HEPATORENAL DYSFUNCTION IN SEPSIS: EPIDEMIOLOGICAL, CLINICAL AND LABORATORY ASPECTS

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HEPATORENAL DYSFUNCTION IN SEPSIS, EPIDEMIOLOGICAL, CLINICAL AND LABORATORY ASPECTS (Abstract): The major impact of sepsis-induced multiple organ dysfunction on healthcare system in the European Union was estimated at 90.4 cases per 100000 inhabitants, compared to 58 per 100000 for breast cancer. The association of organ dysfunctions in terms of both the number of dysfunctions and the degree of organ dysfunction is the most powerful predictor of death in sepsis. Aim: To find medical and statistical correlations in hepatorenal dysfunction in sepsis patients. Material and Methods: This retrospective study included 117 patients diagnosed with sepsis at the Iasi Infectious Diseases Hospital, patients who presented liver/renal and other organ dysfunctions. The clinical, etiological, and laboratory data, and APACHE II prognostic scores were analyzed. The data were processed using SPSS version 16.0. Results: The etiological agents were Gram positive as well as Gram negative bacteria, and 40% of sepsis patients with hepatic/ kidney dysfunction presented hepatorenal syndrome. Conclusions: Over one-third of patients with sepsis-related hepatorenal dysfunction had a creatinine clearance of less than 30 ml/min, and we found statistical correlations between serum creatinine and APACHE II score. There were no statistically significant differences between the survival curves of patients with hepatorenal syndrome and those with sepsis-related hepatorenal dysfunction. Keywords: SEPSIS, HEPATORENAL DYSFUNCTION, KAPLAN MEIER CURVE

The major impact of sepsis-induced multiple organ dysfunction on healthcare system in the European Union was estimated at 90.4 cases per 100000 inhabitants, compared to 58 per 100000 for breast cancer (1). It is estimated that there are 1.8 million cases annually, but this figure reflects low recognition or diagnosis. Recent estimates show an incidence of sepsis in intensive care units of 0.25 to 0.38 per 1000 inhabitants, suggesting two million admissions to intensive care units (2, 3). Data are from intensive care units and research centers in UK Intensive Care National Audit and Research Centre (ICNARC) covering the last months of 2005 reported 8300 deaths from severe sepsis. Mortality rate from severe sepsis was estimated in many studies, ranging from 28% to 50% (4, 5, 6).

In the United States the incidence of severe sepsis is estimated to 300 cases per 100,000 inhabitants of which about half outside emergency units (7, 8). One in four patients who developed severe sepsis dies during hospitalization. Septic shock is as-
associated with the highest mortality rate, approaching 50%. The association of organ dysfunctions in terms of both the number of dysfunctions and degree of dysfunction is the most powerful predictor of death in sepsis. Epidemiological controversy arises when discussing about treated cases, since eligibility for treatment differs according to time and country, with different cultural perspectives on end-of-life, differences in access to emergency departments; level of health insurance other economic and cultural factors (7, 9).

Sepsis encompasses a tremendously heterogeneous group of patients with a great variability of underlying conditions, infection sites, with a multitude of microbial agents with high virulence and variations in concentration, and with differences in inflammatory response and immunological context. Sepsis can be caused by a small inoculum of etiologic agent in conditions of high pathogenicity or reduced host defense capacity. The inflammatory response may be excessive when the microbial toxin or microorganism is very aggressive, or when genetic predisposition leads to important changes at the level of cellular effectors involved in the inflammatory response (10).

MATERIAL AND METHODS
The study was conducted in the Iasi Hospital of Infectious Diseases and included patients diagnosed with sepsis in the interval November 2012 - April 2014. Data in their medical records and annexed documents were analyzed. All patients signed upon admission an informed consent for the use of their data for research purposes. This study was performed in compliance with the Declaration of Helsinki, and was approved by the Ethics Committee of the University of Medicine and Pharmacy of Iasi.

A number of 117 sepsis patients presenting hepatorenal dysfunction, hepatorenal syndrome (HRS), and other organ dysfunctions were included in the study. The demographic data (age, gender, origin), length of hospital stay, laboratory data, etiology, baseline and post-baseline laboratory data, APACHE II prognostic scores, past history of liver/kidney dysfunctions, disease improvement or progression to death were analyzed. The diagnosis of sepsis was made according to the definition of suspected or documented infection and presence of inflammatory systemic response syndrome (at least two of the following criteria: fever/hypothermia, tachycardia, tachypnea, and leucocytosis/leukopenia).

