



APPLICATION OF SELECTED BIOCHEMICAL PARAMETERS IN PREDICTION OF ACUTE KIDNEY INJURY RISK AT THE EARLY STAGE OF BURN DISEASE



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Abstract:

Introduction and objective

Acute kidney injury (AKI) is a common, severe complication of burn disease, developing in the first days after a massive thermal injury and worsening the prognosis of patients. Early diagnosis of AKI plays a crucial role in improving health of patients and therapeutic results. Detection of AKI based on the standard parameters of renal function is insufficient due to too late changes in their values. The aim of the study is to evaluate the relationship between the selected non-renal biochemical parameters and the risk of AKI in this group of patients.

Material and methods

The prospective study involved a group of 33 adult patients (22 men, 11 women) hospitalized after massive burns. The patients were intensively monitored for the first 7 days after the injury, daily assessing the parameters of renal function. The selected parameters were also measured: platelet count (PLT), sodium (Na), potassium (K), albumin (ALB), aspartate aminotransferase (AST), creatine kinase (CK), arterial blood pH, arterial blood bicarbonate (HCO₃⁻), 24-hour urinary sodium excretion (24hUNa) and fractional excretion of sodium (FENa).

Results

AKI was diagnosed in 15 (45.5%) patients. Statistical differences in the obtained average values of selected parameters between the AKI and non-AKI groups were confirmed. A significant univariate relationship was found between CK, AST and ALB in the blood serum and an increased risk of developing AKI in the following days. However, after adjustment for The Abbreviated Burn Severity Index score, only CK remained significant.

Conclusions

The potential clinical benefit of monitoring AST and ALB in blood serum and especially CK was confirmed. The other routine parameters did not seem to be related to the risk of AKI and require further analysis.

Keywords: burn, rhabdomyolysis, renal failure, acute renal injury, thermal injury.

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Background

Burn disease is a group of organ complications developing in response to massive thermal, chemical or electrical trauma, that damages a large area of the skin and mucous membranes. As a result of the disease development, homeostasis of the organism is deeply disturbed, with particular emphasis on the water-electrolyte and acid-base balance. The degree of damage of individual organs and systems depends directly on the strength of the injury as well as on the area and depth of skin and mucous membrane damage and the involvement of respiratory tract. Thermal trauma covering more than 20-30% of the total body surface area (TBSA) dramatically increases the risk of developing multiorgan damage resulting in the simultaneous dysfunction of various physiological systems called multiple organ dysfunction system (MODS), which may occur at any stage of the course of a massive burn, significantly increasing the risk of death. As a consequence of distant organs damage and impairment of their functions, a number of substances are released into the bloodstream. Their increased concentrations exceed the limits of laboratory norms and can be detected, confirming the diagnosis of the development of a burn disease [1].

Acute kidney injury (AKI) and subsequent acute renal failure (ARF) constitute one of the most serious complications of burn disease, significantly worsening its clinical course. Most authors agree that after a massive burn approximately 1/3 of patients develop AKI. 30% of AKI patients have the biochemical and clinical features of ARF, which require renal replacement therapy (RRT) procedures in 5-10% of patients. The transition of AKI renal complications to ARF and/or RRT significantly increases the risk of death in this group of patients, reaching 50-100% in the RRT group [2].

The etiology of AKI in burn patients is multifactorial and depends on the time elapsed since the thermal injury. Basically, the course of burn disease can be divided into two periods, early and late, extending before and after the seventh day since the burn. The early period is associated with the post-traumatic shock phase, the release of pro-inflammatory cytokines from the cells, and increased protein catabolism. At this time acute, non-inflammatory kidney injury predominates. The late period is characterized by a gradual regeneration of damaged tissues and organs, anergy of the immune system and an increased risk of infectious complications, which at this time are the main cause of AKI [3, 4].

There are not fully sensitive and specific AKI prognostic markers in the course of burn disease so far. Diagnosis based on standard changes in serum creatinine and urea concentration values or fluctuations of the estimated glomerular filtration rate (eGFR) seems to have a number of significant limitations. The time inertia of changes in values may significantly delay the diagnosis time. Changes in parameters can also result from non-renal causes, such as the state of protein hypercatabolism characteristic for the early stage of post-burn shock, affecting the correct interpretation of biochemical results. In addition, there is not uniformly adopted optimal eGFR assessment formula for patients with AKI after massive burns, many different ones are used: Cockcroft-Gault (C-G), Modifica-

tion of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [5]. The measurement of the volume of produced urine is also a subject to the risk of subjective error due to incorrect reading and writing. Especially in patients in a serious clinical condition, who require frequent transport between various elements of the health care system, the analysis of diuresis is often inadequate and insufficient.

According to scientific reports, a change in the values of additional biochemical parameters resulting from damage to other organs in the course of MODS and not directly related to the physiology of the urinary system, may suggest AKI dysfunction in the early stages of its development. These substances can be measured both in blood serum and urine [6].

Undoubtedly, the crucial element in improving the prognosis in this group of patients is the diagnosis of AKI at the earliest stage of development. The implementation of properly targeted therapy can have a beneficial effect in reducing mortality and improving the survival of patients. The aim of the study is to identify selected, routinely measured after burn injury biochemical parameters, which can have a relationship with the occurrence of AKI in the early stages of burn disease.

Material and Methods

The study included patients hospitalized in the Clinical Department of Burns, Plastic and Reconstructive Surgery of a specialized multi-profile hospital. The project and all experimental protocols were approved by the Committee for Bioethics in Medicine at Military Institute of Medicine (resolution number 36/WIM/2015 of 20 May 2015). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects. All adult patients treated for massive thermal burns between March 2017 and May 2019 were pre-qualified for the project.

