REVIEW ARTICLE

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The diagnosis of sepsis using POCT in the Emergency Department – Medical and legal implications

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Abstract: *Sepsis, severe sepsis and septic shock are some of the most serious affections which threaten the lives of the patients who come to the Emergency Department and which require fast treatment because the more severe the sepsis was, the higher the mortality, up to 50% higher in severe sepsis. That is why, at present, the 2013 Guides of Surviving Sepsis Campaign recommend that the potential source of infection should be confirmed as soon as possible, in the first 6 hours since the patient arrived in the Emergency Unit if possible, moreover the large spectrum antibiotics therapy must be administered in one hour after the severe sepsis or the septic shock were identified. That is why the identification of these patients at risk is very important and this identification can only be made using POCT type devices.*

This type of devices has the capacity to make precise determinations, in a short time (15-17 minutes), using minimum quantities of integral blood, without using test tubes, sepsis biomarkers and other additional material. The possibility to fast diagnose sepsis, offers the doctors from the Emergency Department, the capacity to fast initiate an antibiotic treatment, to hospitalize the patient and at the same time, it gives them the certainty that they did not miss the sepsis diagnosis, thus avoiding the situation of malpractice. A preliminary study, regarding the sepsis biomarkers, which took place in the Emergency Unit of University Central Emergency Military Hospital, is also presented within this article.

Keywords: *sepsis, POCT, Emergency Department*.

INTRODUCTION

Sepsis, severe sepsis and septic shock are some of the most common affections which are handled in the Emergency Departments and in the intensive therapy sections and they still represent a major cause of morbidity and mortality for critic patients despite the use of respiratory and cardiovascular support, modern antibiotics and resuscitation therapy. In compliance with the newest guides published, fast identification and the speed of implementation of an adequate treatment in the first hours after the patient came to the Emergency Department can influence radically the prognostic of septic patients, facts which determined the concentration on biomarkers for precocious diagnosis, risk stratification and the assessment of these patients' prognostic.[1]

Sepsis is an exacerbated systemic reaction at

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something which would normally be a common infection. Although it was identified from the oldest times, the sepsis is still a challenge for clinicians and it remains, most of the times, a lethal complication. During the last 10 years, in compliance with the Protocol initiated by Surviving Sepsis Campaign for the management of patients with sepsis, the mortality was reduced from 37% to 30%, nevertheless its percentage is still unacceptably high.[2]

The legal framework for the management of patients who come to the Emergency Unit is provided in the Order of the Health Ministry no. 1706/2007 regarding the management and organization of the emergency receiving units and compartments.

The patients who come to the Emergency Department are taken over by the employees of the department and they are selected according to the emergency degree in compliance with the Order of the Health Ministry no. 48/2009 – National Protocol for the Selection of Patients from the Emergency Receiving Structures.[33]Patients' selection is defined by law as follows: the mechanism or procedure by means of which the patients who come to the Emergency Receiving Unit (ERU) or to the Emergency Receiving Department (ERD) are assessed and classified, upon arrival in ERU or ERD, by a competent person (physician or average sanitary employee), taking into consideration their clinical state and the symptoms they declare, correlated with their age and medical history, how stable their vital functions are, the potential of exacerbation of their medical state, the necessity to implement a treatment or to perform some investigations, as well as other information which are considered to be relevant, so that it can be decided which is the priority for each patient to be assisted and the level of assistance necessary for each of them.[33]

Patients' selection within the Emergency Department represents the medical procedure used to assess and categorize the patients arrived within the ERU by a nurse/physician, in order to decide their priority for medical care and its level. The nurse responsible with the patients' selection procedure is the nurse with specific preparation and with appropriate experience and abilities. The recommendation provided by the law is that the time allowed for the patients' selection should not be longer than 2 minutes.[33]

The level of patients' selection refers to all patients who have the same priority degree according to the severity and/or critical state of their pathology and to the necessary resources. Priority levels are the following:[33]

- Level I – *resuscitation* (Red Code): The patient who requires an intervention to save his/her life NOW. Maximum time allowed for the patient to be taken over in the treatment area: 0 minutes.
- Level II – *critical* (Yellow Code): The patient who is in a situation with major risk or altered mental status (acute modification) or any intense pain or major discomfort. Maximum time allowed for the patient to be taken over in the treatment area: 10 minutes.
- Level III – *urgent* (Green Code): The patient with stable vital functions who requires however, two or more medical laboratory or paraclinical investigations. Maximum time allowed for the patient to be taken over in the treatment area: 30 minutes.
- Level IV – *nonurgent* (Blue Code): The patient with stable vital functions who requires only one laboratory or paraclinical investigation. Maximum time allowed for the patient to be taken over in the treatment area: 60 minutes.
- Level V – *examination* (White Code). The patient who requires neither emergency medical assistance nor laboratory or paraclinical investigations. This category includes people who come for one of the following reasons: vaccination; social case without clinical symptoms; clinical and administrative issues (medical certificates, prescriptions, etc.). Maximum time allowed for the patient to be taken over in the treatment area: 120 minutes.

