

Inflammation-Associated Tubulopathy in Patients with Acute Bacterial Infections

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Background: Acute kidney injury associated with the underlying inflammatory process of an acute bacterial infection affects patient morbidity and mortality. Clinicians use creatinine and estimated glomerular filtration rate (EGFR) to assess this renal injury, however, these measures may lag behind and change only once significant kidney injury has occurred. Neutrophil gelatinase-associated lipocalin (NGAL) is up-regulated by inflammation and infection and may serve as an early detection biomarker of kidney injury.

Methods: Patients hospitalized with bacterial infections were assessed demographically, clinically and had their creatinine levels, EGFR and inflammatory biomarker levels, including urinary NGAL measured. Findings were compared between controls and patients across different EGFRs.

Results: Fifty-one participants were included in the study. Among this cohort, 31 suffered bacterial infection. Inflammatory biomarkers including urinary NGAL were found to be higher in the infection group compared to the control group. Urinary NGAL level was significantly higher across all EGFRs of patients diagnosed with infection, including those with normal EGFR.

Conclusion: Urinary NGAL identifies early kidney damage associated with bacterial infection even at normal EGFR and alerts the treating physician to undertake the necessary measures to mitigate the renal injury.

Keywords: acute kidney injury, bacterial infection, estimated glomerular filtration rate, inflammation, urinary NGAL

Introduction

Acute bacterial infection is associated with acute kidney injury (AKI), which contributes significantly to patient deterioration during sepsis secondary to bacterial infection and associated tissue inflammation. Deteriorating kidney function is associated with different metabolic abnormalities including fluid imbalance and electrolyte disturbances, which necessitate close medical management and even use of renal replacement therapy (RRT).^{1,2} Furthermore, kidney damage leads to prolonged hospitalizations and increased medical costs.

Kidney function is readily assessed by the clinician by using the creatinine levels and more accurately by calculating the creatinine clearance as an approximation of the patient's glomerular filtration rate (GFR). In recent years, novel biomarkers have been developed to provide crucial information regarding kidney damage in addition to the creatinine level and the creatinine clearance calculation.³

Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the adipokines superfamily and was shown to be involved in a variety of physiological and pathophysiological processes. These include metabolic homeostasis, transport of fatty acids and iron transport, modulation of inflammation, apoptosis, infection, and immune response.⁴ It is known that bacteria require iron for growth, which is collected and transported into the bacterial cells by the bacterial siderophores- low molecular weight proteins produced by bacteria that bind specifically to the ferric form of iron. NGAL interacts with the

bacterial siderophores and thereby depletes iron stores available to the bacteria. Subsequently, NGAL can inhibit bacterial growth and serve as a component of the innate immune system and the acute-phase response to infection.⁵ NGAL also affects the host iron homeostasis by binding mammalian siderophores, before transporting iron across cellular membranes.⁶ Moreover, NGAL may stabilize the labile iron/siderophore complex. NGAL affects host proinflammatory cytokine expression by limiting iron-mediated oxidative stress. NGAL secretion is regulated by inflammation and infection and its production is induced by tumor necrosis factor alpha (TNF α) and lipopolysaccharide (LPS).

NGAL is expressed in different tissues, mainly white adipose tissue, but also in immune cells, uterus, bone marrow, liver, spleen, kidney, chondrocytes, and in tissues exposed to microorganisms. Physiologically, the level of NGAL in biological fluids is low, however its level is up-regulated in an inflammatory state. This enables NGAL to be used as a biomarker of inflammation. Plasma NGAL is filtered by the glomerulus and almost totally reabsorbed in the proximal tubules. Urinary excretion of NGAL is increased when there is proximal renal tubular injury, preventing NGAL reabsorption and stimulating its production. Indeed, tubular cell damage leads to increased levels of NGAL in plasma and urine.⁷ NGAL is one of the most up-regulated genes and among the most highly induced proteins in the kidney very early after AKI.

NGAL has become a widely used biomarker for kidney injury, specifically indicating kidney damage associated with inflammatory states and metabolic abnormalities.

A normal creatinine clearance might give the clinician the false impression of a relatively mild inflammation caused by bacterial infection, which is not associated with kidney injury.

We sought to use NGAL measurements in patients with acute bacterial infection across a wide range of creatinine clearance in order to assess developing kidney injury.

