

## Urosepsis

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### New Definition of Sepsis and Septic Shock

Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection”, while septic shock is defined as a “subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality” [1]. These new definitions were developed by international consensus of scientific societies and published in SEPSIS-3 document (The Third International Consensus Definitions for Sepsis and Septic Shock). It was developed in a response to growing number of new researches and retrospective analysis about sepsis [1].

First attempts of defining criteria of sepsis and its classification as systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock search took place in 1991 and were updated in 2001. This classification is now outdated because criteria of SIRS, such as: [1]

- Body temperature over 38°C or under 36°C;
- Heart rate over 90 per minute;
- Respiratory rate over 20 per minute or PaCO<sub>2</sub> < 32 mmHg ;
- The number of leukocytes in blood > 12000/mm<sup>3</sup> or < 4000/mm<sup>3</sup>, or presence of over 10% immature neutrophils were met by almost half of patients on some stage of hospitalization regardless of its cause and indicate merely immune systems mobilization [2]. These criteria’s are not precise enough to facilitate patient’s prognosis and are no longer recommended in sepsis diagnostics. Previous classification was also simplified by removal of severe sepsis.

### Epidemiology and Causes of Urosepsis

Sepsis is the most frequent cause of death due to infection [1]. It affects millions of people in the world every year and its frequency of occurrence increases because of aging of population

with additional comorbidities. It affects more often men than women, patients from extreme age groups, with diabetes or undergoing immunosuppression therapy. About 30% of patients admitted to intensive care units have sepsis. Hospital death rate in sepsis with Sepsis-Related Organ Failure Assessment (SOFA) score  $\geq 2$  is 10%, and 40% in septic shock. [3]. The most common cause of sepsis is respiratory tract infection, followed by abdominal infections and genitourinary tract infections. The most frequent pathogens causing development of sepsis are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*. The number of fungal infections is also increasing [4,5]. Urosepsis is a consequence of genitourinary tract infection, most commonly caused by gram-negative bacteria such as *Escherichia coli* (52%), *Proteus* spp., *Enterobacter* spp., *Klebsiella* spp., *Pseudomonas aeruginosa*. It is less often caused by gram-positive bacteria and fungi. Obstructive uropathy which often can lead to urosepsis is the leading cause of urosepsis. There are many causes of obstructive uropathy, for example urolithiasis, prostatic adenoma, tumors, pregnancy, trauma, congenital diseases, radiation therapy on pelvic area in the past, neurogenic bladder or urinary catheters [7-9]. Mortality in urosepsis is lower than in other causes of sepsis [6], most probably because of minimally invasive techniques used for dealing with obstructive uropathy [7]. In the GPIU (eng. Global Prevalence of Infections in Urology) study annual studies so far, 856 urology units in 70 countries have participated, involving a total of 27 542 patients. The initial findings of the GPIU studies showed that the HAUTI (eng. Health care-associated urogenital tract infection) prevalence was 11%. In the overall study, the most frequent HAUTI forms were asymptomatic bacteriuria (29%), cystitis (26%), pyelonephritis (21%), and urosepsis (12%) [10].

### Pathophysiology of Organ Failure

Every patient with urinary tract infection symptoms can develop organ failure and should be diagnosed in its direction.

Similarly, infection should always be considered as reason of organ failure [1]. Formerly it was assumed that organ failure is caused by uncontrolled and impaired pro-inflammatory response, but currently it is known that its symptoms are effects of both pro-inflammatory and anti-inflammation reactions taking place at the same time. Pathogen-Associated Molecular Patterns (PAMPS) are molecules expressed by pathogens which initiate inflammatory process. Examples of PAMPS are lipopolysaccharide, peptidoglycan, DNA, RNA, lipoteichoic acid. They bind with Pattern Recognition Receptors (PRR) of immune cells e.g. Toll-like receptors on neutrophils surface. Afterwards they activate immune cells and start pro-inflammatory response. Inflammatory response and tissue damage cause a release of various agents - heat shock proteins, fibrinogen, hyaluronic acid, nucleic acids from host's cells [11]. These agents can also be released in case of damage without infection - during trauma, burning, acute pancreatitis. That's why mechanisms of organ failure development are similar in sepsis and in non-infectious diseases [5]. As a result of activation of immune cells inflammatory process develops and activates more leukocytes, inflammatory cytokines like Tumor Necrosis Factor- $\alpha$ , interleukin-1 are released, complement system in being activated, reactive oxygen species and proteases are released [11]. All those mechanisms activated to stop the spread of pathogens lead also to host's cells damage which can in turn cause organ failure.