Criteria for inclusion in the study group were:

- Age over 18 years
- 2nd and 3rd degree burns including at least 30% TBSA or at least 20% TBSA with accompanying respiratory tract burn
- No terminal diseases (e.g. generalized neoplastic process) or severe infectious diseases (e.g. sepsis) at the time of hospitalization
- The time from burn injury to hospitalization of less than 72 hours

Assessment of Clinical Condition

In accordance with the project guidelines, a uniform diagnostic and therapeutic procedure was adopted for each qualified patient. After thermal injury the patient was immediately hospitalized and transferred from the hospital Emergency Department (ED) to the target department. At the time of admission, a detailed interview was collected regarding the circumstances of the thermal injury, the condition of the patient and comorbidities. A thorough physical examination was performed, with particular emphasis on the extent and depth of the burn wounds. Basic vital parameters (including blood

pressure, heart rate, body temperature) were measured. Consciousness was assessed using the normalized Glasgow Coma Scale (GCS). The burn injury status was evaluated with the use of the Abbreviated Burn Severity Index (ABSI). Each patient was treated with a unified fluid resuscitation procedure (Parkland formula) in accordance with the applicable standards. They recommend an administration of 4 ml of Ringer's lactate/kg weight/% burn skin during the first 24 hours – half of this should be given in the first 8 hours and the other half in the subsequent 16 hours after the burn. The correct volume status was strictly maintained by the whole time-period of the observation and monitored using clinic examinations and measurement of life-basic parameters (central venous pressure, hematocrit etc.).

Every day, from admission to the clinic until the seventh day of hospitalization, the basic vital parameters of the patient were intensively monitored, with particular emphasis on the fluid balance and the amount of daily urine collection (DUC). In accordance with the research protocol, selected laboratory parameters in blood serum were determined every day in order to assess the damage to systems essential for maintaining homeostasis and their dysfunctions: platelet count (PLT), serum sodium concentration (Na), serum potassium (K) concentration, serum creatinine concentration (sCr), serum urea concentration (U), serum albumin concentration (ALB), serum aspartate aminotransferase activity (AST), serum creatine kinase activity (CK), arterial blood bicarbonate concentration (HCO_3^-), 24-hour urinary sodium excretion (24hUNa), fractional excretion of sodium (FENa).

They were performed in the certified hospital laboratory. In the case of death of the patient, the exact date and time as well as the suggested cause were recorded.

AKI Diagnostics

The diagnosis of acute kidney injury was made based on the AKIN (Acute Kidney Injury Network) and RIFLE (Risk, Injury, Failure, Loss of function, End-stage kidney disease) classification criteria [5].

It was assumed that it is enough to meet at least one criterion in order to qualify for a specific category. The eGFR value was calculated based on 3 variants: the C-G formula, the abbreviated MDRD formula and the CKD-EPI equation based on the sCr.

sCr and eGFR values at the time of hospitalization were accepted as baseline and the results in the following days were referred to them accordingly. Analysis of the difference between the current day value and the baseline value provided the basis for the diagnosis of the appropriate AKI stage. A uniform assumption was made that meeting at least one criterion confirmed the diagnosis of AKI. Based on the diagnosis of AKI, the entire group of patients was divided into two: AKI and non-AKI group.

The DUC values were analyzed starting from the 1st day of hospitalization. The assessment on admission to the hospital was considered unreliable due to the admission of the patient and the commencement of the DUC measurement at different times of the day. Similarly, the de-

terminations of urinary excretion of selected substances were performed from the first day.

Assessment of AKI Prediction

The relation between the selected biochemical parameters, the score in ABSI scale and the risk of AKI occurrence was analyzed. The values were evaluated in the following days of observation, starting from the moment of admitting the patient to the ED. Then, the relationship between the parameter value and the occurrence of AKI on the next day was compared. The analyses concerned both the non-normative values of the parameter as well as the dynamics of changes in the values within and outside the norms.

Statistical Analysis

All obtained information available in medical records was archived in specially prepared, proprietary spreadsheets in the Windows EXCEL format. The distribution of the obtained values of each biochemical parameter in the studied population of patients was examined in individual days after the injury. Parameter value subject to subsequent analysis is presented as mean with standard deviation (SD) in the case of the distribution of normal-type variables or as median considering the interquartile range (IQR) between quartile 3 and 1 for non-normal distribution type. The analyses of the association of each selected biochemical parameter with the risk of AKI occurrence were conducted uniformly for every selected parameter. On each day of observation (days 0 - 7 of hospitalization), the current, average value of a given parameter in both group of patients was compared using t-Student test or Mann-Whitney test, when appropriate. Additionally, the relationship between the value of a given parameter on a previous day and the risk of AKI was analyzed using the chi2 test and forward logistic regression. The results were presented also in the form of relative risk (RR) value with a 95% confidence interval (CI). The p-value <0.05 was considered statistically significant. Statistical analyses were performed with the use of computer software (IBM SPSS ver. 25).

Results

33 patients were qualified for the project finally, including 11 (33.3%) women and 22 (66.7%) men. The exact characteristics of the study group are presented in table 1.

All 33 patients suffered a severe thermal injury in an outpatient setting. 24 (72.7%) patients were transported directly from the scene of the incident to the ED of the destination hospital, and in the case of 9 (27.3%) patients there was a temporary stay in the ED of regional hospitals. The average time from the moment of injury to hospitalization in the ED of the target hospital was usually approximately 1 hour, with a maximum of 24 hours for one patient. Almost 2/3 of the patients presented severe disturbances of consciousness (< 8 GCS points) or required tracheal intubation and mechanical ventilation. More than 63% of patients presented symptoms of hemodynamic instability and required support of the circulatory system with intravenous infusion of pressor amines.

Table 1. Characteristics of the study group.

Number of patients		n = 33
Age (years), mean (\pm SD)		48.0 (\pm 18.6)
Men, n(%)		22 (66.7%)
BMI (kg/m ²), mean(\pm SD)		25.8 (\pm 5.4)
Percentage of body surface area burned (%), mean(\pm SD)		42.2 (\pm 18.1)
3rd degree burns, n (%)		21 (63.6%)
Respiratory tract burns, n (%)		23 (69.7%)
Time from injury to admission (hours), median (IQR)		1 (1-24)
Admission directly from the scene of the incident, n (%)		24 (72.7%)
Consciousness disturbances (GCS) n (%)	Mild	10 (30.3%)
	Moderate	1 (3.0%)
	Severe or intubation	22 (66.7%)
The administration of pressor amines, n (%)		21 (63.6%)
Hospitalization time (days), median (IQR)		23 (2-95)
AKI (According to the criterion of diuresis), n(%)		15 (45.5%)
Renal replacement therapy, n (%)		5 (15.2%)
Day of hospitalization at death, median (IQR)		16 (2-48)

The severity of burn injury according to ABSI scale was shown in the table 2.