The patient has the right to have his health state periodically reevaluated if he has been taken over in the treatment area after more than 30 minutes or if there are significant modifications in his/her state, which means that patients' selection procedure within the Emergency Department is periodically resumed.[33] More than once, this task is a difficult task to be performed, taking into account the big number of patients, insufficient personnel and the permanent stress the personnel from the Emergency Department

has to deal with. In addition to these, the risk of bad evolution for septic patients and not only for them is quite high, therefore it is necessary that the diagnosis methods in this department are fast, precise and trustworthy.

We debate the issue of septic patients in this article because this kind of patients have a rather unpredictable evolution if they are not diagnosed correctly and in due time. More than often, old patients who also suffer from diseases in different stages are neglected or superficially treated at home, fact which makes the sepsis evolve frequently up to advanced stages until patients come to the hospital. This kind of patient is brought to the hospital with the ambulances of the national system 112 (SMURD or Ambulance Service) or by his/her relatives, being already in a critical state, dehydrated, with high temperature or with neurological signs.

Diagnosis of sepsis is not easy, it involves special issues, because at present, the available methods are related to the performance of the following laboratory analyses: the number of leukocytes (WBC) in the patient's blood resulting from a complete hemogram with leukocytes formula, the number of germs, sepsis biomarkers, CRP (reactive protein C) and last but not least the performance of bacterial cultures from blood (hemocultures) and from other fluids. Moreover when the physician from the Emergency Department is under time pressure and under pressure from the patients' relatives as well as from the other patients who do not understand the patients' selection Protocol mentioned above, a fast diagnosis has an even greater importance. The main topic of discussions is the fact that some patients have higher priority than others, meaning that some have to wait longer and others, who have just arrived, are immediately taken over and treated in the Emergency Department. The duty to introduce the patients in the 5 levels of selection belongs to the nurse from the patients' selection and eventually to the physician on duty; the two decide which patients have a higher level of priority.

Therefore, the physician from the Emergency Department should have available all necessary resources in order to make a fast, correct and hard to question diagnosis in the prospect of any malpractice accusations. Sometimes, there are patients who arrive in a state of septic shock and they have a fast evolution to decease because of multisystem organ failure (MSOF), so it is difficult for the patients' relatives to understand the reason why a patient having an apparently good state during the day, dies in hospital in less than 24 hours. That is why the physician from the Emergency Department (emergency medicine physician or intensive care physician) must make the correct diagnosis: SIRS, sepsis, severe sepsis or septic shock, so that a fast, appropriate and complex treatment can be initiated.

According to the law, the physician from the Emergency Department has the possibility to require all necessary examinations from different specialties in order to make a diagnosis, the period of time allowed before the patient is examined varies between 10 and 60 minutes according to the level of emergency – 10 minutes for red code and maximum 60 minutes for green code.[32]

It is important to have in mind that patients must be subjected to a series of laboratory and paraclinical investigations, as soon as possible upon their arrival, especially in the case of patients belonging to the first 2 levels of priority. In view of a better understanding of the phenomenon, we shall make a review of the definitions of the Systemic Inflammatory Response Syndrome (SIRS) and of the sepsis with its stages.

DEFINITIONS

Systemic Inflammatory Response Syndrome (SIRS) is the clinical syndrome which results as a consequence of an inadequate inflammatory response of the body at a noninfectious origin lesion, such as: pancreatitis, vasculitis, autoimmune affection, thrombembolism, burns or surgery interventions.[3] SIRS diagnosis is made in the presence of 2 or more of the following criteria, as follows: temperature >38,5^{o}C or <36°C; ventricular rate >90/min; respiratory frequency >20/min or $PaCO_2$<32 mmHg; leukocytes >12000/mm^3 or <4000/mm^3;

Sepsis is the clinical syndrome which results as a consequence of an inadequate inflammatory

response of the body at an infection. Sepsis can be presumed if 2 or more of the conditions mentioned above are present and the infection is identified either through germs culture or visually.[1]

Severe sepsis: sepsis associated with the organ dysfunction/insufficiency, impercipient perfusion or hypotension.[1]

Septic shock: hypotension within sepsis, with all appropriate replenishment.[1]

Multisystem organ dysfunction – MSOD: organ dysfunction at a patient with an acute pathological state so that homeostasis cannot be maintained without medical intervention.[1]

WHY „POINT OF CARE TESTING – POCT" DEVICES FOR EMERGENCY DEPARTMENTS?

Point-of-care testing (POCT) is defined as a medical testing at or near the site of patient care.[21,22] Another definition would be the following: a group of investigation, diagnosis or screening technologies, which require neither personnel nor laboratory conditions, performed on spot where medical assistance is provided, within or outside a medical unit.The purpose of POCT is to provide immediate, convenient, and easy-to-use diagnostic testing that shortens the therapeutic turnaround time when providing care for a patient.

The objective is to provide rapid diagnostic information that permits immediate clinical management decisions to be made that will improve patient safety and clinical outcomes, not to mention patient satisfaction.It is important to be noticed that these technologies do not require special spaces or additional personnel, other than those that can be found in any hospital/physician office. POCT can be found in more environments: hospital bedside, ambulatory care settings (clinics or physician offices), alternate care (skilled nursing facilities), and home settings.