In septic response multiple anti-inflammation reactions are activated at the same time - expression of IL-4, IL-10, neuroendocrine regulation, inhibition of proinflammatory gene response and apoptosis of immune cells. Anti-inflammation reactions are responsible for increasing susceptibility for secondary infections and late mortality in sepsis [5,11]. In sepsis procoagulant mechanisms outbalance anticoagulant. One of acute-phase proteins is the tissue factor, which takes part in the coagulation process. Moreover, in sepsis not only fibrinolysis but also anti-aggregation processes are reduced. Diffused process of

coagulation can at first lead to changes in coagulation lab tests - most often thrombocytopenia - and in the end to Disseminated Intravascular Coagulation (DIC). Blood clots formed in capillaries lead to local hypoxia of tissues and further increase the risk of organ failure.

## Symptoms and Diagnostics

Urinary Tract Infection (UTI) may manifest itself with slight symptoms at first, but depending on patient and inflammation process it can develop into sepsis or septic shock relatively quick [6]. In order to diagnose it urine culture is needed. The factor differentiating sepsis from infection is impaired host response leading to organ failure. Clinical manifestation of sepsis is affected among others by patient's age, comorbidities, chronic diseases, medicines taken, past surgical interventions as well as factors related to pathogen itself [1]. Sepsis could cause a failure of any organ. Respiratory system failure leads to hypoxia, increased respiratory rate, inflammatory infiltration and development of Acute Respiratory Distress Syndrome (ARDS). Circulatory system failure results in excessive vasodilatation with hypotension leading to peripheral tissues hypoperfusion and raised lactate levels in blood. Kidney failure manifests itself with oliguria, raised creatinine levels and development of acute renal injury (prerenal at first). Nervous system disorders consist of disturbances of consciousness, delirium, polineuropathy. Other organ failure symptoms include intestinal paralysis leading to ileus, decompensated diabetes, liver damage at first manifested in enzymes levels increase, adrenal gland insufficiency and thyrotoxicosis [5]. There is no golden standard for sepsis diagnosis [1]. The latest guidelines recommend applying Sequential Organ Failure Assessment (SOFA) score to patients with infection symptoms or those with suspected infection. It is most often used on intensive care units. It requires evaluation of respiratory, cardiovascular and coagulation systems as well as kidney and liver parameters (Table 1).

System/points	0	1	2	3	4
Respiratory PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg (kPa)	≥ 400 (53,3)	< 400 (45,3)	< 300 (40)	< 200 (26,7) mechanically ventilated	< 100 (13,3) mechanically ventilated
Coagulation Platelets, x10 <sup>3</sup> /μL	≥ 150	< 150	< 100	< 50	< 20
Liver Bilirubin mg/dL (μmol/l)	< 1,2 (20)	1,2-1,9 (20-32)	2,0-5,9 (33-101)	6,0-11,9 (102-204)	> 12 (204)
Cardiovascular administration of vasopressors required μg/kg/min for ≥ 1h	MAP ≥ 70 mmHg	MAP < 70 mmHg	dobutamine or dopamine < 5	Dopamine 5,1-15 or norepinephrine or epinephrine ≤ 0,1	norepinephrine lub epinephrine > 0,1 lub dopamine > 15
Nervous Glasgow coma scale	15	13-14	12-Oct	9-Jun	< 6

Kidneys Creatinine mg/dl (μmol/l)	< 1,2 (110)	1,2-1,9 (110-170)	2,0-3,4 (171-299)	3,5-4,9 (300-440) or urine output < 500ml/d	> 5,0 (440) or urine output < 200ml/d
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**Table 1:** SOFA scale.

The increase in SOFA scale  $\geq 2$  allows identification of organ failure and sepsis diagnosis in patients with symptoms of infection. When there is no way to evaluate the above parameters, simplified version of SOFA - quick SOFA (qSOFA) can be used to urgently evaluate the prognosis of patient suspected of sepsis. Its criteria consist of:

- I. Altered mentation (GCS < 15)
- II. Systole blood pressure < 100 mmHg
- III. Respiratory rate  $\geq 22$

Patients fulfilling 2 of 3 criterias are at risk of being admitted to intensive care unit for over 3 days and have higher risk of death. Such patients should be further diagnosed to check for organ failure (blood tests such as: arterial blood gases, lactate level in the blood, serum level of urea, creatinine with glomerular filtration rate, bilirubin, alanine transaminase, aspartate transaminase, coagulation) and for growth of inflammation process (leukocytes level in blood morphology, C-reactive protein blood level, procalcitonin level) [12]. Patients should also be checked in full SOFA scale. Therapy should be started or current one escalated. The frequency of vital signs (heart rate, respiratory rate, blood pressure, temperature, Arterial oxygen partial pressure, diuresis) monitoring should be increased. Patients admission to intensive care unit should also be considered [1]. Symptoms such as renal colic, urine stagnation, dysuria, prostate or scrotum pain indicate that sepsis could have been triggered by genitourinary tract infection [13]. Aside of urine culture, ultrasound examination, computed tomography and prostate examination can be used to determine the cause [8,13]. Septic shock should be diagnosed in patients requiring vasopressors to maintain mean arterial pressure (MAP)  $\geq 65$  mmHg and those with lactates level > 2 mmol/l (18 mmol/dl) despite having the vascular bed filled with fluids.