Materials and Methods

Patient Population

The study included patients 18 years and older who were hospitalized at Tel Aviv Sourasky Medical Center, a 1050 bed tertiary university affiliated hospital serving an urban population of approximately 500,000 people, and diagnosed as having an infection of assumed or proven bacterial etiology. Assumption of bacterial infection was made according to clinical syndromes associated with bacteria considering the typical clinical presentations of bacterial infection such as fever, shivering, cough, flank pain, urinary symptoms, etc., even though bacterial isolation is not always feasible in these infections (for example, pneumonia or cellulitis, urinary tract infection). All patients had their creatinine level measured, as well as their C-reactive protein (CRP) level and urinary neutrophil gelatinase-associated lipocalin (uNGAL) levels. Age, gender, and body mass index (BMI) were extracted from the patients' electronic medical records.

Control Group Population

Controls were recruited from a pool of either healthy medical staff or patients diagnosed due to non-infectious and non-inflammatory conditions.

Individuals who had recently recovered from an acute illness were excluded. Furthermore, each individual filled out a health check-up form where they were specifically asked whether they are currently suffering from any inflammatory condition. Their medical records were reviewed for any known inflammatory conditions (for example, Systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, etc.) and for any known malignancy. Any affected individual was excluded from the study. The local ethics committee (number 02–049) approved the study.

Laboratory Methods

A 5-mL sample of serum was collected from each patient, on the day of urinalysis, centrifuged at $1500 \times g$ for 10 minutes at room temperature and analyzed for chemistry tests.

Blood tests were performed at the medical center's central laboratory using conventional methods. The ADVIA 2400 automatic biochemical analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY 10591–5097 USA) was used for measurement of serum creatinine and CRP. Plasma creatinine measurements were performed using ADVIA 2400 system (Siemens LTD). The reaction is based on the JAFFE method with modification using rate blanking and intercept

correction. Creatinine reacts with picric acid in an alkaline medium to produce a red-colored creatinine-picric acid complex. The rate of complex formation is measured at 505/571 nm. The method is traceable to the IDMS reference method via reference material SRM967 from the National Institute of Standards and Technology (NIST).⁸ The estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI formula.⁹

Wide-range C-reactive protein (wrCRP) measurements were done by ADVIA 2400 (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). The ADVIA[®] Chemistry wrCRP method measures CRP in serum and plasma by a latex-enhanced immunoturbidimetric assay. It is based on the principle that the analytic concentration is a function of the intensity of scattered light caused by the latex aggregates. The latex particles coated with anti-CRP rapidly agglutinate in the presence of CRP-forming aggregates. Agglutination takes place resulting in an increase in turbidity, which is measured at 571 nm. The CRP concentration in serum is determined from a calibration curve. This method measures the wrCRP concentration range of 0.03–155 mg/L. When the measured concentrations exceed 155 mg/L, a dilution of 1:4 is performed to extend this range.¹⁰

A 20-mL midstream urine sample was collected and centrifuged at $3000 \times g$ for 15 minutes at room temperature to remove debris. 1.5-mL aliquots of the supernatant were placed in sterile centrifuge tubes and stored at -80°C for urine NGAL analysis. During analyses, all samples were thawed only once, and urine precipitates were thoroughly mixed after complete thawing. Osmolality measurement was done by Arkray LTD PM-6060 Automatic osmometer. The Abbott ARCHITECT c1000 automatic analyzer was used for measurements of urine NGAL. Urinary NGAL was measured using a commercially available chemiluminescence method (Abbott, USA) on the ARCHITECT system. The NGAL assay utilizes microparticles coated with monoclonal antibodies for the detection of NGAL.

The ARCHITECT Urine NGAL assay is a two-step immunoassay using CMIA technology. In the first step, sample and wash buffer are combined to create a pre-diluted sample. An aliquot of the pre-diluted sample, wash buffer, and anti-NGAL coated paramagnetic microparticles are combined. NGAL present in the sample binds to anti-NGAL coated microparticles and the reaction mixture is washed. In the second step, anti-NGAL acridinium-labeled conjugate is added. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A relationship exists between the amount of NGAL in the sample and the RLUs detected by the ARCHITECT System.¹¹

Statistical Methods

In order to determine the sample size of our study, we used preliminary creatinine data from healthy individuals (0.12 ± 0.2) and patients with bacterial infections (1.17 ± 0.4). We assumed a significance level of 5% and a power of 80%. The ratio between the control and study groups was 1:5. The sample size can detect a difference of 0.5. Based on these parameters, the control sample size is six, and the bacterial infection group is 27. We used the WINPEPI software, developed by Abramson, J.H., to calculate the sample size.