Ultimately, the diagnosis of AKI was based solely on laboratory criteria: a reduction in eGFR values or an increase in sCr concentration. During the first 7 days of hospitalization, the biochemical features of AKI were diagnosed in a total of 15 (45.5%) patients finally qualified for the project. AKI was first observed in 10 (30.3%) patients on the first day of hospitalization, in 4 (12.1%) patients on the second day, and in 1 (3.0%) patient on the fifth day. A total of 5 (15.2%) patients required renal replacement therapy during the observation. The time to start dialysis therapy was the first day in 2 (6.1%) patients, the third day in 1 (3.0%) patient, and the fifth day in 2 (6.1%) patients.

Table 2. ABSI score.

ABSI score	Number of patients	Threats to life	Probability of survival (%)
2-3	4 (12.1%)	Very low	> 99
4-5	11 (33.3%)	Moderate	98
6-7	10 (30.3%)	Moderately severe	80-90
8-9	6 (18.2%)	Seriuos	50-70
10-11	2 (6.1%)	Severe	20-40
12-13	0 (0%)	Maximum	< 10

In the course of 7-day intensive monitoring, death occurred in 3 (9.1%) patients, on the second, fourth and sixth day, respectively. During this time, no patients (0%) were discharged home. During the entire hospital stay, death was recorded in 16 (48.5%) patients, on day 16 (range 2-48) on average. 17 (51.5%) patients were discharged home, the mean duration of hospitalization ended with discharge (convalescence) was 27 (range 10-95) days. Overall, the average length of stay in hospital from the moment of injury to discharge or death of the patient was 24 (range 2-95) days.

Dynamics of selected parameters in the early period after thermal injury

The obtained mean values of daily diuresis and laboratory determinations divided into two groups according to the presence of AKI (AKI and non-AKI) are presented in Fig. 1A-1J.

The mean value of noticed daily diuresis tended to increase during the observation period, with the lowest values of 0.65 (IQR 0.42-1.3) liters initially observed on admission to the hospital. However, in only 25 (75.8%) patients any information on the amount of urine excreted on that day was obtained. In line with the adopted assumptions, the daily diuresis values obtained on admission to the hospital were disregarded as inadequate. On the first day of hospitalization, the mean daily diuresis was 0.94 (IQR 0.46-1.71) liters with a significantly lower amount in the AKI group 0.58 (IQR 0.29-0.98) vs 1.16 (IQR 0.69-2.4) ($p=0.003$). The tendency to stabilize the average amount of urine produced at the level of over 1.5 liters per day was observed for more than 48 hours of observation with a maximum point of 2.02 (IQR 1.39-2.88) liters on day five with the accompanying blurring of differences between the groups, 1.93 (IQR 1.14-2.65) vs 2.04 (IQR 1.57-3.07) ($p = 0.330$) respectively.

Unfortunately, during the study the problems with adequate measurement of diuresis volume were observed. Due to technical problems with verifying the accuracy and uniformity of diuresis measurement in the first days of hospitalization, this component of AKI diagnosis was excluded from the analyses.

The greatest intensity of disturbances in the values of the analyzed biochemical parameters was observed in the first 2-3 days after the thermal injury, as in the case of AKI biochemical parameters. This concerned both the enzymatic activity in the blood serum, elements of blood

