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Early diagnosis of acute kidney injury

Research Article

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Abstract: There is a considerable lack of data concerning the diagnostic testing for kidney damage after surgical procedures. In this situation the most important variables should be examined with respect to their clinical informative value, the costs associated with their analysis, and their potential use in routine diagnostic testing. Forty patients in the surgical intensive care unit (ICU) with acute kidney injury (AKI) that developed during their stay of 13-18 (median, 16) days in the ICU were examined daily during their entire ICU admission. The bulk of the laboratory research consisted of the measurement of creatinine, urea, and sodium, as well as clearances rates and diuresis. Various tests for diagnosing regional renal damage (enzymes and proteins) were also carried out. The included photometry, nephelometric analysis, and ELISA (enzyme-linked immunosorbent assay). Five days before an AKI became evident, pathologic levels of urinary α1–microglobulin (tubular parameter) could already be confirmed. Serum creatinine values or creatinine clearance indicated the presence of disease only 1 day before the AKI was seen. Our results show that determination of α1-microglobulin and immunoglobulin G (glomerular parameter) levels, in addition to the level of urea in serum, be recommended for patients in surgical intensive care units who are at risk for AKI. Use of these procedures can achieve early recognition and sufficiently precise localization of renal damage.

Keywords: *Acute kidney injury • Proteinuria • Histuria*

1. Introduction

Acute kidney injury (AKI) is a potentially fatal complication amongst polytraumatized patients [1,2]. In the face of a high mortality rate and follow-up costs of treatment for organ insufficiency, the development of a strategy for early recognition, prophylaxis, and treatment of kidney damage is of the utmost urgency. To achieve this, the selected laboratory values should be able to detect damage with a high specificity as early as possible [3].

The variables examined in our study included diuresis, as well as serum concentrations of creatinine and urea.

Additionally, tubular markers like α1-microglobulin (α1-MG), β2-microglobulin (β2-MG), Tamm-Horsfall-protein (THP), excretion fraction of sodium, and the brush border enzyme alanine-amino-peptidase (AAP); glomerular markers such as albumin, immunoglobulin G (IgG), and total protein (TP); the lysosomal marker N-acetyl-β-D-glucosaminidase (NAG); the marker of the glomerular tuft angiotensinase A (ATA); the marker of apoptotic processes (sICAM-1); and a cell surface glycoprotein (sE-Selectin) were also measured.

Limited renal function is identified principally by measuring creatinine clearance, diuresis, and serum concentrations of creatinine and urea. These variables, however, indicate renal damage only late in the disease course, at a time when the noxious agent (poisons, hypoxia, microembolism) need no longer be active. So, it is necessary to look for specific variables that reveal a pathologic process earlier than do creatinine and urea.

2. Material and Methods

More than 150 patients were treated in our surgical intensive care unit during a period of 1 year. During their hospital stay, serum and urine samples were drawn and frozen for further analysis. Study parameters were assessed in those patients in whom AKI developed.

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In total, 40 patients from the surgical intensive care unit were examined after approval by the local ethical committee.

An AKI developed in all patients during their course in the ICU. The 5 days that preceded the start of the AKI and the kidney replacement procedure were evaluated. The disorders leading to admission to the ICU were found to be comparable in all patients, as was the course of the intensive medical treatment. The medication and ventilation therapies were also documented, and the Acute Physiology And Chronic Health Evaluation (APACHE) II score were measured.

No patient showed any clinical or laboratory sign of renal functional insufficiency on admission to the intensive care unit. Furthermore, any history of renal damage was excluded by use of contrast media.

Acute kidney injury was defined according to the RIFLE (R= risk, I = injury; F= failure, L= loss of kidney function, and E = end-stage kidney disease) criteria [4]. Serum creatinine values were higher than baseline values, with the increase amounting to more than 0.5 mg/dl per day.

At the start of hemofiltration, a second criterion was fulfilled. Urine excretion during the period before the renal substitution was less than 3ml/kg/hr during a period of 24 hours [5].

The urine samples were obtained from indwelling urinary catheters and then centrifuged for 10 min at 3000 rpm in a Hettich rotixa /KS centrifuge. Depending on the variable being investigated, samples were separated into aliquots and then either frozen at -20°C or stored at 4°C for a maximum of 7 days.

The concentrations of proteins detected in the urine were related to the excreted amounts of creatinine (per g of creatinine) to compare the varying rates of diuresis and to compare with data published by others.