Categorical variables were described using frequency and percentage. Continuous variables were evaluated for normal distribution using histograms and Q-Q plots. Continuous variables were reported as mean and standard deviation (SD) and skewed continuous variables were transformed and presented in logarithmic scale. All statistical tests were two tailed. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 25, IBM Corp., Armonk, NY, USA, 2017).

Results

Fifty-one patients participated in the study, 16 females and 35 males. A total of 31 patients had bacterial infection, and among them 31.3% were females, comparing to 68.7% males (Table 1).

The most common infection encountered among the patients studied was pneumonia, which was responsible for 45% of infections (Table 2). The leading bacterial agents isolated in culture were *Streptococcus pneumoniae* (15.4%), *E. coli* (15.4%), and *Staphylococcus aureus* (7.7%). Other bacterial agents isolated included streptococci viridans, coagulase-negative *Staphylococci* and *Leuconostoc*.

Comparison of laboratory parameters between the control group and the bacterial infection group demonstrated few significant differences (Table 3).

Table 1 Demographic Characteristics of Study Population

Gender	Age (Average)	BMI	Controls (%)	Bacterial Infection (%)
Female (16)	59±19.6	23.5±4.06	31.3	68.8
Male (35)	56.6±20	23.13±2.1	41.2	58.8

Table 2 Types of Infections Among Patients in the Bacterial Infection Group

Type of Infection	Percentage
Pneumonia	45
Urinary tract infection	9.6
Cellulitis	9.6
Endocarditis	6.4
Diverticulitis	6.4
Other	22.58

Table 3 Differences Between Patients with Bacterial Infection to Healthy Controls Across Laboratory Parameters

	Control (n=20)	Bacterial Infection (n=31)	p value
Hg	13.58±3.5	12.08±1.7	0.05
WBC	5.82±2.07	11.19±4.18	0.00
Neutrophil %	0.54±0.16	0.82±0.08	0.00
Lymphocytes %	0.3±0.1	0.1±0.06	0.00
PLT	209.83±64.94	242.94±119.65	0.22
EGFR	119.01±34.78	82.97±42.52	0.00
Creatinine	0.73±0.2	1.21±0.68	0.00
CRP on Urinalysis	2.34±3.32	165.46±89.06	0.00
OSMU	609.58±284.48	439.86±241.17	0.03

Abbreviations: CRP, C-reactive protein; EGFR, estimated glomerular filtration rate; Hg, hemoglobin; OSMU, Urine osmolality; PLT, platelets; WBC, white blood cells.

The inflammatory biomarkers CRP and white blood cell (WBC) count were, as expected, significantly higher in the bacterial infection group compared to the control group (165.46 ± 89.06 vs 2.34 ± 3.32 and 11.19 ± 4.18 vs 5.82 ± 2.07, respectively). Regarding renal function, the creatinine level was higher and the estimated glomerular filtration rate (EGFR) was lower in the bacterial infection group compared to the control group (0.73 ± 0.2 vs 1.21 ± 0.68 and 119.01 ± 34.78 vs 82.97 ± 42.52, respectively). The uNGAL parameter measured significantly higher in the bacterial infection group compared to the controls (99.33 ± 140.7 vs 9.52 ± 10.09, p value = 0.008) (Figure 1).

Inflammation properties of uNGAL were demonstrated by its correlation with the inflammatory biomarker CRP level (r = 0.41) (Figure 2).

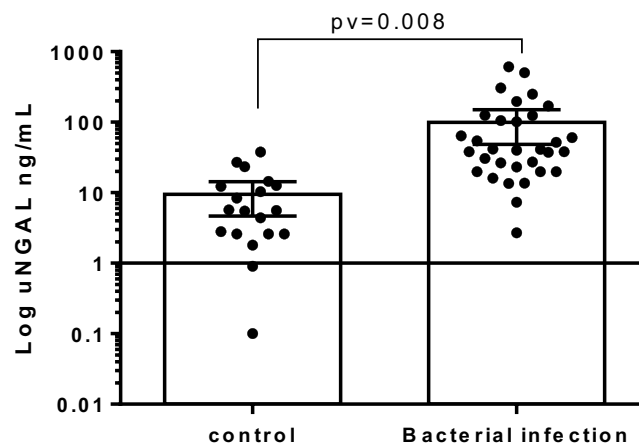


Figure 1 Comparison of uNGal concentrations between control group and bacterial infection group.
Abbreviations: uNGAL, urinary neutrophil gelatinase-associated lipocalin; pv, p value.

