Laboratory Parameters and Treatment Applied to Septic Patients

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Abstract

Systemic illness caused by microbial invasion of normally sterile parts of the body is referred to as "sepsis", which is an increasingly common cause of morbidity and mortality, particularly in the elderly, immunocompromised, and critically ill patients (Dellinger, 2013). Sepsis develops in 750,000 people annually, and more than 210,000 of them die in US. A cohort study shows that mortality ranged between 28.3 % and 41.1 % on different continents.

The aim of this study was to clarify septic patients' clinical course, laboratory parameters and to assign a therapy.

The retrospective analysis of 72 patients' medical records was carried out. The research included patients of both sexes and all ages hospitalised at Riga Eastern Clinical University Hospital inpatient "Gaiļezers" between 2011 and 2014. All the patients involved in the study had severe sepsis and at least one organ dysfunction.

Majority of patients – 67 (93.05 %) – had immunocompromised background – tumours, intra-abdominal infections, complicated soft tissue infections, cardiovascular, endocrine, lung, liver, kidney diseases, HIV, viral hepatitis and alcohol addiction. All patients, at the time of hospitalisation, had elevated C reactive protein (CRP).

In-hospital patients sought medical attention too late, and at a prehospital stage, no patients received antibiotic therapy. In-hospital patients had received a broad-spectrum of antibiotic therapy.

Keywords: septic patients, intensive care units, sepsis treatment, antimicrobial therapy.

Introduction

Derided from the Greek word *sipsi* (make rotten) sepsis is a syndrome associated with severe infection, typically pneumonia or gastrointestinal or urinary tract infection, and its successful treatment continues to represent a very important unmet clinical need. Causes thereof are heterogeneous, and its clinical features are diverse, making one of the most challenging syndromes both to recognise and to manage (Hall, 2011).

Sepsis is widespread among hospitalised patients worldwide. Severe sepsis and septic shock is a major cause of patient admission and mortality in intensive care units and the difficulty to diagnose the initial stage of the disease is a major obstacle to the reduction of mortality from sepsis. Patients

with sepsis spend longer in hospital, and longer in intensive care units than patients admitted for other reasons and a substantial proportion of these patients have long term functional, cognitive, and psychological deficits at one year (Iwashyna, 2010; Davydow, 2008).

In patients with severe sepsis, mortality remains higher than 25–30 %, and even 40–50 % when shock is present (Vincent, 2014).

Despite the advances in medicine, such as vaccination, antibacterial treatment options and acute patient care, mortality is high prom sepsis. No effective specific anti-sepsis treatments exist; therefore, management of patients with sepsis relies mainly on early recognition allowing appropriate therapeutic measures to be started rapidly, including administration of appropriate antibiotics, source control measures when necessary, and resuscitation with intravenous fluids and vasoactive drugs when needed.

Aim

The aim of the research was to evaluate the disease course of severe sepsis patients, indicators of laboratory analyses and applied treatment at Riga Eastern University Hospital clinical centre "Gaiļezers".

Material and Methods

The retrospective analysis of 72 patients' medical records was carried out, stratified by year of treatment outcome (dead/alive). The research included patients of both sexes and all ages hospitalised at Riga Eastern Clinical University Hospital inpatient "Gaiļezers" between 2011 and 2014. All the patients involved in the study had severe sepsis and at least one organ dysfunction. Blood test on sterility and identification of blood culture was performed for all patients.

The research was carried out with the approval of the ethics committee of Riga Eastern Clinical University Hospital "Gaiļezers".

Statistical methods. Data was described using means with standard deviations (SD) and median with interquartile range (IQR) for continuous variables and percentages for categorical variables. For the comparison of the study data, the non-parametric methods were used: Mann–Whitney U for continuous data and chi-square tests for categorical data. P value, less than $p < 0.05$, is accepted as statistically significant. Data statistical analysis was done in IBM SPSS Statistics.