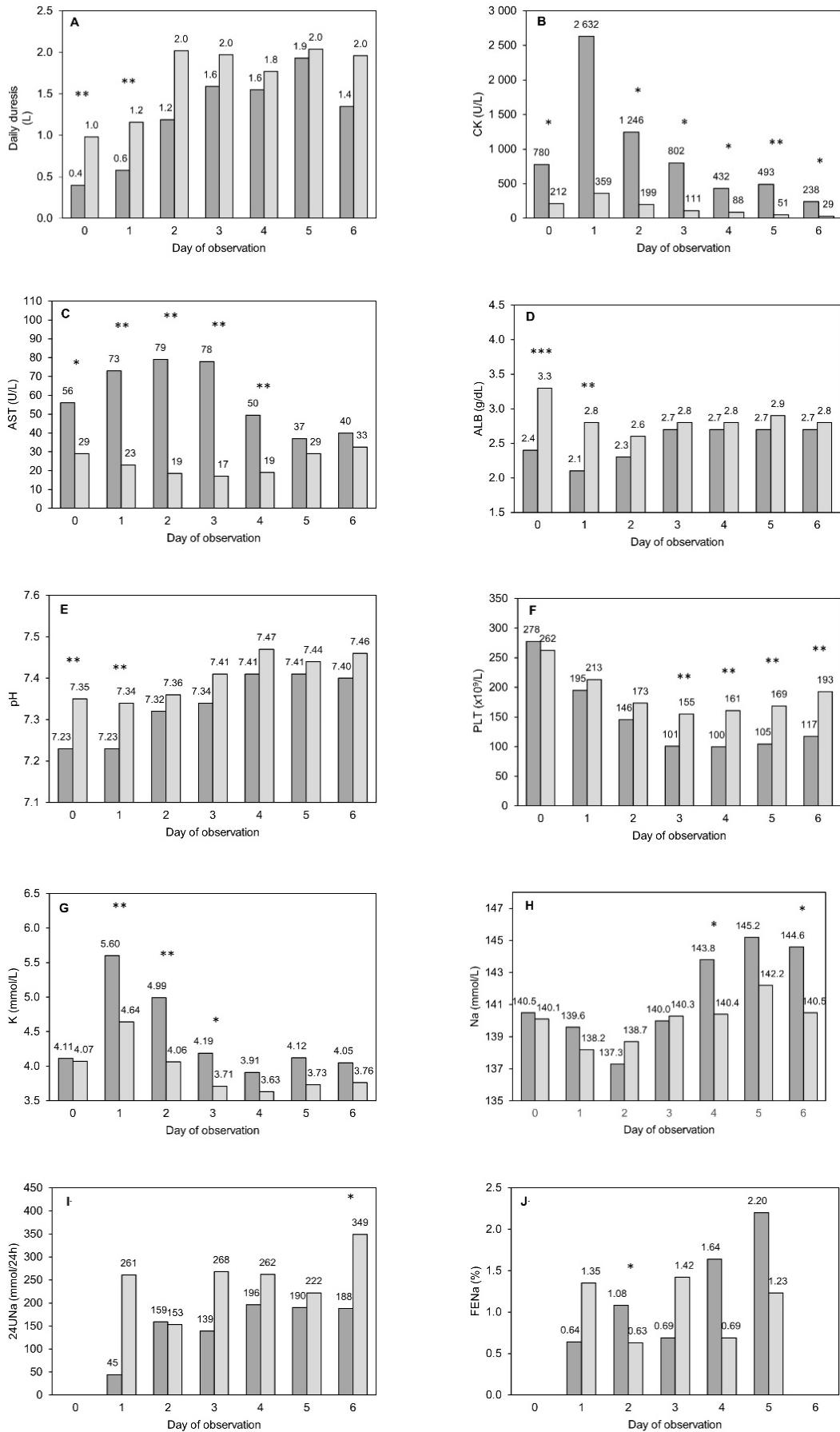


Figure 1. Candidate prognostic parameters in patients with AKI and without AKI in the first 7 days after burn injury. AKI group – dark grey, non-AKI group – light grey. Daily diuresis, CK, AST, 24hUNa, FENa. – medians; ALB, pH, PLT, K, Na – means. *** p < 0.001, ** p < 0.01, * p < 0.05.

count, plasma proteins and the concentrations of other bioactive substances.

Serum enzymatic activity (CK, AST) was highest in the first 3 days after injury. The mean CK values recorded the peak of activity and variability of results during the second day, amounting to an average of 772.0 (IQR 212.5-4952.0) U/L in the whole group with a subsequent gradual reduction to 50.0 (IQR 24.8-245) U/L on the seventh day. During the entire observation period, the values changed simultaneously in both groups, but in the AKI group they reached significantly higher maximum values of 2632 (IQR 389-5661) U/L vs 358 (IQR 170.5-3459.5) U/L in the non-AKI group ($p < 0, 05$).

Fluctuations in AST activity for the whole group were two-phase: the first peak was recorded in the first two days of hospitalization – 38.0 (IQR 23.0-58.0) U/L and 30.0 (IQR 21.0-73.5) U/L, respectively, with a subsequent decrease to 24.0 (IQR 16.3-82.0) U/L and the re-escalation of the value to 39.0 (IQR 23.0-60.0) U/L on the sixth day. The analyses of the curves in groups divided for the occurrence of AKI revealed a significantly different dynamics of changes in the compared groups during the first 4 days. In the AKI group, the values initially showed a tendency to increase with a maximum point of 79 (IQR 28-185) U/L on the second day and a subsequent decrease in the following days. In the non-AKI group, the AST values gradually decreased from the moment of the injury, reaching the value of 17 (IQR 14-28.5) U/L on the third day, significantly differing from the values measured in the AKI group ($p < 0.001$). Differences in both groups were blurred in the following days, getting closer to each other at the end of the observation period, with 48 (IQR 19-79) U/L in the AKI group vs 30 (IQR 27-45) U/L in the non-AKI group ($p = 0.421$).

ALB concentrations in the whole group showed a tendency to decrease on the second day to a minimum of 2.4 (± 0.7) g/dL with a subsequent increase and stabilization from the fifth day at an average level of 2.8 (± 0.4) g/dL. In both groups, the course of changes in the values was parallel, but in the AKI group, the hypoalbuminemia developed earlier, already on the first day and the disturbances were deeper, respectively 2.1 (± 0.5) g/dL vs 2.8 (± 0.7) g/dL ($p=0.005$). In the final phase of observation, the values found in both groups were similar, respectively 2.7 (± 0.5) g/dL vs 2.9 (± 0.5) g/dL ($p = 0.326$).

The tendency to metabolic acidosis continued during the first 24 hours of the observation with the lowest pH values at 7.28 (± 0.1). At the same time, disturbances in blood gas tests were clearly more marked in the AKI group compared to the non-AKI group: 7.23 (± 0.08) vs 7.34 (± 0.05) ($p=0.001$). In the course of further observation, the pH values tended to increase, normalize and stabilize the pH at an average level of 7.42 (± 0.09) with the simultaneous blurring of differences between the groups, respectively 7.41 (± 0.1) vs 7.46 (± 0.04) ($p=0.102$) on the sixth day.

The mean PLT value during hospitalization gradually decreased, reaching the minimum point of 130.5 (± 51.2) $\times 10^9/L$ on the third day, simultaneously narrowing the spread of results. In the following days, a tendency for the value to increase again and normalize at the average va-

lue of 178.6 (± 91.7) $\times 10^9/L$ with increasing scattering of results was observed. Thrombocytopenia was more pronounced in the AKI group, respectively 100.5 (± 51.6) $\times 10^9/L$ vs. 155.1 (± 36.4) $\times 10^9/L$ ($p = 0.002$).

The tendency to electrolyte imbalance was found mainly in the initial period of observation. The mean value of potassium tended to increase on the first and second day to 5.08 (± 1.0) mmol/L and 4.48 (± 0.89) mmol/L respectively, with the subsequent normalization of the value at an average level of approximately 4.0 mmol/L in the following days, with this feature being more pronounced in the AKI group compared to the non-AKI group, 4.99 (± 0.88) mmol/L vs 4.06 (± 0.65) mmol/L, respectively ($p = 0.001$).

The average values of Na were within the limits of laboratory norms. The sodium balance curve showed a slight reduction in value and an increase in the scattering of the results to 138.8 (± 5.4) mmol/L and 138.0 (± 4.5) mmol/L on the second and third day, respectively. In both groups, the graphs of the curves were arranged in parallel, the average values obtained usually showed no significant differences ($p > 0.05$). On the other hand, the average values of 24hUNa gradually increased during the observation, with the threshold value exceeded on the third day, reaching the maximum point of 280.5 (IQR 182.5-392.0) mmol/24 h on the sixth day. The sodium excretion values were higher in the non-AKI group, but the threshold statistical significance was achieved only on the sixth day of observation with 349 (IQR 215.3-444.3) mmol/24 h vs 188 (136.3-320.6) mmol/24 h in the AKI group ($p = 0.035$).