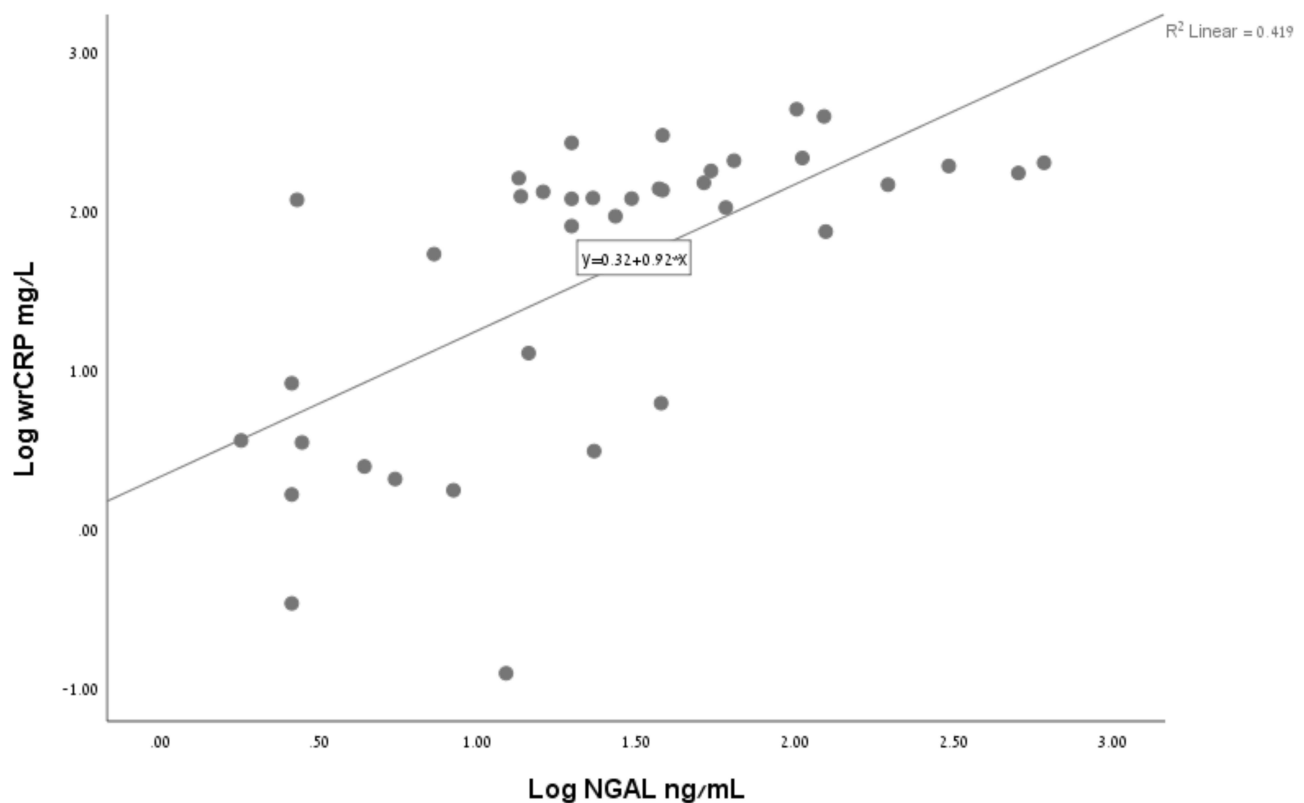


Figure 2 The association between wrCRP and uNGAL.
Abbreviations: uNGAL, urinary neutrophil gelatinase-associated lipocalin; wrCRP, wide range of C-reactive proteins.