2.1. Routine variables

The urine quantity was measured hourly for all patients and was included in the total urinary balance after 24 hours. Serum concentrations of creatinine were measured with an autoanalyzer (Model 30 R, WAKO Chemicals, Neuss, Germany). Measurement of urea in the serum samples was performed with a kinetic ultraviolet assay. Creatinine clearance was determined by the standard formula: creatinine clearance (ml/min) = (urine creatinine concentration (mg/ml) x urine volume (ml/min))/plasma creatinine concentration (mg/ml). The serum creatinine level at the start of each period was used to determine the creatinine clearance during that period. All creatinine clearances and urine outputs were normalized for a standard body surface area of 1.73 m^2. The quantification of sodium concentrations in urine was carried out with an autoanalyzer. The fractional sodium excretion was calculated as $sodium_{urine/serum}$ / $Creatinine_{urine/serum}$ * 100.

2.2. Proteinuria

Urinary concentrations of α1-MG, β-2-MG, THP, albumin, IgG, and total protein were assessed by immunonephelometry (Behring nephelometer analyzer, Marburg, Germany). The urine was neutralized in order to assess the β-2-MG fraction in the urine, since this protein is stable only in an acid environment. The proteins to be determined form immune complexes with their corresponding antisera. The amount of light scattered by an immune complex from a primary beam of light determines the concentration of the immune complex [7].

2.3. Histuria

3-cresolsulfonephthaleinyl-N-acetyl-ß-D-glucosaminide is hydrolytically cleaved by N-acetyl-ß-D-glucosaminidase (NAG), so that 3-cresolsulfonephthalein is released and then measured photometrically at 580 nm. Addition of sodium carbonate arrests the reaction [8].

A spectrophotometric color test was used for determining urinary ATA. L-α-glutamyl-4-nitroanilide and H_2O are cleaved by angiotensinase A into 4-nitroaniline and glutamic acid and the nitroaniline that arises is measured spectrophotometrically at 405 nm [9].

With this assay, L-alanine-4-nitroanilide is cleaved into l-alanine and 4-nitroaniline by alanine-aminopeptidase-M (AAP). After adjustment of the pH value, measurement is carried out photometrically.

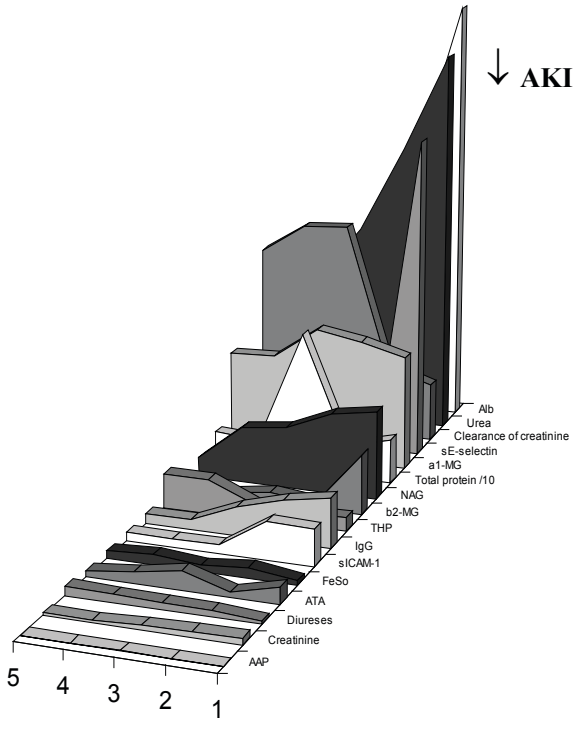
2.4. Adhesion molecules

sICAM-1 and sE-selectin concentrations were measured with an ELISA technique. No standardized reference values exist for urine.

2.5. Statistical Methods

The results were checked for the normality of their distribution and expressed as means ± standard deviation. Further evaluation was carried out by multivariate variance analysis for repeated measurements (MANOVA) and a subsequent Kruskal-Wallis test. Statistical significance was assumed at $p < 0.05$.

Figure 1. Diagram of time flow of all parameters until occurrence of AKI.



3. Results

3.1. Patients, scores and treatment regimes

The hemodynamic variables of MAP and CVP, as well as the APACHE II score, were comparable with the biometric data on the patients' admission to the intensive care unit (Table 1). The pattern of AKI amongst patients and the patients` treatment were also comparable (Table 1).

3.2. Routine variables

Diuresis was 2 days before an AKI evident (Fig. 1 and Table 2). The level of creatinine in serum increased 3 days before an AKI. Five days before the start of an AKI, pathologic levels of urea were found. The creatinine clearance indicated damage only 1 day before the start of an AKI. The FeSo was pathologic 3 days before an AKI was seen.