In Romania, medical devices are governed by Law no. 176/2000 regarding medical devices, within this law, in article 2 point a) and b) we find their definition as follows[29]:

a) Medical device – any instrument, device, mechanism, material or another article used alone or in combination with others, including the necessary software for its correct use, designed by the manufacturer for human use and which does not fulfill the main action for which it was designed in/or on the human body by pharmacological, immunological or metabolic means, but which can be helped in its function by such means, with the purpose of: diagnosis, prevention, monitoring, treatment…;
b) Active medical device – any medical device whose functioning is based on another source of power or of energy than the one generated by the human body or by gravity;

POCT benefits are numerous, below we are presenting the most important of them[21,22]:

- Positive patient identification;
- Immediate diagnostic test results (maximum 15-17 minutes) – reduced test and therapeutic turnaround time, 24/24 hours;
- Reduction and/or elimination of specimen/sample transport;
- Elimination of blood collection tubes and centrifugation with fresh whole blood specimen;
- Reduced blood specimen volume;
- Reduced volume of reagents – POCT is a less invasive method from the clinical point of view;
- Data management and connectivity – POCT systems can be connected to the informatics systems of the hospitals having as result: less transcription errors, immediate data analysis – utilization, quality control, compliance and data mining, development of disease specific algorithms;
- Good cost-benefits report – although generally the tests are more expensive, they can offer large economical benefits, by reducing the number of visits in hospital, days spent in hospital and repeated hospitalizations.

Potential disadvantages[21,22]:

- Weak analyses quality;
- Lack of results interpretation;
- Wrong results which are difficult to trace;
- The possibility to make a battery of tests can lead to the performance of unnecessary and inadequate

analyses;

- Lack of alignment with laboratory results – reference intervals and results can be different to those issued from the classical laboratory which makes the comparison difficult.

The current diagnostic laboratory system has been slow to change and is in need of change to a more patient-centered system. Thus, today we need personalized medicine and a patient-centered medical system.

The model of centralized lab testing was developed in the late 1960s but the new technologies and the evolution of the health system demanded more rapid testing which led to a significant increase of POCT. The development of new technologies, such as „lab on a chip"[23,24]and DNA/RNA-based molecular diagnostic tests[25,26, 27,28], will expand the menu of POCT tests and will lead to an increase in the use of this device.

Taking into consideration all the benefits mentioned above, POCT improves the diagnostic activity; the most important aspects are immediate and precise diagnostic, the use of whole blood specimen in an extremely small quantity and reduction of specimen/sample transport to the laboratory. Due to the fact that it provides information to the Emergency Department physician upon diagnosis and patient's critical state, it also offers him/her a certain safety which, at the same time, eliminates the stress related to malpractice.

The physician from the Emergency Department can ask for interdisciplinary examinations, as already mentioned, however, if he/she does not have any investigations to show to his colleagues in order to make at least a presumptive diagnosis, the physician extends patient's hospitalization time in the Emergency Department waiting for the laboratory analyses made in the central laboratory.

In addition to that, the Romanian legislation, more precisely, the Order of the Health Ministry no. 1706/2007 – which regulates the activities from the Emergency Departments, in Annex 1 – stipulates a series of minimum mandatory paraclinical and laboratory investigations which should always be available for the patients from the Emergency Departments.

These investigations complexity depends on the type of the Emergency Department (I or II), as related to imaging, but if we refer to basic analyses (hemogram, blood glucose meter, electrolytes, sanguineous gases), these are mandatory and it is preferable for them to be made in the Emergency Department in order to reduce the time until a diagnosis is made.

High level Emergency Departments – type I, must also have the possibility to make toxicology analyses. All these mandatory analyses, but also other analyses which can lead to an immediate and precise diagnosis, can only be made with the help of POCT technology.

SEPSIS DIAGNOSIS

Biomarkers

Biomarkers can have an important role in proving the presence, absence or stringency of sepsis and they can make the difference between fungal and viral infections, between systemic sepsis and local infection.Other potential roles of the biomarkers include prognostic, antibiotic therapy, evaluation of treatment answer and postsepsis recovery, differentiation between gram-negative and gram-positive germs, the possibility to predict sepsis complications and the development of organ malfunctions (heart, kidneys, liver or multiple organ malfunctions)[4]

Biomarkers definition. At present, the accepted definitions for biomarkers are in compliance with the studies made by U.S. National Institute of Health (NIH) and by European Medicines Agency. A biomarker is a "biological characteristic, objectively measured (with acceptable accuracy and reproducibility) and used as an indicator for a physiological or pathological process or for the activity of a medicine".

In compliance with NIH standards, biomarkers can be classified in two categories: *prognostic markers* – which allow for the patients to be classified according to the individual risk to have a specific prognostic,

regardless of the treatment (or lack of treatment) and *predictive markers* – which allow the forecast of the potential benefit (efficacy) and/or the risks (toxicity) of a treatment according to the status of a biomarker (absent/present)[5].