Results

Summarising the results, 40 (55.6 %) patients involved in the study were men, 32 (44.4 %) were women. The age of patients ranged between 22 and 90. The average age was 63.4 (SD 15.9) years. Most patients 65 (90.3 %) were taken to hospital with medical emergency.

The average duration of the patient's illness and hospitalisation time was 5.6 (SD 8.2) days. Median 3.0 (IQR 2.0 to 5.0) days.

The study included 40 (55.5 %) retired persons, 9 (12.5 %) second group disabled people, 15 (20.8 %) working age patients, but not daily employed and 8 (11.1 %) daily employed patients.

From all 72 (100 %) patients included in the study, 67 (93.05 %) had immunocompromised background – tumours, intra-abdominal infections, complicated soft tissue infections, cardiovascular, endocrine, lung, liver, kidney diseases, HIV, viral hepatitis and alcohol addiction. 5 (6.9 %) patients were not diagnosed with related diseases.

All patients at the time of hospitalisation had elevated C reactive protein (CRP), ranging from 46.35 mg/L to 926.65 mg/L. More than a half of patients' 56 (77.7 %) CRP was above 259 mg/L. 60 (83 %) patients at the time of hospitalisation had elevated IL-6. Leukocytosis was diagnosed with 59 (81.9 %) patients. Leukopenia was diagnosed with 6 (8.3 %) patients. 32 (44.4 %) patients had elevated liver indicators (ALAT, ASAT). 39 (54.1 %) patients had elevated kidney indicators. Nevertheless, the renal

replacement therapy during hospitalisation was received by 13 (18.1 %) patients. For dead patients (n = 36.50 %) the renal replacement therapy was received by 25 % (p = 0.12).

None of the patients before hospitalisation had visited family doctor to get the necessary treatment.

All patients included in the study had severe sepsis and at least one organ dysfunction.

Plating of blood was positive in 32 (44.4 %) patients. Blood agent in culture grows – *Streptococcus* beta-haemolytic group B was 1 (3.1 %), *Escherichia coli* – 3 (9.37 %), *Staphylococcus epidermidis* – 5 (15.6 %), *Staphylococcus hominis* – 1 (3.1 %), *Staphylococcus aureus* – 7 (21.9 %), *Staphylococcus haemolyticus* – 1 (3.1 %), *Prevatella oralis* – 1 (3.1 %), *Streptococcus pneumonia* – 10 (31.3 %), *Klebsiella pneumonia* – 1 (3.1 %), *Clostridium difficile* – 1 (3.1 %), *Streptococcus* beta-haemolytic group A – 1 (3.1 %).

Evaluating the antibiotic therapy received by severe sepsis patients, results indicate that intravenous injection was most frequently prescribed – ceftriaxone 1 gram, tazocin (piperacillin and tazobactam) 4.5 grams, tienam (imipenem and cilastatin) 500 milligrams, meronem (meropenemum) 1 gram, metronidazol 500 milligrams, ciprofloxacin 200 milligrams.

Discussion

The sepsis is one of the most frequent reasons for hospitalisation in intensive care units worldwide. Early sepsis detection and timely treatment administration with appropriate antibiotics are the most important factors in improving the outcome of sepsis. However, initial sepsis clinical signs and symptoms are non-specific, creating the risk of late diagnosis. Our medical investigation also indicated that sepsis diagnosis was made too late, as long as patients were stationed after 5.6 days of sick days. None of the patients had turned to their family therapist with complaints before.

Surviving Sepsis Campaign (SSC) is an international programme that makes guidelines to improve the management of this serious clinical condition and to reduce the high mortality rates. The first SSC guideline which was published in 2004 classified the recommendations as resuscitation bundle including elements for first six hours resuscitation and management bundle including elements for first 24 hours management. The guideline was renewed in 2008. Many studies revealed that clinical implementation of these bundle elements improve the quality of sepsis care; reduce the hospital mortality. In 2012 the SSC 2008 guideline was updated and in 2015 updated again; recommendations classified as to be completed within three hours and to be completed within six hours (Tufan, 2015). Of note, the 6-hour bundle has been updated; the 3-hour SSC bundle is not affected.

