clinical evidence of ARF; however, their value in sepsis remains unclear. Finally, we found that an increase in urinary excretion of selected biomarkers (i.e. cystatin C, α_1-M, IL-18) may have prognostic importance and forecast the need for RRT and mortality.

We believe the findings of our review have particular importance for the septic critically ill patient. Sepsis is a highly prevalent syndrome in critical illness and is the leading precipitant of AKI [1], with mortality rates in excess of 70% [6–8]. Moreover, the distinction between septic and non-septic AKI may have clinical relevance. Experimental and clinical data suggest that septic AKI may be characterized by a distinct pathophysiology [44–47]. Thus, we believe septic AKI may be a unique condition. We further hypothesize that in septic AKI there may be distinguishing patterns in the urinary excretion of biomarkers. Our review presents some evidence to support this hypothesis by finding that urinary IL-18 excretion was higher in septic than in non-septic AKI [31]. In addition, selected biomarkers, such as PAF and IL-18, may directly or indirectly induce AKI, and a broader knowledge of their pattern of excretion in septic AKI may lead to further understanding of the pathophysiology of septic AKI. Regrettably, however, we still have little understanding of urinary biomarkers in this condition [48].

The availability of urinary biomarkers as a non-invasive tool to identify early AKI may provide important diagnostic and prognostic data for the septic critically ill patient. In particular, the detection of abnormally elevated urinary biomarkers consistent with AKI may provide lead time and allow for initiation of supportive therapies and/or interventions before the development of overt functional ARF [49–51]. Delay in diagnosis and in initiation of supportive care may adversely impact clinical outcome [49] while the early application of such care may show clinical benefit [52]. Urinary biomarkers (i.e. IL-18, NHE3, NGAL, KIM-1, cystatin C) may play an important role in future clinical trials by identifying early those patients most likely to benefit. Likewise, these urinary biomarkers, once characterized in larger studies, may represent ideal non-invasive markers for the stratification of septic critically ill patients with early AKI in future randomized clinical trials of novel interventions or changes in process of care.

The ideal urinary biomarker in AKI would have several characteristics, including reliable detection of AKI; being sufficiently sensitive to detect early subclinical injury; reflecting the location of kidney injury; reflecting time-dependent changes in the severity of injury (i.e. analogous

to serum creatine kinase levels in acute myocardial infarction); and being simple, cheap and easy to measure. Unfortunately, no single urinary biomarker currently fulfils all these ideal traits. In addition, there are problems with the routine use of many of these urinary biomarkers. For example, there may be a low threshold of injury for many urinary enzymes (high sensitivity), while at the same time increased excretion with a variety of clinical conditions other than AKI (i.e. chronic glomerular diseases) (low specificity) that would limit their value. Moreover, many newer and more promising urinary biomarkers described in our review are at present not widely available or are too expensive, making their application outside of research settings limited. More importantly, perhaps, most studies to date have used these urinary biomarkers to simply discriminate pre-renal ARF from ATN [11]. Rather, future prospective investigations of urinary biomarkers in septic and non-septic AKI should aim to describe the timing of detection (i.e. onset of injury) and the peak and duration of excretion (i.e. severity of injury) and to correlate these findings with both traditional measures of kidney function (i.e. serum creatinine, urea) and clinically important outcomes (i.e. need for RRT, renal recovery, mortality). Moreover, future experimental models of septic AKI should correlate the detection and course of urinary biomarker excretion with kidney haemodynamics and kidney tubular cell histopathology [47, 53]. Finally, the performance of several urinary biomarkers should be assessed to determine whether any particular pattern of excretion has greater diagnostic and prognostic value than single urinary biomarkers alone. These uncertainties need to be examined in large prospective studies of critically ill patients with sepsis.

There are limitations to our study. First, despite a rigorous search, we may have missed some reports that fulfil our inclusion criteria. For example, we may have missed reports that focused solely on urinary biomarkers for the detection of aminoglycoside nephrotoxicity. In the end, however, we believe that our findings would not be significantly prejudiced as a consequence. Second, our findings have limited generalizability to the critically ill patient for the reasons discussed. Finally, few studies assessed the temporal profile of these urinary biomarkers and correlated their time to detection and peak value with traditional markers of kidney function, thus making inferences about diagnosis and prognosis difficult. Furthermore, despite normalization to urinary creatinine these biomarkers may in part be dependent on urine output and concomitant diuresis [14, 54].

Conclusion

While there are numerous urinary biomarkers that have been characterized for the early and non-invasive detection of AKI, few have been documented in septic AKI, and available studies have notable limitations. However, there is evidence to suggest that selected urinary biomarkers may aid in the early detection of AKI in sepsis and have predictive value. The early detection of AKI may facilitate the development of new therapies, as the early detection of myocardial ischaemia has done in cardiology. Thus, prospective studies are needed to accurately describe the role and course of these biomarkers in septic AKI and their significance for clinical practice.

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