The ideal biomarker in infectious diseases is used to identify a high risk group or predisposing factors, as a tool for disease identification or for treatment prescription and classification of patients according to their specific factors as well as/or as indicator of the therapeutic management in order to avoid reinfection.An ideal marker for infections would combine the diagnostic, prognostic and treatment follow-up characteristics and it should be easily and fast available for clinic use[6].Biomarkers should evaluate the severity of an infection or predict an evolution excluding complications to help the clinician make a decision regarding the best therapeutic approach in the most appropriate environment (hospital or specialty ambulatory, intensive therapy or hospital section). Furthermore, it should help the clinician decide if it is necessary to introduce or to continue antibiotic therapy.

Concluding, the "ideal" biomarker for sepsis diagnosis should make different diagnosis between SIRS and sepsis, between viral infections and bacterial ones, it should also "detect" sepsis fast, reflect de severity of the disease so that therapy can be monitored, have a high predictive value, be stable in different samples and eventually be quantified fast using "Point of Care" devices.

During the last few years, more potential biomarkers for infection were suggested and their analysis is a complex task. The present tendency is to use biomarkers – especially cytokine – in correlation with multiple tests which measure simultaneously more biomarkers from only one biological sample. The main purpose is to examine if the clinical performance and utility can be transposed in every day clinical situations, taking into account the great number of patients which come to the Emergency Departments and the necessity to make a diagnosis fast.

A fast diagnosis allows physicians from the Emergency Department to implement a precocious treatment which increases the patient's survival rate and which, at the same time, offers them the certainty that they are not wrong and that they have not passed by an infectious affection with lethal potential for that patient.Thus, the malpractice risk for the physicians from the Emergency Department is lower, since it is known that they have to deal with a great number of patients every day.

Available routinebiomarkers

Three biomarkers fulfill the criteria mentioned above and are available at all times: C reactive protein (CRP), procalcitonine (PCT) and presepsin (PSEP).

CRP was tested in different studies but only some of these studies focused on its use for the improvement of antibiotic therapy. Further to these studies – completed or ongoing – the use of CRP cannot be recommended at present as a criterion for the initiation or end of antibiotic therapy in adults; however, for children, CRP can be probably used as an indicator to end the antibiotic treatment although the proofs obtained up to present are limited[5].

Procalcitonine – PCT was testedon a larger scale for the improvement of antibiotic therapy, both for adults and for children. The conclusion of more studies completed recently, which involved a significant number of patients, is that the introduction of procalcitonine values in the decision algorithms for infection management in specific infections is most likely adequate. It is however necessary to continue researches for specific infections which have not been examined enough up to the present time, for a more precise definition of procalcitonine role in the management of antibiotic therapy[5].

Presepsin – PSEP. In this article, we shall present a new biomarker, which is a viable option for sepsis precocious diagnosis – **presepsin *(sCD14-ST)*** and we shall present its correlation with a score (MEDS score) to supply the gaps which are related to this biomarker, in comparison with what is used in present in clinical practice. The biomarker was used for the first time in 1993[32] and then in 1994 (*Durieux et al. Eur J Immunol 1994;24:2006-12*). Presepsin was

studied starting with 2005 and it became an important new marker for the diagnosis and prognostic of sepsis in the last years.[8,9,10,11,12].

CD14 is a glycoprotein expressed on the surface of the monocytes/macrophages membrane (mCD14) and it serves as receptor for lipopolysaccharides (LPS) and for the protein which ties the LPS (LPBP). CD14 co-locates using a receptor 4, Toll-like type (TLR4). When tying LPBP complex, CD14 activates the specific pro-inflammatory signalizing cascade TLR4, thus initiating the host inflammatory reaction against any type of infectious agents.

LPS-LPBP-CD14 complex is released in circulation, canceling CD14 from the cellular membrane, thus soluble CD14 (sCD14) is produced. Nevertheless the activity of the proteose from the plasma generates another molecule sCD14, referred to as subtype sCD14 (sCD14-ST) or presepsin – a protein of 13 kDa which is actually a part of CD14, lysated at N-terminal head (*Durieux et al. Eur J Immunol 1994;24:2006-12*).

PSEP levels were significantly higher at septic patients than at those with SIRS or at those apparently healthy. The increase of PSEP levels was more precocious than the increase of IL-6 and D-dymers levels in a study which created a model of bacteremia on animals (cecal ligation and puncture on rabbit – CLP). The determination of presepsin concentration can be used not only for the diagnosis and prognostic of sepsis, but also to monitor disease evolution and feedback at therapeutical interventions.[8,9,10,11,12]

Recently discovered biomarkers of potential interest in the near future

At present, intensive efforts are being made in the research field of some new prognostic and diagnostic biomarkers which can be useful in antibiotics therapy management from acute infections. For adults, three of these seem promising: sTREM-1 (soluble Triggering Receptor Expressed on Myeloid cells-1), suPAR (Soluble urokinase-type Plasminogen receptor) and ProADM (proadrenomeduline). These biomarkers are accessible, they have proved sensitivity and/or specificity and they were studied on a significant number of patients so that they are worth to be taken into consideration further on. For children and babies other studies are also necessary.[5, 13]

STREM-1 is a member of immunoglobulins big family, surface receptor which appears at mature monocites and polimorphonuclears, they contribute at native immunity. Its expression is upregulated when phagocytes are exposed to bacterial fungic pathogens but not during other noninflammatory processes. TREM-1 amplifies the inflammatory response by increasing the proinflammatory cytokines production, inhibiting the synthesis of IL10. During the up-adjustment of the surface receptor TREM-1, the soluble form sTREM-1 increases in biological fluids (blood, bronchoalveolar lavage fluid, cerebrospinal fluid) and it can be determined with ELISA commercial kits. According to some recent studies, the dosage from the infection spot seems to be more significant than the measurements made from plasma.[5,13]

SuPAR (Soluble urokinase-type Plasminogen Activator Receptor) or CD87 is a receptor for inflammatory response spread on a large scale. It appears only on the surface of a few cell types, such as: endothelial cells and leukocytes (monocytes/ macrophages,polymorphonuclears).