To be completed within 3 hours of time of presentation[1]:

1) measure lactate level;
2) obtain blood cultures prior to administration of antibiotics;
3) administer broad spectrum antibiotics;
4) administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L. According to the guidelines, level of lactic acid was established within the first three hours for all the patients, samples of blood culture before the initiation of antibacterial therapy were also received and broad-spectrum of antibiotic therapy was ordered afterwards. Injection of 30 ml/kg crystalloid in case of hypotension was not investigated.

To be completed within 6 hours of time presentation:

1) apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mmHg;
2) in the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥ 4 mmol/L, re-assess volume status and tissue perfusion and document reassessment of volume status and tissue perfusion with: repeat focused exam (after initial fluid

[1] "Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings. Or two of the following: Measure CVP, Measure $ScvO_2$, Bedside cardiovascular ultrasound, Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge;

3) re-measure lactate if initial lactate elevated (Dellinger, 2013; The ARISE Investigators and the ANZICS Clinical Trials Group, 2014; Levy, 2014; Mouncey, 2015; Yealy, 2014).

Several studies show, and guidelines will, early initiation of antimicrobial therapy has reduced the duration of hospitalisation of patients and limiting the development of resistance to antibiotics (Angus, 2013; Van den Bosch, 2014).

Studies indicate that older patients, male gender, African Americans, patients with chronic health problems are particularly prone to the development of severe sepsis, so the prevention strategies should be targeted to these groups (Mayr, 2014). Our data indicated that most patients were in the age group between 60 and 79 (n = 32.44 %) and 20 (62.5 %) died. Severe sepsis occurs more often to patients with chronic obstructive pulmonary disease, tumours, chronic kidney, liver diseases and diabetes. Other risk factors that increase the possibility of developing sepsis are long-term care at care establishments, malnutrition, use of immunosuppressive medications, immunocompromised patients. Data of our investigation were similar to the worldwide data – 93.05 % of all patients involved in the investigation had immunocompromised immunological status and that is a significant risk factor. The significance on the relationship between socioeconomic status and blood stream infection has also been reported (Mendu, 2012). In our examination it was *Streptococcus pneumonia* that increased the most (31.3 %) to patients aged 60–79 years old. However, blood culture was mostly positive for less than a half of patients (44.4 %); it makes diagnosis and treatment of sepsis even harder.

Chronic obstructive pulmonary disease exemplifies a chronic health disorder that predisposes patients to increased risk of severe sepsis. The risk arises because of increased risk of lower respiratory tract infection and, if infection is present, an increased risk of organ dysfunction, such as acute respiratory failure, because of decreased physiological reserve. Many other chronic diseases, such as cancer, cirrhosis, AIDS, are associated with an increased risk of sepsis or organ dysfunction (Mrus, 2005). Social behaviours are also associated with sepsis, with an increased incidence and worse outcomes in people who misuse alcohol (O'Brien, 2009) and an increased risk of death from pneumococcal pneumonia in smokers, despite sparse data on the effects of smoking in sepsis.

Diagnostic considerations – unlike troponin for acute coronary syndrome or a radiograph for fracture, sepsis does not have only one diagnostic test and instead is a clinically defined syndrome subject to revision (Bone, 1992). The prodrome of sepsis can be non-specific or brief and the short term mortality high.

Diagnostic microbiology stands at the epicentre of the tests for sepsis in patients. Microbiological studies for the detection of bacteria or fungi in blood, blood fluids, or relevant tissues continue to rely for the most part on conventional culture-based systems, which remain the gold standard. Blood cultures are positive in 30–40 % of patients with severe sepsis and septic shock (Bochud, 2004). In our study we were similar, blood plating was positive in 32 (44.4 %) patients.

