

Community-acquired pneumonia as a cause of sepsis

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Introduction

Sepsis is an infectious agent attacking (invading) the organism, the immune response of the organism, the consequence of the cumulation of complex interaction developing between the inflammatory and coagulation systems [1-6]. The fundamental cornerstone of the determination of sepsis is the assumed or proved infection and the systemic inflammatory response reaction of the organism, (SIRS=systemic inflammatory response syndrome) accompanied with symptoms and clinical signs of fever, tachycardia, tachypnoea, hypotension and leucocytosis [1,7,8].

The characteristic of *severe sepsis* is multiorgan dysfunction associated with sepsis (MODS=multiorgan dysfunction syndrome) due to the microcirculation disfunction of the individual organs, accompanied with clinical signs of decreased consciousness, oliguria, icterus, lactate acidosis, thrombocytopenia and laboratory differences [5,6,9,10]. When severe sepsis is accompanied with expressed hypotension (systolic value $RR < 90$ Hgmm or arterial mean pressure drops by 40 Hgmm) despite of adequate fluid resuscitation, then we speak of the development of *septic shock* (infection+SIRS+hypoperfusion+hypotension) [3,4,6,10].

Assessment of the characteristic clinical symptoms (high fever or hypothermia, tachycardia, tachypnoea, decreased consciousness, oligoanuria, diarrhea, icterus, thrombocytopenia, acute DIC) plays very significant importance in recognition of the sepsis in the right time: because early diagnosis of the sepsis gives the chance of full recovery for the patient [1]. Based on the data of the literature, in case of goal-directed treatment in the early phase of the sepsis lethality is about 10-15 %, while in severe sepsis 20-30% and in septic shock it is around 40-70 % [11].

Knowledge of the *predisposing diseases (comorbidity)* is of great assistance in recognizing of the clinical symptoms: chronic alcoholics, patients suffering from diabetes mellitus and hepatic cirrhosis, those lastingly treated with steroids, patients with reduced protective response (patients treated with cytotoxic chemotherapy, those suffering from malignant haematologic disease, transplanted and HIV positives), people permanently tied to bed, and especially patients in a phase following stroke are faced with increased risk [5,10]. The different statistical data prove that sepsis develops in clinical practice most often in case of lasting use of catheter, wound infection, urogenital infection, soft tissue infection, intraabdominal infection *mainly as a result of the infections in the lower respiratory tract (pneumonias)* [3,4,5,11]. Sepsis developing as a consequence of peritoneal infections and pneumonias involve high mortality rate because of the frequent multi-organ disfunctions [11].

During retrospective examination of many patients with pneumonia we have analysed the frequency of the development of sepsis, the predisposing factors, the characteristic clinical, laboratory

and radiologic differences, concerning also certain features of the prehospital disease phase. We deal with the importance of the prognostic factors of pneumonias in our work (severity indices) as well as the fundamental issues of the pathomechanism of sepsis.

Patients and results

In the period between 2012 and 2017 we have diagnosed community-acquired pneumonia in 1654 patients (CAP=community-acquired pneumonia) on the basis of the characteristic clinical symptoms, laboratory features and radiological differences. The detailed laboratory examinations included red blood ESR, CRP and D-dimer, quantitative and qualitative blood parameters, determination of serum electrolytes and blood glucose. Bi-directional chest X-ray record and ECG was made in each case, and oxygen saturation was measured (with a pulse oximeter). In case of 90 % or lower oxygen saturation also blood gas determination was performed. In 192 (11.6%) out of the 1654 CAP cases clinically severe pneumonia was diagnosed. 32 patients of them were transferred directly after the first examination into the Central Intensive Care Department of our hospital, because we have noticed symptoms referring to severe inflammation (high fever, tachycardia, tachypnoea, leucocytosis) together with the dysfunctions characteristic for septic shock (hypotension, arterial hypoxaemia, oligo-anuria, metabolic acidosis).

The other patients with clinical symptoms of sepsis (n=160) (9.6%), who did not show the symptoms of severe sepsis or septic shock, were kept and treated at our department. We have summarized the general clinical symptoms of septic patients in Table 1. The most frequent are fever, cough, pain in the chest and dyspnoea. Existence of the general symptoms (weakness, malaise) is very characteristic. Table 2 includes the characteristic clinical difference and the laboratory values.

Table 1. General clinical symptoms in CAP* leading to the development of sepsis (n=160)

Age	64.4 years (43-79)
Sex	male: n=81, female: n=68
Fever	n=146
Pain in the chest/pleural	n=88
Cough	n=106
Dyspnoea	n=124
Purulent expectoration	n=66
General symptoms (weakness, malaise)	n=135
Decreased consciousness	n=38

*CAP= community-acquired pneumonia)

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Received: March 07, 2019; **Accepted:** April 09, 2019; **Published:** April 12, 2019

In majority of our patients we noticed tachycardia, tachypnoea, hypotension, reduced arterial hypoxaemia, leucocytosis and increased blood glucose and urea-nitrogen level. Most of our patients showed toxic granulation in the granulocytes.