3.3. Proteinuria

Since α1-MG pathologic levels were observed 5 days before an AKI, they proved to be the earliest detectable pathologic change. β2-MG was found to be pathologic only 1 day before an AKI was seen. Tamm-Horsfall protein fell 3 days before the start of the acute kidney failure. Albumin excretion was pathologically increased 3 days before an AKI was evident. Three days before AKI the elimination of immunoglobulin G as another glomerular protein was increased, and the excretion of total protein was increased. Large fractions of the total protein consist of albumin and immunoglobulin G.

Table 1. Patients' biometric data, hemodynamics, score values, operation and transfusion data.

Number of patients (n)	40
Age (years)	51,2 ± 16,2
Sex (m/f)	11 / 29
Height (cm)	173.7 ± 7.5
Weight (kg)	73.3 ± 13.9
Body surface area (m^2)	1.87 ± 0.20
Days on Intensive Care Unit (median, range)	13 –18 (16)
Days with hemodiafiltration therapy (median, range)	3 –12 (8)
Mortality	33 %
Diagnosis	
Head and brain traumata	8
Thorax traumata	10
Abdominal traumata	8
Extremity traumata	17
APACHE-II-Score	
Upon admission	19
Maximum (day)	25 (7)
Mean arterial pressure upon admission (MAP, mmHg)	68
Central venous pressure upon admission (mmHg)	7
Cause of death	
Circulation arrest	5
Multi organ failure	6
Septic shock	2
Patients` treatment	
Patients with operations (median, range)	14 (0-7)
Patients with blood products (median, range)	15 (3-20)
Patients with antibiotic therapy	40
Patients with aminoglycosides	15

3.4. Histuria

Days before an AKI the excretion of NAG was increased. Also, 4 days before the onset of an AKI, the excretion rates of ATA increased, but 2 days before an AKI, they were no longer increased. The AAP increased only 2 days before an AKI.

3.5. Adhesion molecules

sICAM-1 in the urine showed pathologically increased levels only 2 days before an AKI. Soluble E-selectin in the urine showed a pathologic increase in excretion rate only 1 day before an AKI.

Table 2. Significant chronological courses for the examined parameters.

	Day 5 before AKI	Day 4 before AKI	Day 3 before AKI	Day 2 before AKI	Day 1 before AKI	AKI
Diureses	3.8 ± 1.2	3.4 ± 1.3	3.1 ± 0.6	1.5 ± 1.2 ↓	1.2 ± 1.1 ↓	
Creatinine	1.2 ± 0.4	1.0 ± 0.3	2.3 ± 0.9 ↑	2.5 ± 0.4 ↑	2.6 ± 0.8 ↑	
Urea	54.1 ± 25.3	66.7 ± 25.1 ↑	92.3 ± 43.2 ↑	132.4 ± 40.7 ↑	176.9 ± 46.9 ↑	
Clearance of creatinine	101.3 ± 11.9	96.7 ± 27.7	98.0 ± 18.8	29.8 ± 17.0 ↓	26.4 ± 16.6 ↓	
FeSo	3.4 ± 2.5	4.5 ± 3.1	2.7 ± 2.0 ↓	4.5 ± 2.1	1.9 ± 1.0 ↓	
α1-MG	45.3 ± 5.2 ↑	45.9 ± 7.7 ↑	60.7 ± 11.4 ↑	57.1 ± 4.7 ↑	51.8 ± 5.7 ↑	
β2-MG	2.3 ± 1.5	2.1 ± 1.0	5.0 ± 3.0	2.7 ± 1.8	27.0 ± 9.6 ↑	
THP	15,5 ± 6.5	15.3 ± 8.1	6.8 ± 0.4 ↓	5.9 ± 3.3 ↓	6.1 ± 4.5 ↓	
Alb	19.3 ± 11.8	18.7 ± 8.5	96.5 ± 45.8 ↓	123.9 ± 67.6 ↑	195.8 ± 37.6 ↑	
IgG	4.5 ± 0.2	4.6 ± 0.2	13.2 ± 3.2 ↑	18.6 ± 4.9 ↑	22.3 ± 5.5 ↑	
Total protein	141.4 ± 7.7	128.8 ± 3.4	643.1 ± 123.7 ↑	150.1 ± 9.25	200.8 ± 13.8	
NAG	8.6 ± 0.9	25.5 ± 7.3 ↑	27.7 ± 4.5 ↑	36.6 ± 3.6 ↑	39.7 ± 0.7 *	
ATA	2.7 ± 0.3	4.8 ± 1.3 ↑	8.3 ± 2.0 ↑	2.1 ± 1.8	7.3 ± 1.3 ↑	
AAP	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.01 ± 0.005 ↓	0.04 ± 0.01	
sICAM-1	4.0 ± 0.6	3.7 ±0.6	3.9 ± 0.6	16.8 ± 3.8 ↑	16.2 ± 2.7 ↑	
sE-selectin	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	1.2 ± 0.4	146.4 ± 61.4 ↑	