Expression of its gene is under the control of immune and inflammatory effectors, such as bacterial products (LPS), cytokines (IFN-γ, TNF-α, IL-1β) and growth factors (FGF-2, VEGF, TGF-β, EGF). During the inflammatory and immune response, suPAR expression is upregulated by epithelial cells, white blood cells (lymphocytes), smooth muscle cells and fibroblasts. Expression is also upregulated during tumor growth and metastatic spread. The dosage may be achieved using commercial ELISA kits available on the market, but also as part of the multiplex kit with multiple cytokines. However, suPAR seems to be of limited value as a diagnostic test in specific pathologies (patients at risk, HIV patients on antiretroviral therapy, monitoring patients with non-pulmonary bacterial infection and children with malaria with Plasmodium falciparum).[5,13]

Pro-ADM Adrenomedulinis a52amino acidpeptide, a marker ofCALCgene familythat worksasa mediator

ofcell proliferation, hormonalregulationandembryogenesis. ADMis produced by theendothelial cellswhere itinducesvasodilationand maintainshomeostasis. Pro-hormonal fragments(pro-ADM) are more stable thanthe complete peptideandtheir levelsin biological fluidscan be measuredbyautomated methodsTRACE(TimeResolvedAmplifiedCrypt-Emission) after the capture of immunoassays. The secretion ofproADMincreases duringan immune response againstviral or bacterialproductsaccording to the sizeof the stimulus. Pro-ADM is avaluableprognosticmarker. Aspart of anevaluationscore ofpneumonia severity, it can identifypatients in rather critical state which would requiremonitoring/hospitalization inanintensive care unit.[5,13]

Future Biomarkers

Micro-RNA (miR)are newly discovered potential biomarkers. miR are small molecules (approximately 20 nucleotides) present in eukaryotic cells, which act as biological regulators by modulating post-translational regulation. They are ubiquitous and present in abundance in the lungs, liver and kidneys. After binding to the appropriate smRNA sequence, they regulate the expression of the gene by a repressor effect or by altering the target sequence. A fragment of miR can bind several smRNA. Their expression can be measured by RT-PCR and quantitative PCR. miR are potential candidates for early diagnosis and/or prognostic markers in sepsis, but other numerous studies are necessary to understand their role in biochemical and immunobiological processes before it can be used to stratify, to make prognosis or therapeutic decision in septic patients.[5,13]

The diagnostic and prognostic evaluation of***presepsin*** in sepsis in the Emergency Department was studied in comparison to other available routine biomarkers, in a study involving 859 patients, conducted by an university hospital which has between 240,000 and 260,000 hospitalizations per year.[10] These findings were published recently, and the conclusions are consistent both with literature data available in today specialty literature and with personal observations generated during similar studies in our hospital which has 25,000 presentations through the Emergency Department per year.

The efficiency of using presepsin to diagnose cases of sepsis, severe sepsis and septic shock was significantly increased by using MEDS score in evaluating these patients as it will be shown below. It is also worth mentioning that although PCT (procalcitonin) can be used as a biomarker for the diagnosis of sepsis, it increases in other situations, such as: multiple injury, extensive burns, pancreatitis, organ transplantation, major surgery and SIRS – not only in infections, therefore, only the positive and negative predictive values are not enough to exclude or confirm sepsis.[10] A recent meta-analysis showed that the diagnostic performance of PCT was reduced, with 71% (95% confidence interval 67-76%) sensitivity and specificity for serum PCT, as a biomarker for sepsis. In conclusion PCT can not clearly differentiate sepsis from other diseases in critic adult patients.[10,14,14,16,17,18] Thus, to diagnose sepsis, severe sepsis and septic shock, PSEP proved to be superior to PCT, moreover, PSEP together with the assessment by MEDS score was superior to PSEP taken as sole indicator.[10,19]

In the 28-day mortality prognosis PSEP was inferior to PCT, but these were lower to the correlated interpretation and MEDS score. For septic patients and prognostication of mortality after 28 days, PSEP, MEDS and APACHE II score proved to be independent predictors unlike PCT which did not have this capacity. The mentioned study showed that plasma levels of PSEP were a parameter closely related to the severity of sepsis.[10,19,20]

Compared to the PCT, PSEP is a highly specific biomarker for the diagnosis of a bacterial infection because it is produced in conjunction with bacterial phagocytosis.

PSEP was higher than PCT and had greater sensitivity, specificity, positive predictive value, negative predictive value and accuracy of prognosis in early stages of sepsis which is consistent with the data from the updated literature.