The values of FENa AKI in the whole group remained below 1% from day 1 to day 3 and slightly above 1% on day 4 and 5 of hospitalization, not reaching the 2% threshold characteristic for nephrogenic etiology of sodium excretion imbalance. No significant differences between the groups were also observed, except for day 2, in which a significant dominance of the FENa value in the AKI group 1.08 (IQR 0.71-2.54)% vs 0.63 (0.12-0.88)% ($p=0.011$) was found. In the AKI group on day 5, the mean value of FENa was 2.2%, but this result cannot be considered representative ($p = 1.0$).

The association between selected biochemical parameters and the risk of AKI in the early stage of burn disease development

The results of statistical analyses of AKI predictors are presented collectively in table 3.

The following predictors of AKI determined in the blood serum before its occurrence were identified as statistically significant: high activity of creatine kinase (CK) and aspartate aminotransferase (AST) as well as low concentration of albumin (ALB).

Three - and more than three times the upper limit of the normal CK activity, was related to almost two- and threefold increase in the risk of developing AKI on the next day, respectively (ptrend = 0.047; RR = 1.6 and 2.86). The increase in AST activity was associated with a nearly three-fold increase in the risk of AKI (ptrend = 0.034;

Table 3. Selected biochemical parameters and the risk of developing AKI on the next day.

Parameter	AKI		p-value*	RR (95% CI)	
	Yes % (n)	No % (n)			
CK	Normal	25.0% (1)	75.0% (3)	0.047	Ref.
	2 times the upper limit of normal	14.3% (1)	85.7% (6)		0.57 (0.05-6.86)
	3 times the upper limit of normal	40.0% (2)	60.0% (3)		1.60 (0.21-11.92)
	>3 times the upper limit of normal	71.4% (5)	28.6% (2)		2.86 (0.49-16.62)
AST	Normal	28.6% (4)	71.4% (10)	0.034	Ref.
	2 times the upper limit of normal	40.0% (4)	60.0% (6)		1.40 (0.46-4.31)
	> 2 times the upper limit of normal	77.8% (7)	22.2% (2)		2.72 (1.11-6.69)
ALB	≥ 3.9g/Dl	0.0% (0)	100.0% (1)	0.012	Ref.
	3.5-3.9g/Dl	0.0% (0)	100.0% (4)		0.40 (0.01-14.07)
	2.5-3.5g/Dl	38.5% (5)	61.5% (8)		1.57 (0.13-18.90)
	<2.5g/Dl	66.7% (10)	33.3% (5)		2.63 (0.23-29.71)
Metabolic acidosis	No	22.2% (2)	77.8% (7)	0,090 3,0 (0.85-10,63)	Ref.
	Yes	66.7% (12)	33.3% (6)		
PLT	≥150x10 ⁹ /L	44.8% (13)	55.2% (16)	1.000	Ref.
	<150x10 ⁹ /L	50.0% (2)	50.0% (2)		1.12 (0.39-3.22)
Na	<135 mmol/L	33.3% (1)	66.7% (2)	0.692	0.75 (0.14-3.92)
	135-145 mmol/L	44.4% (12)	55.6% (15)		Ref.
	>145 mmol/L	66.7% (2)	33.3% (1)		1.50 (0.61-3.71)
K	<5 mmol/L	48.0% (12)	52.0% (13)	0.699	Ref.
	≥ 5 mmol/L	37.5% (3)	62.5% (5)		0.78 (0.29-2.09)

*) *chi2* test for trend.

RR = 2.72). Hypoalbuminemia in the range between 2.5 and 3.5 g/dL increased the risk of AKI almost twice (RR = 1.57), and in the range below 2.5 g/dL it almost tripled (RR = 2.72) (ptrend = 0.012).

Parameters increasing the risk of AKI occurrence, but not reaching the statistical significance criterion, are: decreased PLT values below 150 000 /mL in blood count (RR = 1.12; p = 1.0), metabolic acidosis with pH below 7.35 (RR = 3.0; p = 0.09), increase in K concentration above 5 mmol/L (RR = 0.78; p = 0.699), increase in Na concentration above 145 mmol/L (RR = 1.5; ptrend = 0.692).

In a forward logistic regression analysis, when the values of CK, AST or ALB separately were adjusted for ABSI score, only CK was not excluded from the model and remained statistically significant. In case of AST or ALB these parameters were excluded from the model.

The parameters of the sodium excretion (24hUNa, FENa) required evaluation in a 24-hour urine collection. The first meaningful results obtained, which, according to the assumptions of the project, were to be treated as baseline, were obtained only on the first or second day of hospitalization (Fig.1I-J) in which some patients already presented the laboratory features of AKI. Therefore, further analysis of sodium excretion parameters in terms

of the potential impact on the risk of AKI development was abandoned.

Discussion

The current criteria for the diagnosis of AKI after massive thermal injuries do not differ from those used routinely in other clinical conditions and are based on the observation of hourly and daily diuresis and changes in classic parameters of renal function, i.e. an increase in serum creatinine concentration or a reduction in the value of eGFR. World reports suggest that this leads to a too late diagnosis, already at the stage of developed ARF.

Identification of measurable, non-renal biochemical parameters that precede the appearance of classic AKI markers may positively affect the course of this serious complication of burn disease in the initial stages of its development. The parameters presented above are biochemical substances that can be routinely marked in the blood and urine of each patient after a thermal injury.

The aim of the presented prospective research project involving 33 severely burned patients was an attempt to identify statistically significant parameters predicting the increasing risk of AKI occurrence in the early period (≤ 7 days) after a thermal injury. Initially a number of biochemical parameters were tested, and after in-depth

mathematical analyses, the ones directly related to the occurrence of AKI were selected.

Increase in creatine kinase and rhabdomyolysis

Creatine kinase (CK), also called phosphocreatine kinase, catalyzes the translocation reaction of phosphate groups to regenerate ATP in order to mobilize energy sources in tissues with high energy needs, such as striated muscle. Increased CK activity in the blood serum occurs in the case of massive disintegration of skeletal muscle cells, especially as a result of extensive crush injuries. One of the most serious complications of rhabdomyolysis is acute kidney injury. Acute lysis of myocytes accompanied by high CK concentration may cause AKI mainly by the mechanism of excessive accumulation of glomerular-filtered myoglobin. Impaired renal function occurs because of blockage of the renal tubules, secondary to protein precipitation, intratubular inflammation, contraction of renal vessels and direct destruction of tubular cells by locally released oxygen free radicals. Apart from myoglobinuria, renal dysfunction results from the usually accompanying low blood pressure leading to ischemia of the renal parenchyma, and the crystallization of uric acid molecules in the tubular lumen, accompanying myoglobin complexes [7].