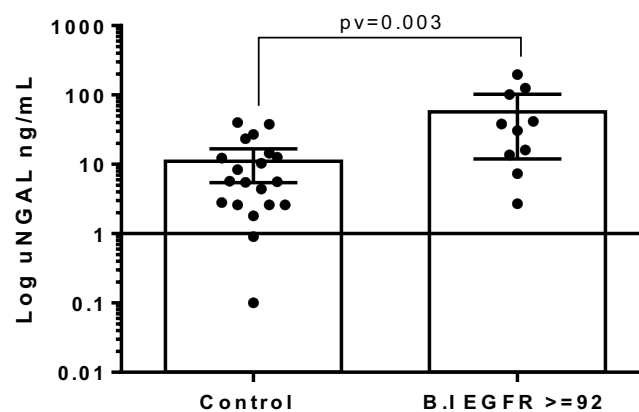
We further assessed the relationship between the inflammatory biomarker uNGAL and kidney function by subdividing the bacterial infection group into three subgroups according to the EGFR (>92, 55–92, and <55) (Table 4). The CRP level was significantly higher in all EGFR bacterial infection subgroups compared to the control group (P value < 0.001), while its level did not differ between the three EGFR subgroups (Table 4). In comparison, uNGAL levels did differ significantly between the three bacterial infection EGFR subgroups. Ten patients had EGFR within the normal range

Table 4 Laboratory Parameters Across Study Groups: Control Group vs Bacterial Infection Groups Divided According EGFR

	Control group Mean±SD (C.I.)	Bacterial Infection Group Mean±SD (C.I.)			PV Anova
		EGFR>92	EGFR 55–92	B.I EGFR <55	
Hg	13.584±3.405 (11.94–15.22)	12.73±1.241 (11.84–13.61)	11.375±1.925 (10.15–12.59)	12.288±1.635 (11.03–13.54)	0.12
WBC	6.2315±2.686 (4.936–7.526)	11.39±4.044 (8.496–14.28)	11.133±5.147 (7.862–14.40)	11.05±3.25 (8.55–13.5)	0.001
Neutrophil %	0.55±0.16 (0.47–0.63)	0.80±0.07 (0.75–0.86)	0.81±0.09 (0.76–0.87)	0.83±0.08 (0.76–0.89)	<0.001
Lymphocytes %	0.28±0.10 (0.23–0.34)	0.11±0.06 (0.06–0.15)	0.09±0.06 (0.05–0.13)	0.07±0.05 (0.03–0.11)	<0.001
PLT 10 ⁻³ /μL	206.47±64.78 (175.24–237.69)	291.3±154.85 (180.52–402.07)	238.75±102.17 (173.82–303.67)	194.77±82.42 (131.42–258.13)	0.12
Creatinine mg/dL	0.77±0.269 (0.64–0.89)	0.68±0.130 (0.58–0.77)	1.06±0.179 (0.94–1.17)	1.99±0.752 (1.41–2.57)	<0.001
CRP mg/L	2.33±3.315 (0.74–3.93)	162±118.8 (70.65–253.34)	165.9±88.44 (102.63–229.16)	169.29±49.50 (123.50–215.08)	<0.001
Osmolality Mosmo/Kg	605.45±277.5 (475.57–735.32)	479.17±293.3 (253.71–704.63)	559.08±161.6 (456.40–661.76)	241.57±147.0 (128.57–354.57)	0.004
uNGAL ng/mL	11.045±11.93 (5.45–16.63)	57.32±63.50 (11.89–102.74)	75.066±79.06 (24.83–125.29)	184.95±227.6 (9.937–359.97)	<0.001

Abbreviations: EGFR, estimated glomerular filtration rate; C.I, confidence interval; CRP, C-reactive protein; Hg, hemoglobin; PLT, platelets; PV, p value; SD, standard deviation; uNGAL, urinary neutrophil gelatinase-associated lipocalin; WBC, white blood cells.

similar to the control group (EGFR 132 ± 31 vs 115 ± 37 , respectively). However, the uNGAL concentration was significantly higher in this EGFR > 92 subgroup compared to the control group (57.32 ± 63.50 vs 11.045 ± 11.93) (Figure 3). Furthermore, the uNGAL concentration is inversely proportional to the EGFR (Table 4).

**Figure 3** Comparison of uNGal concentration in the control group vs bacterial infection with EGFR≥92 group.

Abbreviations: B.I. EGFR, bacterial infection estimated glomerular filtration rate; uNGAL, urinary neutrophil gelatinase-associated lipocalin; pv, P value.

Discussion

It is known that acute bacterial infection can lead to renal injury. Acute kidney injury is associated with high mortality rate in critically ill patients, despite significant advances in therapeutics including RRT such as dialysis. Mortality rate associated with AKI can be as high as 50%.