The more severe the sepsis was, mortality also

increased with over 50%, that is: mortality in severe sepsis. Dellinger et all., in Early-Goal Directed Therapy from 2013 guides of the Surviving Sepsis Campaign, recommends that the potential source of infection should be confirmed as quickly as possible, if possible within 6 hours since presentation and that large spectrum antibiotic therapy should be administered within one hour from the identification of severe sepsis or septic shock. Therefore identifying these patients at risk is very important.

Table 1. MEDS Score (Mortality in Emergency Department Sepsis Score)[30,31]

Variables for MEDS Score	Points
Comorbidityfastterminal– fast terminalassociated disease(metastatic canceroranothercondition that cancause deathin30 days)	6
Age >65 years	3
Septic shock (PAs<90 mmHg with all volemic repletion)	3
Number of plates <150000/mm^3	3
Leukocytesprematureunsegmented-bands(>5% of totalleukocytes)	3
Lowerrespiratory infection(clinical infiltratedpneumoniaor chestRxG)	2
Altered mental status(level ofalert or another change in the levelof consciousness)	2
Chronic patients treated at home	2

STUDY ON THE IMPORTANCE OF PRESEPSIN IN ASSOCIATION WITH MEDS SCORE, SEPSIS PRECOCIOUS DIAGNOSIS. PRELIMINARY DATA

In the Emergency Department of the Universitary Central Emergency Military Hospital, a study was made during a year, involving 300 patients suspected of sepsis that came to the Emergency Department, patients brought by their relatives or by the ambulances from the national emergency system.

From these, 32 patients were introduced in the study (19 men and 13 women), for which the following inclusion and exclusion criteria were used:

Criteria for inclusionin the study:

•Age ≥18yearswith clinical signs ofsevereinfectionsrequiringbloodsampling;

•The presence of2 of 4SIRScriteria: fever > 38^0C<36^0 C; heartrate>90/ min; respiratory rate >20/minor existence of hyperventilation($PaCO_2$<4.3 kPa/ 32mmHgin arterial blood); leukocytosis>12,000/ml, leukopenia<4000/mlor >10%prematureunsegmentedgranulocytes(bands);

Exclusion criteria: age under 18andrefusal to sign theconsent.

All patients were examined by doctors of emergency medicine and ATI employees of the Emergency Department and after the former signed the informed consent, venous peripheral approach was made, blood was collected for laboratory testing and they were subjected to other paraclinical investigations (abdominal ultrasound, CT in different regions, x-rays) in order to make a diagnosis and start the appropriate treatment immediately.

The following laboratory tests were made: complete blood count with differential, coagulation (Quick time, fibrinogen), biochemistry (glucose, urea, creatinine, ionogram, samples of liver, etc.), presepsin, procalcitonin.

Analyses were performed in the Central Laboratory of SUUMC, and the Emergency Department's own laboratory, using "Point of care testing - POCT" and PATHFAST® device type.

Evaluation of patients admitted to the Emergency Department was made with the score MEDS - Sepsis Mortality in Emergency Department[19, 30, 31]. The score was developed to predict mortality for patients with SIRS hospitalized in the Emergency Department. The maximum score is 27 points, score variables and the score awarded to each variable can be found in Table 1.

For all these variables, a score are awarded, score which is summed up for each patient, the sum of the obtained points offers a prognostic for mortality at 28 days.

The determination of presepsin was made using a POCT type device, more precisely PATHFAST®, and the evaluation of the patient's state according to the values/concentration of presepsin obtained was made using the correlations from Table 3.

The patients included in the study were aged between 18 and 92 and they were selected using the inclusion and exclusion criteria mentioned above. The existence of SIRS criteria was considered, the results are those from Figure 1 (14 patients with fever, 25 with RR>20/minute, 22 with leucocytosis, 22 with HR> 90/minute).

Table 2. Correlation between MEDS score and mortality at 28 days as percentage[30,31]

MEDS Score range	Mortality at 28 days (95% CI)
0-4	0,6% (0-3%)
5-7	5% (1-13%)
8-12	19% (11-29%)
13-15	32% (15-54%)
> 15	40% (12-74%)

Table 3. Correlation between PSEP values, diagnosis and measures to be taken [14,15,16,17,18,19]

PSEP (pg/mL)	Diagnosis	Case management
Under 200	Sepsis absence	It is not necessary to sample hemocultures
200-300	Small probability of systemic infection	Other investigations are also necessary among which bacterial cultures (hemocultures etc.)
300-499	Possible systemic infection (SEPSIS)	Therapy with medicines starts after samples were taken for bacterial cultures
500-999	High risk of infection progression in the body (SEVERE SEPSIS) High risk of unfavorable prognostic	Surgery treatment must also be taken into consideration
Over 1000	Major risk of systemic infection progression (SEVERE SEPSIS/ SEPTIC SHOCK), major risk of mortality at 30 days – comparable with score 25 on APACHE II	„Maximal" therapy

Further to patients' anamnesis, we obtained the data represented in Figure 2, in which we resumed the types of affections (number of cases): neurological – 9, neoplastic – 7, cardiac – 1, global cardiac insufficiency – 5, coronary artery diseases – 5, valvular heart diseases – 3), chronic renal diseases – 4 , diabetes – 4, pulmonary diseases (pneumonia – 5, BPOC/asthma – 5), thyroid diseases – 2, others – 27 (HTA, digestive diseases etc).