Thermal injury causes an increase in CK activity as a result of the disintegration of muscle tissue under the influence of thermal energy and mechanical damage to myocytes in the crushing mechanism. The mechanism of damage to kidney function is similar to that of other causes of rhabdomyolysis [8]. The incidence of this complication is estimated at approximately 1% in the population of patients with severely burned TBSA above 25%. Rhabdomyolysis increases the risk of AKI occurrence by 70-75% and death by approximately 50%, and the risk of AKI increases with increasing CK activity [9, 10]. During the implementation of the project, it was found that CK activity is highest during the first 72 hours after the thermal injury. This was especially observed in the AKI group, where the values were significantly higher compared to the non-AKI group almost throughout the observation period, until the seventh day after the injury. Exceeding the upper limit of normal for CK by more than 3 times also significantly increases the risk of AKI by 3 times. Moreover, this effect remained independent on ABSI score after adjustment in forward logistic regression. This is consistent with the conclusions contained in the above-cited works. The close association between the increase in CK activity and the risk of developing AKI confirms the clinical usefulness of CK determination in this group of patients. This should be a base to postulate routine, early and intensive measurement of CK activity during the first hours after thermal injury. Tendency to abnormal CK results should induce intensive and strict control of renal function, even in case of the normal results of standard parameters.

Elevated aminotransferase level

Aspartate aminotransferase (AST) is an enzyme from the group of transaminases involved in the metabolism of amino acids that catalyze the transamination of α -amino groups from α -amino acids to α -keto acids, thus allowing the synthesis of amino acids from carboxylic ketoacids

and the removal of excess nitrogen from the body. Increased concentrations of serum transaminases are most frequently observed in the course of liver diseases and in rare cases of damage to the heart muscle, kidneys, striated muscles, as well as during intense physical exercise and hemolysis. They indicate damage to the cytoplasm and mitochondria of cells [11].

Acute liver failure (ALF) with elevated AST level is a rare but serious complication of massive thermal trauma causing liver dysfunction, impaired synthesis of plasma proteins, including albumin, and disorders of the blood coagulation cascade [12]. The development of ALF is caused by a "cytokine storm" in the form of a series of inflammatory mediators released in response to a thermal stimulus [13]. At the cellular level, it is the result of damage to the structure and function of the endoplasmic reticulum and mitochondrion inside hepatocytes, causing dysfunction of their functions [14]. The etiology of AKI in the course of ALF is complex, and the main causes are renal tubular hypoperfusion due to rapid vasodilation of the celiac visceral bed (similar to hepatorenal syndrome), increased rhabdomyolysis, vascular endothelial dysfunction and septic complications [15].

The dynamics of changes in AST activity was significantly different in both studied groups. AST activity in the AKI group tended to double: for the first time right after the thermal injury and again after 5-7 days. The observed early aminotransferase elevated level is consistent with the previous reports confirming the occurrence of significant liver damage in the first several hours after the burn. Liver enzyme hyperactivation is most likely due to rapid hepatocyte necroptosis caused by massive infiltration of immunocompetent cells secreting several pro-inflammatory cytokines, such as IL-6, IL-1 β and TNF. Further escalation of the inflammatory process and generalization of the cytokine release syndrome beyond the hepatic area can lead to the subsequent sudden development of MODS, including AKI [16].

It was shown that an increase in activity of liver enzymes in the serum can be significantly associated with an increased risk of developing AKI. However, after adjustment for ABSI score, AST was excluded from the logistic regression model. The thing worth to mention is, that the non-AKI group tended to maintain the average AST values within the laboratory norms at the time of observation, and even to reduce during the first 4 days, in contrast to the AKI group. This tendency can suggest a close association between the activity of liver enzymes and the scale of damage to the renal parenchyma, and the usefulness of intensive monitoring the dynamics of their value changes, especially in the early post-trauma period, which is indicative of the risk of AKI. However, the negative result in logistic regression can indicate, that this parameter can be less important than previously described CK activity. The association between the liver enzymes and renal function can be indirect and can require further, advanced studies.

Hypoalbuminemia

Pathological reduction in serum protein concentration, including albumin, may be due to two main causes: im-

paired synthesis or increased loss. The process of synthesizing plasma proteins takes place in the liver. Severe and chronic dysfunction of this organ may cause hypoproteinemia, and its severity is usually correlated with the degree of damage to this organ. Loss of proteins can take place through many metabolic pathways: with urine - as a component of the nephrotic syndrome, with feces - through the damaged wall of the gastrointestinal tract, and with serous fluid and lymph through damaged layers of the skin. In the course of burn disease, the latter element has a major influence, and the degree of deviation in protein resources is closely correlated with the extent and severity of burn wounds. Hypoproteinemia, and in particular hypoalbuminemia, is associated with the risk of developing AKI, which was observed, *inter alia*, in patients after surgical procedures complicated with a significant loss of plasma proteins. The cause of this phenomenon is not entirely clear, but attention is drawn to the role of impaired renal flow, the effect on the disturbance of the structure and function of the renal proximal tubules, modification of binding of endogenous toxins by plasma proteins, escalation of oxidative stress and interaction via the lysophosphatidic acid pathway [17].

In severely burned patients, a relationship between low serum albumin and an increased risk of AKI has been suggested. In the case of burns covering more than 20% of TBSA, there is a massive loss of extracellular fluid containing a significant amount of proteins, leading to destabilization of intravascular oncotic pressure, development of hemodynamic disturbances and the phase of hypovolemic shock. Extensive thermal trauma induces an immediate, intense, generalized inflammatory response increasing the permeability of vessels, especially capillaries, to albumin and larger proteins. In addition, hypoproteinemia impairs the healing process of traumatic wounds, prolonging the time of damage to the skin layers, increasing the risk of hypovolemia and septic complications [18].