The diagnosis of severe sepsis referred to patients with the acute organ dysfunction: cardiac, renal, hepatic, respiratory and circulatory failure disseminated intravascular coagulation or shock. Biological samples were analyzed in the laboratory of bacteriology by direct examination, cultures, fixation method, and latex agglutination. We created an EXCEL database including the descriptive data and the qualitative and quantitative parameters, and used SPSS version 16.0 for data processing. The following tests were used: t student test, chi-square test, Pearson correlation for normally distributed variables, and Spearman rank-order correlation independent of data distribution types. When data were not normally distributed we used the Mann-Whitney test for comparing two sets of variables, the Pairwise Comparison test when sample sizes were small; Kruskal-Wallis test was used to compare multiple sets of data.
Hepatorenal dysfunction in sepsis: epidemiological, clinical and laboratory aspects

RESULTS

In age groups 50-70 and over 80 years there was a female prevalence; rural/urban distribution of the study patients was approximately equal.

The identified etiologic agents varied widely: methicillin-sensitive Staphylococcus aureus (MSSA), methicillin-resistant Staphylococcus aureus (MRSA), Staphylococcus epidermidis, Streptococcus spp., Enterococcus spp. as well as beta-lactamase producing and not-producing Gram negative bacilli: nonfermenting Gram negative bacilli, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.

Patients with hepatorenal dysfunction were predominantly referred from cardiology, diabetes, neurology and gastroenterology departments (fig. 1). At baseline the inflammatory syndrome was well represented, with an average of 13200 white blood cells/mm³ in the case of hepatorenal syndrome, average CRP level equal in patients with or without hepatorenal dysfunction, average fibrinogen level of 6.2 g/L in patients with hepatorenal syndrome compared to 5.8 g/L in those with hepatorenal dysfunction.

Only 40% of patients with hepatorenal dysfunction presented a hepatorenal syndrome (fig. 2), the average creatinine clearance rate in these patients as calculated by the Cockroft-Gault formula being 33 mil/min.

Over 37% of the patients had a creatinine clearance below 30% (fig. 3). Using the Kruskal Wallis test (equivalent to ANOVA), we found a statistically significant relationship between creatinine clearance values and the severity of sepsis calculated by the APACHE score (calculated \( p = 0.44 \)).
The outcome of patients with hepatorenal dysfunction was favorable in most cases (69%), sometimes requiring referral to other departments (10.2%) and less than one-third (29%) died (fig. 4).

**DISCUSSION**

Until 2006 definitions for HRS showed that it is a reversible functional kidney damage that occurs in patients with advanced liver cirrhosis or fulminant liver failure and is characterized by reduction in glomerular filtration rate and renal plasma flow in the absence of other causes of renal dysfunction (11). With the rise of knowledge, it was shown that the original definition lacked concision with respect to a large number of exclusion criteria, sepsis being one of them (12). Before revision, guidelines proposed, in 2007, the exclusion of bacterial infections for the HRS diagnosis (13).

The major mechanism of HRS consists of an extreme renal vasoconstriction caused by activation of Na retention and vasoconstrictor systems, resulting in a very low glomerular filtration rate (14). HRS type I occurs as a consequence of a severe reduction in the circulating volume caused on one hand by a major splanchnic vasodilatation and, on the other, by decreased cardiac output, this type of disorder being present in sepsis.

In our study, twenty-two percent of the patients with hepatorenal dysfunction received antibiotic therapy prior to admission, some of them having a change in their antibiotic regimen during hospital stay: most patients (73.9%) received a single antibiotic regimen, one third required only one change in their antibiotic regimen, while one patient received three antibiotic therapy schemes.

According to statistical analysis data, no statistically significant difference in the two functions defining the survival curve between the patients with hepatorenal dysfunction and hepatorenal syndrome was found.

**CONCLUSIONS**

Over one-third of the patients with sepsis-related hepatorenal dysfunction had a creatinine clearance below 30 ml/min, and we identified statistical correlations between serum creatinine and calculated APACHE II score.

No statistically significant differences were found between the survival curves Kaplan Meier of patients with hepatorenal syndrome and of those with sepsis-related hepatorenal dysfunction.

**REFERENCES**

Hepatorenal dysfunction in sepsis: epidemiological, clinical and laboratory aspects


DISCOVERY OF CLOSTRUBIN, AN ANTIMICROBIAL AGENT ISOLATED FROM ANAEROBIC BACTERIA

Genome analysis of Clostridium beijerinckii revealed several cryptic gene clusters for secondary metabolite biosynthesis. When cultured under various conditions, C. beijerinckii produced a novel metabolite - a deep purple pigment, named clostrubin which was further isolated and its structure elucidated. The pentacyclic polyphenol folds in a manner that forms a perifused ring system (benzo[al]tetraphene), unusual for natural products. This is the first reported aromatic polyketide from an anaerobic bacterium. The study demonstrated that clostrubin is a potent antibiotic with activity against various pathogenic bacteria, such as MRSA, VRE, and mycobacteria (MICs of 0.12-0.97 μM) (Pidot S, Ishida K, Cyriales M, Hertweck C. Discovery of Clostrubin, an Exceptional Polyphenolic Polyketide Antibiotic from a Strictly Anaerobic Bacterium. Angew Chem Int Ed Engl. 2014. doi: 10.1002/anie.201402632. [Epub ahead of print]).