Significance level: $p < 0.05$ in admission exam ↑: depicts an increase; ↓: depicts a decrease

4. Discussion

We found that the large proportion of deceased patients (13 of 40 patients, 33%) in our study was within the reported range of mortality for patients in the ICU who had undergone surgery [1,2,10]. All patients had an acute kidney injury, some had a sustained loss of renal function, but no patient maintained end-stage kidney disease [5]. The severity of disease was also illustrated by the APACHE II scores (Table 1). This score was developed as a means to evaluate the severity of disease, and in this way it represents a satisfactory parameter for comparing the patients.

4.1. Routine variables

The standard variables for routinely investigating renal function are diuresis and serum concentrations of creatinine and urea. Diuresis decreased 2 days before a manifest kidney failure, and oligo-anuric kidney failure (Table 2) was found [11]. This confirms that the ability of the patients to eliminate fluids during an AKI disappears late so that the hourly quantity of urine is not very suitable for assessing renal function.

S_{crea} increases 3 days before a manifest AKI (Table 2). An increased S_{crea}-value is almost present when renal damage occurs, and an AKI can be excluded with certainty when the S_{crea}-value is normal.

Pathologic levels of creatinine were found much later than pathologic levels of other variables, particularly of tubular renal function. This is almost certainly determined by the so-called creatinine-blind spot; according to current knowledge, a proximal tubular malfunction precedes a glomerular malfunction caused by ischemia-reperfusion renal damage, and creatinine as a marker for the glomerulus cannot represent tubular effects. Also, it is well known that serum urea levels increase only after a clear reduction in glomerular filtration rate occurs. In our study it was not only the change in kidney function, but also the metabolic state and the activation of the renin-angiotensin-aldosterone system that played the key roles in determining the post-aggression phase involving the increased accumulation of urea [12].

The FeSO showed an uneven course. Three days before an AKI a reduction was found that was no longer 2 days before the AKI, but which regained one day before the AKI. This can be explained by the differing levels of sodium elimination caused especially by the rapidly changing water balance and the administration of diuretics, as well as by loop of diuretics.

4.2. Proteinuria and histuria

α1-microglobulin (α1-MG), β2-microglobulin (β2-MG) and Tamm-Horsfall-protein were measured to reveal structural alterations in tubular regions and to serve as specific parameters for tubular function [13,14]. α1-MG is one of the best markers for tubular function. Increasing excretion rates are often seen before reduced levels of serum creatinine and generalized proteinuria are observed.

Table 3. Evaluation of the examined parameters.

Parameter	Indication / assay	Analytical time	Costs	Time of appearance	in routine use	Remark
Diuresis	water balance	short	small	late	yes	also with normal diuresis renal damage is possible, poorly interpretable due to diuretic use
Creatinine in serum	screening	short	small	late	yes	most frequently measured parameter
Urea	screening/protein metabolism	short	small	early	yes	informative value problematic due to many influential factors
Clearance of creatinine	GFR	moderate	small	late	yes	routine or for specific questions
FeSo	sodium-, water balance	moderate	small	average	no	difficult interpretation after diuretic administration
α1-MG	proximal-tubular reabsorption disorder	moderate	high	early	no	measurement of further tubular and glomerular parameters necessary, reasonable addition as routine parameter
β2-MG	proximal-tubular reabsorption disorder	long	high	late	no	spontaneous breakdown of protein
THP	distal-tubular reabsorption disorder	moderate	high	average	no	test kits no longer available on the market
Alb	glomerular integrity	short- moderate	average-high	average	not with surgery patients	semiquantitatively as a screening method, reasonable as an additional glomerular parameter
IgG	glomerular integrity	moderate	high	average	no	most suitable for diagnostics of glomerular damage
Total protein	screening	short	average	late	not with surgery patients	suitable for screening, with normal values there can still be tubular proteinuria, costs can vary according to analytics
NAG	tubular integrity	moderate	average	early	no	reasonable addition to the routine parameters
ATA	glomerular integrity	long	average	early	no	can be used for follow-up of glomerular damage
AAP	tubular integrity	long	average	late	no	circadian rhythm, moderate correlation with other tubular parameters
sICAM 1	apoptosis	moderate	high	late	no	only recently investigated for this problem, no reference values available for renal elimination
sE-Selectin	apoptosis	moderate	high	late	no	only recently investigated for this problem, no reference values available for renal elimination

Pathologic levels of α1-MG (Table 2) were shown 5 days before the onset of the AKI. One day later (4 days before AKI), an increase in NAG-and ATA elimination was shown (Table 2). This was especially striking, since α1-MG and NAG are sensitive variables for tubular integrity. NAG is a specific lysosomal marker and is present in large amounts in renal tubules. Increased excretion rates are seen in patients treated with specific tubolotoxic agents such as aminoglycosides [15].