## Treatment

It is important to diagnose the patient and apply proper treatment as soon as possible after symptoms appear. Sepsis should be treated on pair with medical emergencies such as cardiac arrest, stroke or multiple trauma, because untreated it is as serious threat to patient's life. Preliminary procedure includes fluid resuscitation, rapid antibiotic administration and control of source of infection. One of the most important actions recommended by Surviving Sepsis Campaign guidelines from 2016 is early fluid resuscitation, which is applied to prevent hypotension and hypoperfusion. Infusion

of 30 ml per kg of crystalloids is recommended during the first three hours, with continuous evaluation of hemodynamic effects. In case of maintaining hypotension, norepinephrine is used as a catecholamine of choice. In a situation of inefficiency of reaching Mean Arterial Pressure over 65 mmHg vasopressin and epinephrine may be added. Administering 200 mg of hydrocortisone could be taken into consideration when MAP > 65 mmHg still can't be reached [14]. At least two blood cultures and urine culture should be obtained before administering antibiotic, but it shouldn't delay antimicrobial therapy. Broad spectrum antibiotic should be administered intravenously during the first hour after diagnosing sepsis, while best results are achieved after administering them in the first 30 minutes. Antibiotics recommended for patients in serious condition include piperacillin with tazobactam, III generation of cephalosporin (especially one active against *Pseudomonas aeruginosa*- ceftazidime) and carbapenems with or without aminoglycoside. If antibiotic is ineffective after 48-72 hours, it should be changed following pathogen identification. In case of septic shock two antibiotics with different way of action are recommended. Patients with long term urinary catheters, nephrostomy, UTI in past medical history, recent hospitalization or antibiotics intake are at risk of being infected with multidrug resistant bacteria and it should be taken into consideration while choosing antibiotic. SCC guidelines suggest that effective antibiotic therapy (e.g. based on reducing procalcitonin level) in patients with urosepsis could take less (< 7 days) than in other causes of sepsis. Daily evaluation of treatment is recommended, because prolonged unnecessary antibiotic therapy increases the risk of acquiring drug resistance by microorganisms, exposes patient to coinfections e.g. with *Clostridium difficile* and increases death risk [14]. It is recommended to analyze infection's source early. After stabilizing patient's state and no later than 6-12 hours, necessary interventions such as abscess drainage, renal pelvis decompression and relief of urinary tract obstruction should be performed, preferring a method the least aggravating to the patient [14].

Sepsis is one of the main reasons of acute kidney injury. Maintaining MAP > 65 mmHg with adequate fluid therapy and vasopressors is the most important factor maintaining renal perfusion. Time of initiating renal replacement therapy is not yet defined in recommendations. While oliguria and raised creatinine level by themselves do not indicate the need for a hemodialysis, in the case of persistent oliguria with fluid overload symptoms, resistant to treatment hyperkalemia and metabolic acidosis, renal replacement therapy should be started. The therapy may be carried

out in a continuous or intermittent way [15]. Hyperglycemia >180 mg/dL, hypoglycemia and significant variation in glucose levels are connected with higher mortality. Therefore, in case of glucose levels over 180 mg/dL insulin pump infusion with glycemia control every 1-2 hours should be applied, and afterwards repeated every 4 hours to avoid hypoglycemia [16,17]. In case of respiratory failure mechanical ventilation may be necessary. Lung protective ventilation with tidal volumes up to 6 ml per kg, positive end expiratory pressure over 5 cm H<sub>2</sub>O, plateau pressure up to 30 mH<sub>2</sub>O, head elevation between 30-40 degrees and reduction of sedatives are recommended in intensive care units patients with organ failure are sedated if necessary. Propofol, benzodiazepines and opioids are the most commonly used drugs.

## Summary

Creation of guidelines about identifying and treating patients with sepsis has increased the awareness of the problem among healthcare providers. Early adoption of recommended procedures and hospitalization in ICU have a significant effect in reduction of mortality in urosepsis.

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