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# Fund “Nauka” Project № 18004 Resume – Competition-Based Session 2018:

“Pharmacokinetic and pharmacodynamic evaluation of septic patients. Personalization of antimicrobial dosing regimens. Introduction of new inflammatory markers in clinical practice – NGAL and Procalcitonin as diagnostic and prognostic tools, determining the therapeutic approach for sepsis”

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Sepsis is a global health problem characterized by a systemic inflammatory process in response to microbial infection. It is a frequent complication in hospitalized patients. A worldwide problem, mortality rates of 30% in patients with sepsis, 50% in severe sepsis and 80% in patients with septic shock have been reported. The incidence is from 0,2 to 3/1000 patients affected annually. In case of sepsis, the most funds spent for a given medical condition are reported – 23,6 billion dollars in the US in 2017. Early diagnosis, correct treatment and optimal antibiotic exposure in these patients are of utmost importance to improve mortality and morbidity (disability of patients), the expected economic advantages – reduced hospital stay, shorter period of antibiotic treatment, prevention of antibiotic resistance and selection of multiresistant nosocomial strains. The pharmacokinetic and pharmacodynamic profile of drugs in critically ill patients is seriously altered. Serious deviations in the plasma levels of the antibiotic with a standard dose regimen is often observed. In these patients, extracellular fluids and tissue edema that impair antibiotic penetration are increased. The septic patient is characterized by the hyperdynamic type of circulation (↑CO, ↓SVR), which can increase the renal clearance of hydrophilic antibiotics up to three times above the usual and an unsatisfactory clinical response can be observed in a patient with an infection sensitive to the applied antibiotic. There is also an increased clearance in case of hypoalbuminemia and administration of medicinal products, which bind to plasma proteins in a large percentage. The volume of distribution is also unstable in septic patients and depends on their adequate fluid replacement. In contrast to hydrophilic, lipophilic antibiotics’ volume of distribution also includes the intracellular component and they are mainly eliminated by a hepatic mechanism. These antibiotics (flurquinolones, glycylcyclines, macrolides, metronidazole, lincosamides, tetracyclines) require a loading dose, which in critically ill patients is recommended not to be administered. The current laboratory markers used in daily clinical practice – C-reactive protein, leukocytes, TNF, interleukins (the last two used mainly for scientific purposes) are non-specific diagnostic parameters for the diagnosis of sepsis and are unreliable as guiding factors in antimicrobial therapy. Current and unsolved problems in intensive care units are:

1. The uncontrolled administration of antibiotics – incorrect use;
2. Use of inappropriate antimicrobial agents;

3. Unreasonably prolonged exposure to antibiotics with all the resulting consequences for the patient, for the antibiotic policy at the hospital, national and global level;
4. The excessive use of targeted antibiotics; Selection of MDR (multi drug resistant) microorganisms;
5. Failure to recognize sepsis of mycotic origin and unsubstantiated use of broad-spectrum antibiotics in these patients.

The introduction into daily clinical practice of laboratory markers with screening and significant diagnostic value, such as the procalcitonin test and NGAL, would lead to optimization of the diagnosis and treatment of sepsis.

Procalcitonin is a member of the calcitonin-super family, it is a specific diagnostic and prognostic marker for bacterial sepsis, and it can be applied as:

1. A rapid differential diagnostic criterion in the verification of bacterial, viral or mycotic infection;
2. A fast, informative and reliable parameter for the effectiveness of antibiotic treatment;
3. A prognostic sign of severe infection with the development of acute organ failure;
4. Limiting factor for antibiotic exposure.

In healthy individuals, procalcitonin is synthesized by the C-cells of the thyroid gland and its production is induced by elevation of serum calcium levels, glucocorticoids, glucagon, gastrin, and beta-mimetic stimulation. Normally, procalcitonin levels are extremely low (< 0.05 ng/mL). During an inflammatory process in the body, procalcitonin begins to reproduce through two alternative mechanisms: direct (induced by lipopolysaccharides and other toxic metabolites of the microorganism) and indirect (induced by inflammatory mediators, such as IL-6, TNF, etc.). Many studies indicate that procalcitonin levels in bacterial septicemia rise significantly between 2-6 hours, peaking between 6-24 hours.

NGAL (neutrophil-gelatinase-associated lipocalin) is an early specific marker correlating with the severity of sepsis that is predictive of subsequent acute kidney injury (AKI) and chronic kidney disease (CKD). The early recognition of patients with AKI and the avoidance of additional damaging factors (nephrotoxic ABs, inadequate fluid replacement, nonsteroidal anti-inflammatory drugs (NSAIDs), sympathomimetics, etc.). Serum creatinine is an unreliable marker for early detection of AKI, studies suggest that about 40% of patients with AKI are missed.

**Objective:**

To introduce a personalized antibiotic regimen in a patient with sepsis, introducing procalcitonin and NGAL, as key biomarkers in the early diagnosis, differentiation and adequacy of antibiotic treatment in patients with sepsis -/+ AKI.