Patients were evaluated using MEDS score which varied between 3 – 21 points according to the health state of each patient. Some of the laboratory analyses were made in the Central Laboratory, that is the blood cultures and other cultures sampled from 15 patients, out of which only 3 were positive. POCT (Point of Care Testing) devices were used to determine the biomarkers, in the case of PSEP; presepsin had values between 102 – 7129 pg/mL, as it can be seen in figure 3. In the case of procalcitonine, the results were negative or they reached the maximum value of >10 ng/mL, and for PCT, the determination method that was used, was a semiquantitative one, THERMO SCIENTIFIC BRAHMS,

which has the following intervals as possibilities:< 0,5; ≥0,5-≤2,0; ≥ 2,0-10; >10 ng/mL. Regarding the diagnosis of sepsis in its different stages, there were 13 patients with SIRS, 8 patients with sepsis, 6 patients with severe sepsis and 5 patients with septic shock who also had the highest values of presepsin.

Considering the affections which led to sepsis (Figure 4), the patients from the study can be divided as follows: pulmonary diseases (COPD, asthma, pneumonia) – 12 cases (5 ♀, 7 ♂), urinary infections – 9 cases (5 ♀, 4 ♂), digestive infections (acute gangrenous appendicitis with generalized peritonitis – 2, gangrenous acute cholecystitis – 4, bowel obstruction – 1, diarrhea – 1, acute angiocholitis – 1) – total 9 cases (3 ♀, 6 ♂), gynaecologycal infections – 1 case and acute endocarditis – 1 case (♂).

Figure 1. The correlation between the number of cases and SIRS criteria

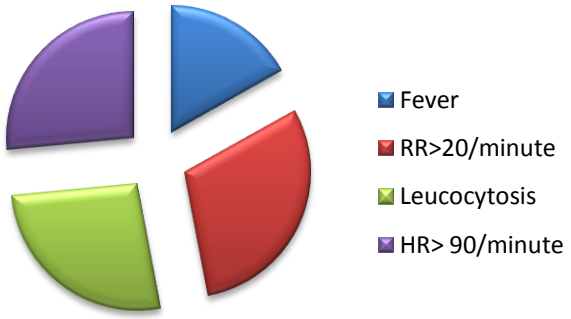
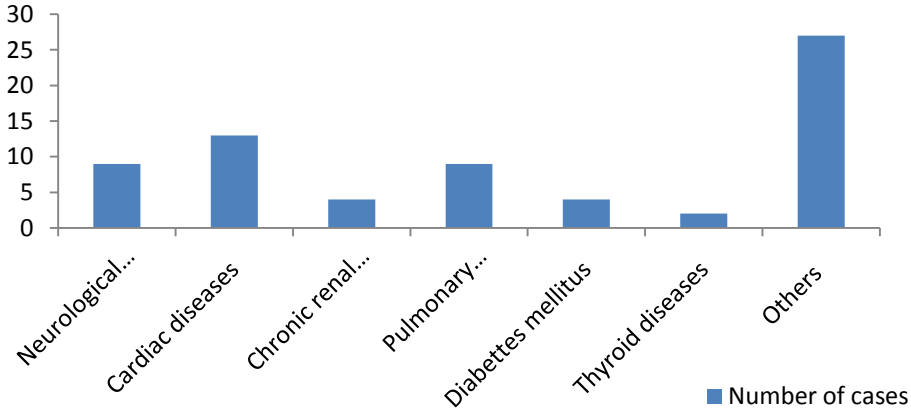


Figure 2. Anamnesis of the patients from the study
– number of cases according to the type of affection –



A total of 26 cases were hospitalized in Universitary Central Emergency Military Hospital (81.25%), out of which: 15 cases in medical wards, pulmonology – 2, gastroenterology – 3, internal diseases – 4, oncology – 1, neurology – 2, cardiology – 2 and dermatology – 1 case) and 11 cases in surgical departments (gynecology – 1, urology – 2, general surgery – 8). Out of the total of hospitalized patients, 11 were admitted to ICU and 7 were mechanically ventilated.

Out of the 32 patients included in the study, 8 died in hospital (25%) who had MEDS with values ranging between 8-21 points, the values obtained for presepsin were between 593-6745 pg/mL. 3 cases were diagnosed with sepsis, 2 cases were diagnosed with severe sepsis and 3 cases were diagnosed with septic shock. The affections which were the starting point for the development of sepsis were the following types of infections: respiratory – 5 cases, endocarditis – 1 case, diabetic ketoacidosis coma – 1 case, bowel obstruction – 1 case. Patients who died had a number of associated diseases, some of which were extremely serious, namely: neurological diseases – 4 cases, malignancies – 2 cases, ischemic

heart disease – 3 cases.