Recently, a quantity of publications have revealed that genetic variation especially single nucleotide polymorphism of cytokines in the innate immune system may influence the risk of sepsis. Among these cytokines, Interleukin-6 (IL-6) is one of the most important members which may be associated with sepsis risk and outcome. Some studies have indicated that IL-6 may play a key role in the inflammatory response to microbial invasion (Gao, 2015). Our data indicated a heightened level of IL-6 for a majority of patients – 83 %. Previous studies revealed that high IL-6 level was associated with increased severe sepsis mortality and risk.

Nowadays, clinicians have greatly improved care for septic shock. Urgent resuscitation using intravenous fluids and vasopressors as well as rapid administration of broad spectrum antibiotics are probably the most basic and universally accepted interventions. Various trials have compared different types of vasopressors, associations of vasopressors and inotropes, and pressure targets. End goal-directed therapy

algorithms are designed to optimise oxygen delivery by use of fluids, vasopressors, inotropes, and blood products. Patients who have a poor response to resuscitation and patients with known severe ventricular dysfunction might merit advanced hemodynamic monitoring (Gelinas, 2016).

Prompt initiation of appropriate antibiotics is crucial. The SSC guidelines (Angus, 2013) suggested that antibiotics should ideally be started within one hour of the diagnosis of severe sepsis or septic shock. But our study, it should be taken into account that in this case at the moment of hospitalisation, sepsis was not developed or proven yet to all the patients, because for diagnosing sepsis, by definition, a number of physiological indicators and the results of laboratory investigations, as well as the identification of focuses of infection that caused these modifications are required. And it was the possible reason for dilatory diagnosis of sepsis in other therapeutic departments (not emergency department), or at prehospital stage. Because early initiation of antimicrobial therapy reduces bacterial load and hence the mortality of septic patients.

The empiric antibiotic regimen should be broad enough to cover all likely pathogens and be guided by local epidemiological data and the medical history of the patient, including previous infections, susceptibility profiles of colonizing microorganisms, and recent exposure to antimicrobial drugs. Pharmacokinetic and pharmacodynamics considerations related to appropriate tissue penetration and the presence of hepatic or renal dysfunctions should also be taken into account. Drug clearance of mainly renally eliminated drugs, and thus the required dose can differ up to 10-fold due to the variability in renal function in patients with severe infections. Effect of antibacterial therapy was possibly affected also by the dysfunction of kidney, established by our investigation in 54.1 % of cases and hepatic damage, established in 44.4 % of cases.

The empirical antibiotic regimen could rely on either one antibiotic or on two or more antibiotics. Monotherapy consists typically of an extended-spectrum penicillin with or without a beta-lactamase inhibitor, a third or fourth generation cephalosporin, or a carbapenem, Combination therapy is usually an association of a beta-lactam with an aminoglycoside, a fluoroquinolone, an anti-Gram-positive drug, or an antibiotic active against multiresistant Gram-negative bacteria (Ferrer, 2014).

In the last decade much effort was put in the development of early risk scales, to recognize sepsis patients timely, but it is still necessary to improve patient recognition and response. Basically, there are necessary such scales that can be used outside intensive care units, directly in the emergency or hospital wards. But in daily routine such scales are not applied, because they are complicated and only provided for particular group of patients. There are applied many scales in the world, for example, APACHE (Acute Physiology and Chronic Health evaluation), SOFA (Sepsis-related Organ Failure Assessment), MODS (Multiple Organ Dysfunction Score), RAPs (Rapid Acute Physiology Score), which are used to divide patients into categories after severity of disease, indicating the level of organ dysfunction and predicating potential risk of death. Therefore, the aim is to recognise patients with systematic inflammation timely, before it transforms, endangering tissues and organs. The mortality of sepsis correlates with disease severity, it increases from systemic inflammatory response syndrome (SIRS) to septic shock; therefore, appropriate beginning of treatment is important. However, investigations of one ideal scale are being continued worldwide.

Conclusions

After the results of laboratory analyses, we can conclude that patients enter hospital too late and consequently, therapy is not initiated on time. Blood culture was mostly positive for less than a half of patients (44.4 %); it makes diagnosis and treatment of sepsis even harder. But all patients received broad-spectrum of antibiotic therapy, as stated in the guidelines.

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