**Tasks:**

1. Introduce into clinical practice a clinical algorithm for the treatment of a patient with severe sepsis, septic shock;

2. Prepare an individual AB regimen by a multidisciplinary team based on clinical, functional and laboratory indicators and its daily optimization, taking into account the changed terrain in the septic patient from the point of view of PK and PD of the drugs used;
3. Introduce into clinical practice the procalcitonin test and NGAL for early diagnosis of sepsis, sepsis + AKI;
4. Confirm the differential diagnostic value of procalcitonin in the verification of bacterial, mycotic and viral sepsis;
5. Precise antibiotic therapy – type, escalation, de-escalation, duration according to conventional markers + procalcitonin, NGAL;
6. Follow, compare and evaluate the two groups according to indicators – morbidity, mortality, duration of antibiotic treatment and hospital treatment, complications, disability, socio-economic profile;
7. Establish the presence of correlation between plasma levels of procalcitonin and NGAL, SOFA score and mortality and morbidity and evaluate the role of procalcitonin as a prognostic factor.

**Description of research design**

A suspected patient with sepsis was admitted to the Anesthesiology and intensive care clinic (AICC) at UMHAT "St. Marina", meeting the study's "inclusion criteria". A patient randomized to group 1 was treated according to a clinical algorithm ("Protocol"). Depending on the clinical, functional (monitor measurements, imaging) and laboratory results, a multidisciplinary team will prepare a personalized antibiotic regimen. The treatment of the patient will continue according to the indicated clinical algorithm. Evaluation of therapy, respectively escalation and de-escalation will be carried out in two stages: between 48-72 hours after admission to AICC and limitation of therapy on the $5^{th}$ – $7^{th}$ – $10^{th}$ day. The information from the protocol will be processed in order to produce results in response to the tasks set. A patient randomized to group 2 will be managed conventionally.

**Material and methods:** The study is prospective and was conducted in AICC, UMHAT "St. Marina", within three calendar years 2020-2023. Patients were randomized into two groups: group 1 – 41, in which a procalcitonin test + NGAL will be included for the diagnosis and treatment of sepsis to the conventional group of methods (clinical, laboratory, imaging, etc.); group 2 – patients in whom conventional clinical, laboratory and imaging methods were used for diagnosis and treatment. The level of procalcitonin will be monitored twice (at initialization, at 48-72 hours), up to three times in patients with difficulties in limiting antibiotic therapy. The measurements were carried out in Clinical Laboratory at UMHAT "St. Marina". Serum and plasma from patients randomized in group 1 were used, determination method – latex enhanced immunoturbidimetric analysis.

Adult patients over 18, regardless of gender, are included. Severity of sepsis was assessed using the SOFA scale. Patients included in the observation will be premorbid up to ASA III, without organ failure > of I (mild) degree.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Patients with clinical evidence of sepsis | Patients with polytrauma |
| Age >18+ years < 70 years | Patients, up to 14 days after cardiac surgery treatment |
| ASA< or = III | Patients < 18 years, pregnant |
| Patients who signed an informed consent | Premorbid advanced organ failure, > of I (mild) degree |

When antibiotic treatment was initiated, it was discussed with a clinical pharmacologist, laboratory physician, and intensivist.

At randomization of the patient and daily should be monitored BGA, lactate, CVP, Scv, MAP, ultrasound measurements of VCI to determine adequacy of fluid restitution. On the $1^{st}$, $3^{rd}$, $6^{th}$ day urea, creatinine, albumin, C-reactive protein, procalcitonin, CBC should be tested, and, in case of lipophilic drugs and liver damage, liver indicators (AST, ALT, cholinesterase) should be tested at least twice.

In patients with severe sepsis and with increased levels of procalcitonin, C-reactive protein and lactate 24 hours after randomization, plasma NGAL was tested for early recognition of septic patients with AKI, as a higher-risk group with increased mortality and morbidity. The measurements were carried out by a determination method latex enhanced immunoturbidimetric analysis.

Tissue edema assessment was done physically, as well as ultrasonographic assessment of extravasal pulmonary water (Kerley lines B >3, which is a sign of pathology.

The following criteria were accepted for a sign to stop antibiotic treatment: improvement in the patient's clinical status and plasma procalcitonin level < 0.5 ng/ml or a decline > 80% from baseline in clinically stable patients. Procalcitonin values > 1 ng/ml will be accepted as a significant indicator for antibiotic treatment.

Due to the pharmacokinetic profile of beta-lactam antibiotics, as well as glycopeptides (time-dependent, bactericidal is dependent on the time interval during which the plasma concentration of the amtibiotics exceeds the MIC), these antibiotics are included in a continuous infusion minimum > t ½ in all patients of group 1. For lipophilic antibiotics, patients with clinical septic shock, high lactate levels > 4 and decompensated metabolic acidosis, a "loading dose" was not performed.

72 hours after initiation of the antibiotic treatment, plasma levels of the administered antibiotics were monitored, according to the specific capabilities of the clinical laboratory at the UMBAL "St. Marina".

Morbidity, mortality, duration of antibiotic treatment and hospital treatment, complications, disability, socio-economic profile were indicators assessed within the hospital stay in both observed groups. Mortality was also tracked within a 30-day period.

**Results**: Group 1 demonstrated a lower incidence of mortality, morbidity, disability, as well as a lower incidence of AKI. Shorter exposure to antibiotics, with associated socioeconomic benefits.

**Conclusion:** Management of the patient with severe sepsis continues to be an enormous clinical challenge. The patient's pathophysiological changes can lead to a disturbed PK/PD profile of the administered medications, leading to ineffective dosage regimens of otherwise effective medications. Antibiotic selection, dosage regimens, duration should be individualized and adapted to the specific clinical situation. Procalcitonin and NGAL are unique biomarkers that have a wide range of application compared to other conventional biomarkers. Their application together with conventional laboratory markers could optimize early diagnosis, treatment, prognosis and socio-economic aspect in patients with sepsis and those with sepsis + AKI.