Figure 3. The evolution of presepsin values for the patients involved in the study

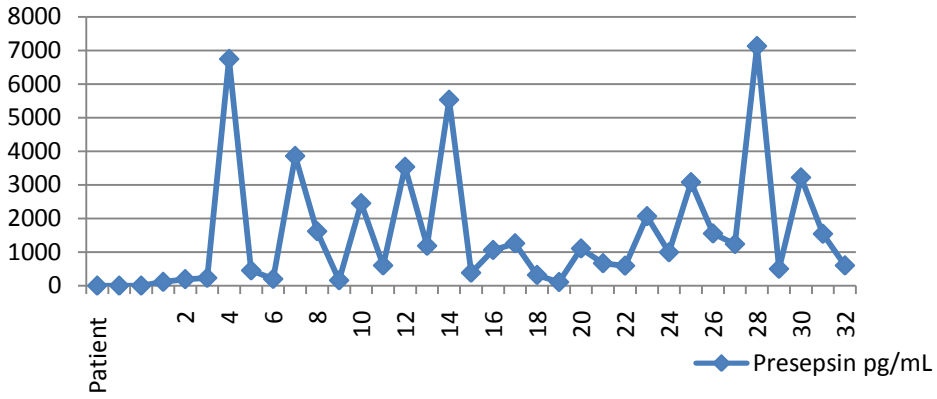
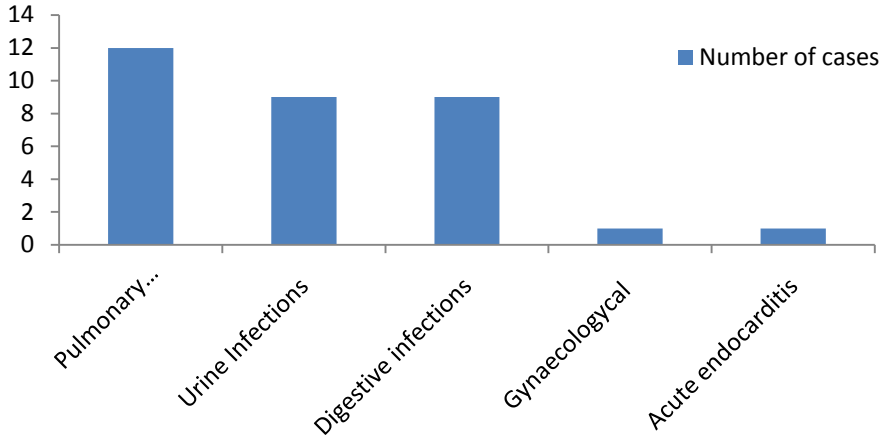


Figure 4. Correlation between the number of cases and the affections which led to sepsis



Preliminary conclusions of the study

Presepsinul is an important biomarker having a role in rapid diagnosis of sepsis (17 minutes) to 30 minutes for PCT (on the type of test that we had available), it allows the patient evaluation and classification in a risk category, and its association with MEDS score increased the possibility to provide a correct evaluation of the patients. Rapid diagnosis allows to early start any kind of treatment, primarily the antibiotic, right from the Emergency Department, and in the unclear cases, the physician from the Emergency Department requires further investigations to elucidate the diagnosis.

In selected cases - patients with unrecognized sepsis, the determination of PSEP allows the physician from the Emergency Department, to present their situation to the doctors within Universitary Central Emergency Military Hospital and to suggest and if necessary to hospitalize the patient in cases with diagnostic on the edge according to legal provisions.[32] In our experience related to the sepsis cases presented to the Emergency Department, PSEP determination had a special importance because we could demonstrate the presence of sepsis and not of SIRS as it would have been diagnosed unless for this biomarker. Diagnosing sepsis favored the decision of hospitalizing the patient, his/her close supervision, the commencement of antibiotic treatment in the Emergency Department, in some cases earlier surgical intervention. All patients hospitalized in the Emergency Department and then in the hospital,

were investigated using the imaging tools available in the hospital (ultrasound, X-rays, CT with or without contrast, etc.).

In addition to that, determination of the dynamic values of PSEP in hospitalized patients with sepsis allowed monitoring the effectiveness of the implemented treatment, the cost-effectiveness ratio was very good, given the early start of antibiotic treatment and beyond.

In our study, we used the device type PATHFAST® of the company Mitsubishi Chemical that has all the advantages of POCT, namely: the results are quantitative (using a chemiluminescence method type), fast (between 17 minutes), they can be obtained in our own laboratory at local level - from the Emergency Department, can be printed easily, there is a unit memory to store patient data, it uses whole blood – 150 µL (no spin) as sampled from the patient without the need for tube collection.

Moreover, the device is extremely precise (CV <5%), quantitative results are obtained from the blood tests carried out at the same time, because it results in the same test / or up to 6 different assays for six patients at the same time. Such determinations can be made for 1 to 6 patients, making any combination of 1 to 6 tests required.

Presepsin determination by this method allowed risk stratification in criticc patients, monitoring of disease progression and very important, monitoring of the response to drug therapy and other measures (surgery, supportive treatment in the ICU, etc.).

As for forensic results by POCT, given that the sheets can be printed and attached to Emergency Department presentation sheets and general clinical observation sheets, these are of particular importance. It certifies permanent care of the patient under close monitoring of blood different parameters and not only those. With this type of equipment, we can quickly modify patient treatment in real time to correct the dysfunctions and inadequacies thus arisen.

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