Assessment of renal function includes serum creatinine and blood urea nitrogen measurement, and this remained unchanged for several decades. It is commonly accepted that these biomarkers display poor sensitivity and specificity for detection of acute changes in kidney function and do not differentiate between the renal function itself represented by the functional nephron number and the extent of an existing renal lesion as an indicator of active kidney damage.¹² Changes in creatinine concentration primarily reflect functional changes in filtration capacity and are not reflective of tissue injury. NGAL is expressed in many tissues such as kidney, heart, liver, vascular system, lung and neutrophils and its level increases in inflammation states such as sepsis, cardiovascular diseases and cancer pathogenesis. NGAL measurement was studied as a marker of adverse renal and cardiovascular outcomes among patients undergoing primary coronary intervention¹³ and cardiac surgery.¹⁴ A meta-analysis estimated the diagnostic and prognostic accuracy of NGAL and its value in AKI found NGAL to be a useful early predictor of AKI. Additionally, NGAL level had prognostic value for clinical endpoints, such as initiation of dialysis and mortality.^{15,16} However, another meta-analysis examining plasma NGAL as a predictive biomarker of AKI in septic patients found that despite its high sensitivity and high negative predictive value for detection of AKI in adult septic patients, its low specificity and low positive predictive value could limit its clinical utility.¹⁷

In a recent study, Xie et al examined biomarkers for the diagnosis of sepsis associated with AKI and found that, among the different biomarkers studied, the diagnostic value of urinary NGAL was slightly higher than that of blood NGAL.¹⁸

Clinicians use estimated GFR as an indication of renal injury, however our findings indicate that patients with acute bacterial infection who do have an established renal injury, will have elevated urinary NGAL levels before any reduction of the estimated GFR is seen. This may be used in addition to repeated CRP measurement.¹⁹

The principal finding of this study is that acute bacterial infection is associated with kidney damage even in patients with normal creatinine clearance as demonstrated by the increased uNGAL levels found in this patient population. Therefore, uNGAL measurement allows the physician to rapidly assess a developing kidney injury not yet observed by creatinine clearance calculations and alerts the physician to potential metabolic deterioration associated with kidney injury.

uNGAL is measured by simple urine sampling at the patient's bedside and does not require blood draw, a more invasive, time-consuming investigation, which may be painful and even cumbersome to perform. Utilizing uNGAL measurement may enable substantial healthcare cost-saving by reducing the number of hospitalization days and reducing the requirements for renal replacement therapy.

Physicians are accustomed to assessing kidney function in acute bacterial infection by using creatinine levels and estimated GFR calculation. Hence, this practice may result in an underestimation of kidney damage, and subsequently an underestimation of disease severity. Elevated UNGAL levels can alert the physician to the developing kidney damage associated with the infection and better prepare for kidney function deterioration.

Our findings have important clinical implications, since the notion of an existing and ongoing renal injury despite normal estimated GFR in patients with acute bacterial infections, should alert the clinician to cease nephrotoxic drug treatment or exposure to nephrotoxins and administer intravascular fluid treatment in a timely manner despite the patient's normal estimated GFR, in order to mitigate the developing renal injury.

One limitation of our study is the variation of clinical scenarios amongst our intervention arm – not only were there different causative organisms but also different clinical diseases including infection involving the kidneys (pyelonephritis) as well as extra-renal infections. However, we consider this to be advantageous as it emphasizes the concept of kidney damage in a variety of different kinds of infections. The second limitation is the relatively low number of cases, which should be increased in future research. Another limitation is that blood NGAL levels were not measured, therefore, the source of elevated uNGAL level, whether from plasma or from local production, could not be discriminated. Another limitation is that the collected data lacks the correlation between peak serum creatinine and uNGAL, which should be a subject for future research.

We hope that the long-term prognosis expressed as kidney function, morbidity, and mortality of patients presenting with acute bacterial infections and elevated uNGAL levels will be the goal of future research.

Conclusions

This study demonstrated renal injury, detected by uNGAL levels, in a population of patients with acute bacterial infections despite normal estimated GFR. This could serve as an early detection marker, warning physicians treating such patients of the potential kidney damage associated with these infections.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Informed consent was obtained from all subjects involved in the study. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Tel Aviv Sourasky Medical Center (number 02–049).

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Disclosure

The authors declare no conflict of interest.

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