Observations during the implementation of the research project confirmed the earlier findings of other authors. During the first 3 days of hospitalization in the entire study group, the tendency to reduce ALB was clearly visible, more intense and earlier in the AKI group. Hypoalbuminemia in the first days after the injury is an expression of the disproportion between the amount of their loss through damaged skin layers and the impaired synthesis in the multi-organ failure syndrome as well as insufficient supplementation of external proteins. Normalization of ALB values observed at an approximately similar level in both study groups only above the fifth day should be treated as an expression of too late or too economical compensation of already existing protein deficiencies in the previous days.

The analyses showed a significant relationship between hypoalbuminemia and the risk of AKI in the first days of hospitalization. However, after adjustment for ABSI score, ALB was excluded from the logistic regression model. It confirms that ALB, similar to AST, can play rather minor role in early AKI diagnostic. Both parameters are dependent on liver function. As was previously mentioned, the association between liver and renal dysfunctions can be not obvious and needs more studies.

This indicates the importance of strictly maintaining the correct level of protein metabolism parameters as important components of the therapeutic process of thermal injuries, already at an early stage of the disease development. Prophylactic and adequate supplementation of colloid solutions, which is an integral part of the fluid resuscitation system immediately after a thermal injury, may also significantly reduce the AKI/ARF percentage and improve patient survival. Consideration of implementing prophylactic protein supplementation should take place at the earliest stage of the disease development, without waiting for a decrease of their values in laboratory tests. Additionally, intensive, daily monitoring of the protein concentration in the blood serum would allow for a precise assessment of the adequate demand for their preparations in the following days.

Metabolic acidosis

Metabolic acidosis is a disorder of the acid-base balance characterized by an excessive accumulation of acidic substances (H^+ ions) in the blood serum or a deficiency of alkaline substances (HCO_3^- bicarbonate anions). The diagnosis is based on the analysis of the arterial blood gas test showing a simultaneous decrease in the pH value with the accompanying low concentration of HCO_3^- ions. Acute systemic acidosis is a common complication in patients after massive burns, especially in a severe clinical condition, contributing to the deterioration of the clinical course [19]. The main causes are acute renal failure with impaired excretion of non-volatile acids, as well as hypovolemic and septic shock. A particular, non-renal, cause of acidosis is intoxication with substances released from specialized antibacterial dressings, widely used in severely burned patients, containing silver preparations as well as propylene and ethylene glycol. The risk of developing acidosis for this reason is proportional to the area of damaged skin layers, the depth of the injury and the length of the period of applying toxic compounds, thus it usually develops only in the distant day of hospitalization [20, 21].

In patients qualified for the project, the occurrence of metabolic acidosis was observed already during the first day after thermal injury, much more pronounced in the AKI group. Although all patients were treated with extensive dressings containing potentially nephrotoxic substances, the early incidence of acid-base disturbances contradicts this etiology. Therefore, developing AKI may be considered a cause of acidosis. The project showed a relationship between the decrease in serum pH and the occurrence of AKI, but without reaching the adopted threshold of statistical significance, which concerned both the same and the next day. In addition, it should be emphasized that the cases of acidosis of purely metabolic etiology were analyzed. Blood gas disturbances of other etiology, such as pulmonary pathologies, were not analyzed. The above observations can lead to the conclusion that although the occurrence of systemic acidosis is a consequence of AKI, its laboratory parameters may change earlier than the classical markers of renal function. Changes in pH occur at a very early stage in the development of burn disease, which additionally increases the potential predictive value of intensive determination of blood gas parameters in this group of patients. Unfortunately, there is currently

no available literature that extensively describes the occurrence of this disorder.

Thrombocytopenia

Platelets are formed from the progenitor cells of the megakaryocytic system located within the bone marrow. Circulating in the blood, they play several important roles in maintaining proper homeostasis of the body. They are cells of the immune response, participate in the initiation of the inflammatory process and the formation of the hemostatic plug. The survival time of platelets in peripheral blood ranges from 7 to 14 days, and their number is the resultant between bone marrow synthesis and loss through bleeding or autoimmune degradation [22].

Hemostatic disorders, resulting from fluctuations in serum PLT concentration, often occur in the course of burn disease, especially in the early stages of its development. Their intensification usually correlates with the severity of the injury and suggests the possibility of organ complications during the clinical course. As a result of extensive thermal trauma, there is often mechanical and thermal damage to the surrounding tissues, disruption of the continuity of the walls in large vascular trunks and massive bleeding from damaged vessels with the loss of a significant part of circulating blood, leading to the rapid development of post-hemorrhagic shock. Additionally, because of the implementation of anti-shock treatment based on the principle of fluid resuscitation and the transfusion of large amounts of crystalloids, generalized hemodilution and a decrease in the PLT value occur. Burn shock already at an early stage leads to the development of an acute, generalized inflammatory response with the activation of a number of immunocompetent cells. Numerous pro-inflammatory and pro-aggregating cytokines, such as: platelet-activating factor (PAF) P, prostaglandin G₂ (PGG₂) and H₂ (PGH₂) and thromboxane A₂ (TXA₂) are released. The effect of their action is a rapid increase in the prothrombotic state with increased adhesion and aggregation of PLT, disseminated intravascular coagulation (DIC) and the formation of numerous blood cell conglomerates. The immobilization of a significant portion of the platelets in the aggregation plugs results in a decrease in the number of free circulating platelets. A rapid decrease in the value of PLT causes a reflex stimulation of their synthesis in the bone marrow. However, in the case of massive burns and the advanced stage of burn disease accompanied by MODS, the level of platelet loss often exceeds the compensatory capacity, reducing the total number of PLT. The intensity of thrombocytopenia corresponds to the existing organ disorders and may be an indicator of the severity of the disease, as well as a poor prognostic factor for the survival of patients [23].

During the implementation of the project, the tendency for a significant decrease in the average value of PLT, most marked during the third day of hospitalization, was confirmed, which is consistent with the observations of other authors. The study by Shou B. et al. also showed a tendency to develop thrombocytopenia in the first days after a thermal injury, additionally emphasizing its negative impact on the survival of patients. Thrombocy-

topenia, as an indicator of an increased process of inflammatory response and intravascular coagulation, may also be a very early marker of the risk of septic shock, which usually develops fully only in the second or third week after thermal trauma. In this work, immediate administration of anti-infective treatment in all burn patients with thrombocytopenia was postulated [24].