The activity of angiotensinase A, a glycoprotein found in the glomerular tuft as well as in the microvilli of proximal tubules, was analyzed as a glomerular marker enzyme. The population of remaining glomeruli after injury showed no signs of segmental sclerosis, although one can assume that these glomeruli did undergo hyperperfusion. The compensatory rise in ATA activity within the endothelia and podocytes of the residual glomeruli may have prevented certain metabolic effects [9]. The ATA as a physiologic marker of glomerular integrity is a measure of the occurring damage [16]. These damage do not necessarily need to be functionally effective, and as such, one frequently

sees no changes in the glomerular filtration rate.

One day later (3 days before AKI) other glomerular variables (IgG, Alb) were found to be pathologic, along with THP, as markers for the early distal tubule and total protein values (Table 2).

Albumin, immunoglobulin G (IgG), and TP were recorded as specific markers for glomerular function [17,18]. The maximum IgG elimination occurred at the same time as the tubular damage, whereas the maximum ATA elimination occurred 1 day earlier. This result shows that the increased permeability large molecules such as IgG (molecular weight 150 kDalton) occurs later than the actual damage to the cellular structures (endothelium) [16,19].

Since our sample of patients was composed of polytraumatized patients, the expected acute damage is located at the tubulointerstitial area. The glomerular damage would be expected in thrombotic microangiopathy and cortical necrosis such as sepsis; it was caused in our patients perhaps by ischemia and crush injury of the muscles.

The brush border enzyme alanine-amino-peptidase is localized on the luminal side of the cytoplasmatic membrane of the proximal tubule. Its functions are correlated with amino acid metabolism. Changes in the brush border structure lead to increased rates of excretion [20,21].

Two days before the onset of the AKI the AAP fell. However, this effect was no longer detectable 1 day before AKI, whereas 1 day before AKI the β-2 MG was found to be pathologic. Both variables are unstable molecules in alkaline media and rapidly decay before they are analyzed.

After the tubular damage (α1-MG), another tubular parameter (NAG) and the first glomerular variable (ATA) revealed themselves. Three days before AKI all the important tubular and glomerular variables, including S_{crea}, were at pathologic levels; however, the oligo-anuria began 2 days before the AKI. Although the patients had mainly a circulation-induced renal failure in which both tubular and glomerular damage can occur simultaneously, these results were variable from day to day [14,22].

4.3. Adhesion molecules

ICAM-1, together with sE-selectin, plays a central role in the origin and control of apoptotic processes participating in the development of acute renal failure [23]. In 1997 Gauer et al. were able to verify that ICAM-1 is expressed in the area of the kidneys only if kidney damage occurs [1,24]. Their observations suggest a control function of sICAM-1 for preventing uncontrolled apoptosis and the irreversible destruction that occurs with it [25].

However, serum levels correlated only poorly with the pathologic alterations found in the nephrohistological preparations [26]. An obvious step was therefore to assess the value of measuring sICAM-1 in urine in patients with acute kidney failure. A study by Bechtel et al. in 1994 reported a very strong correlation in this respect [27]. sICAM-1 showed pathologic values only 2 days before the AKI, whereas sE-selectin values were pathologic only 1 day before the AKI (Table 2).

sE-Selectin is expressed transiently as a cell surface glycoprotein on endothelial cells after stimulation by cytokines [28]. Since sE-Selectin in the area of the kidney epithelium is expressed only with renal damage, it is conceivable that an increased sE-Selectin level in urine may act as an early indicator for kidney disease [6].

E-Selectin is also expressed transiently as a cell-surface glycoprotein on endothelial cells after stimulation by cytokines [29]. Since E-selectin is expressed in the area of the kidney epithelium only after damage, it appears conceivable that the increased sE-selectin levels might be an early indicator of renal damage in the urine [28]. Neither of these two adhesion molecules are suitable as early indicators of renal damage, but diagnostic approaches have still been considered, since ICAM-1-deficient mice are protected against post-ischemic renal failure [30].

Our results show that determination of α1-microglobulin and immunoglobulin G in addition to urea in serum can achieve early recognition and sufficiently precise localization of renal damage.

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