During the implementation of the project, a trend for the occurrence of significantly deeper thrombocytopenia in the AKI group was observed, which is consistent with the conclusions of the study by Chen et al. [25]. An association between low PLT values and the risk of AKI was found both on the day of the test and on the following days of observation, but without reaching statistical significance. The most likely explanation for this relationship is the presentation of thrombocytopenia as one of the early elements of the developing MODS. Thus, thrombocytopenia should be regarded as a direct predictor of ARF development and as one of the components of the multi-organ failure syndrome.

Hyperkalemia

Elevated potassium concentration in the blood serum may result from excessive supplementation of this ion, its release from disintegrated cells or dysfunction of its excretion through the kidneys. It is a relatively common symptom accompanying acute renal disorders, and its underlying cause is a dysfunction of ion transmission at the level of the renal tubules. Elevated values of potassium concentration, especially above 6.5 mmol/L, pose a significant threat to the life of patients as they increase the risk of ventricular arrhythmia.

Massive burn may contribute to the occurrence of hyperkalemia in the course of metabolic acidosis, hemolysis and erythrocyte breakdown, rhabdomyolysis and the development of acute kidney injury [26]. Which of the above-mentioned metabolic pathways is most marked depends on the type and strength of thermal injury, complications and the choice of treatment. A relatively high risk of hyperkalemia in this group of patients exists in the case of the coexistence of the crush syndrome with the destruction of numerous organs, tissues and cell disintegration, rhabdomyolysis with damage to a significant mass of striated muscles, and the development of ARF. Importantly, hyperkalemia in the course of burn disease may result from AKI and is one of its early symptoms.

In the course of the project, it was shown that hyperkalemia occurs early in the development of burn disease, non-normative values were observed already in the first 48 hours after the injury with a clear tendency to higher values in the AKI group. It was found that hyperkalemia may precede the occurrence of standard laboratory symptoms of AKI and correlate with an increased AKI risk in the following days. Taking into account the potential diversity of the etiology of the increased potassium concentration in the blood serum, it should be emphasized that monitoring of potassium can be a beneficial element in the early diagnosis of AKI development in this group of patients, but after excluding non-renal causes.

Sodium disturbances

Sodium disturbances are common in patients in a serious clinical condition usually as a consequence of the underlying disease development or an iatrogenic error in the composition of administered fluids and medications. Abnormal blood sodium levels are associated with increased mortality in this group of patients. Patients after massive burns often develop disturbances in blood sodium concentration. Hypernatremia is more common (in approximately 10% of patients) than hyponatremia (in approximately 7% of patients) [27]. The main cause of hypernatremia is profound hypovolemia, resulting from rapid fluid loss through damaged skin layers or insufficient control of the negative fluid balance [28]. Hypernatremia in this group of patients is associated with prolonged hospitalization, worse prognosis and increased mortality [29].

The causes of hyponatremia are usually: excessive intake of electrolyte-free fluids, the development of ARF with damage to renal tubules and salt loss syndrome, or hormonal disorders [30].

During the observation, the average Na values remained within the accepted laboratory norms, both in the profile of the entire study group and in the AKI and non-AKI groups. It was most likely related to the adoption and strict implementation of a uniform procedure for the management of a severely burned patient, based on the principles of dynamic, high-volume fluid resuscitation, significantly minimizing the risk of dehydration and electrolyte imbalance. However, from the fourth day of observation a slight tendency to increase the average sodium values, especially in the AKI group, was observed. This is consistent with the information contained in the above-cited study by Lam et al., in which the mean time of occurrence was estimated at approximately 8.3 (\pm 4.3) days, and the lack of exceeding the laboratory norms was perhaps due to the limitation of the observation time to 7 days.

During analyses, a correlation between the non-normative increase in sodium and the risk of AKI was found, but without obtaining the threshold of statistical significance.

Hypernatremia physiologically causes a reflex increase in the excretion of sodium ions in the urine in order to get rid of their excess and regulate electrolyte disorders. In addition, increased values of sodium excretion may indicate damage to sodium ions reabsorption in renal tubules as part of renal interstitial dysfunction. The above findings were not confirmed during the observation. It is true that after the third day of hospitalization a tendency for an extra-normative increase in the average 24-hour urinary sodium (24hUNa) excretion is observed, but it applies only to patients from the non-AKI group and the results mostly do not meet the statistical significance criterion. On the other hand, values of fractional sodium excretion (FENa) above 2%, which could potentially indicate an intrarenal etiology of disorders, were found in the AKI group, but also without statistical significance. Additionally, due to incomplete data, reliable analyses of sodium excretion disorders as the predictors of AKI proved to be impossible to perform.

In conclusion, despite the insignificant association between hypernatremia and the risk of AKI development, the obtained results of sodium metabolism elements do not clearly indicate their potential use in the early diagnosis of AKI in patients after burns.

Limitations

The main limitation of the project was the relatively small size of the study group. The main reasons for disqualifying patients were too low percentage of damage to layers, too long time from injury to hospitalization, changing the place of hospitalization during the project, and a limited number of stations for intensive burn treatment.

In some patients, especially in the first hours after the injury, technical problems with the adequate measurement of daily urine output occurred, which prevented a reliable assessment of daily diuresis and the analysis of biochemical parameters in the excreted urine.

The significant clinic problem was to keep the correct euvolemic status during fluid resuscitation. To minimize the risk of water-balance disorders we use the same fluid protocol according to Parkland's formula for each patient and the treatment was carried out by the same medical team in one burn department. The current volemic status was strictly monitored and corrected during all time of observation.

Conclusions

AKI is a common, serious complication after massive thermal injuries. Intensive monitoring of renal function parameters as well as a detailed and systematic analysis of the dynamics of their value changes can improve the diagnosis of AKI in this group of patients.

Selected biochemical parameters, such as increased CK and AST values and decreased serum ALB concentration can be considered early markers of increased risk of AKI development. The increased CK activity, especially in the rhabdomyolysis range, seems to be the most important parameter and can play the crucial role in the early AKI diagnosis. It seems important to add routine, daily determinations of the above-mentioned parameters to the current treatment regimens immediately after thermal injuries in order to early diagnose AKI, implement adequate therapy and reduce the percentage of ARF and RRT significantly worsening the prognosis of patients.

Other investigated parameters, such as metabolic acidosis, thrombocytopenia and hyperkalemia, can have a potential diagnostic benefit, but require further in-depth analyses involving larger groups of patients.

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