In majority of the cases multilobe localization, massive alveolar coverage was seen on the bidirectional X-ray records (Table 3) and in almost 50 % the radiological difference was bilateral. Existence of chest fluid collection and cavitation is also frequent. Despite of beginning goal-directed treatment immediately we have noticed progressive radiological difference in case of 29 patients, that is 48–72 hours after the X-ray record new abnormal radiological signs (cavitation, pleural fluid in more lobes) occurred.

Studying the history of our patients in respect of the presence of other diseases (comorbidity) (Table 4). It can be stated that associated diseases can be shown in almost two-third of the cases, most frequent of them are COPD, diseases of the cardiovascular system and malignant diseases.

More than 90 % of our patients suffering from CAP leading to sepsis belonged to the severe form of the disease: to risk groups IV and V as per the pneumonia severity index (PSI) [12,13]; and based on the CURB-65 severity score [14,15] all of them belonged to the category V.

It must be outlined from the characteristics of the prehospital period that the diagnosis of pneumonia occurred in about 70 % of the

remissions, but sepsis was indicated in no cases. Chest X-ray record was made in more than 50 % of the patients with pneumonia (92 patients). Treatment with antibiotics at home: most often amoxicillin and clavulanic acid medicines were administered and only a few patients received medicines from the macrolide group. None of the patients received combined treatment with antibiotics. Remarks as to the severity of the pneumonia were not found on any of the remissions.

Discussion

Sepsis is a cumulation of complex interactions developing between the infective microorganisms and the immune, inflammatory coagulation system of the organism [1]. Both the response reactions of the organism on the infection and the characteristics of the microorganisms causing the infection play important role in the development of the sepsis [1,3,11]. The pathogens do not directly induce sepsis, but by affecting macrophages, monocytes, leucocytes and endothelium they promote increased production and release of endogenous mediators (proinflammatory, inflammatory, anti-inflammatory cytokines) [3-6,8,10,11].

Microvasculature of the vital organs is damaged in sepsis directly and indirectly and as a result of the co-effect of the pathogen microorganism and the complex response reactions of the organism the final result will be the development of the multi-functional disorder (MODS) [1,3,8-10].

Gram-positive, Gram-negative bacteria, viruses and fungi have uniform molecular pattern (pathogen-associated molecular pattern), which are recognized by the “toll-like receptors” (TLRs) on the surface of the immune cells of the organism and bind to them [1,3,9]. [Similar receptors are found on the surface of the macrophages and B-lymphoid cells, as in drosophila, that is why are these receptors marked “toll-like receptors”=TLRs (3)]. Endotoxin of *lipopolysaccharide (LPS)* content of the Gram-negative bacteria and the *peptidoglycan* participating in the cell membrane of the Gram-positive bacteria are considered to be the main monocyte-, macrophage activator [3,9]. LPS making a complex with the LPS transporting protein produced in the liver (lipopolysaccharide-binding protein=LBP) (LPS-LBP complex) binds to the CD14 and TLR-4 receptors on the surface of the macrophages and monocytes [1,3,5]. Peptidoglycan endotoxin in the cell membrane of the Gram-positive bacteria binds to the TLR-2 receptors of the immune cells. The activated TLR-2, TLR-4 receptors activate the nuclear factor κ B through the intracellular signal transmission system, and it induces—getting from the cytoplasm to the nucleus—the transcription of the immune modulatory cytokines (TNF- α =tumor necrosis factor α IL-1 β =interleukin-1 β , IL-10=interleukin-10.)

Proinflammatory cytokine activation has double effect: on the one hand it activates adaptive immunity and as a result, different mediators (prostaglandins, leukotrienes, proteases) are released and on the other hand it induces direct and indirect damage to the microvasculature of the organism [1]. The proinflammatory cytokines exert favourable influence on the neutrophil leukocytes, making them apted to destroy the microorganisms. However, the mediators released from the neutrophil leucocytes have endothelium damaging effect, they improve permeability of the endothelium, thus fluid rich in protein gets into the interstitium of the lung and the other organs, thus damaging their function [1].

The activated endothelial cells fulfil essential pathogenetic role in the development of septic shock, since mediators of vasodilator effect (nitrogen-oxide) are released from them [1].

Table 2. Characteristic clinical differences and laboratory values in CAP leading to the development of sepsis (n=160)

Fever (°C)	38.8 (37.8-39.4)
Heart rate/min	114 (92 – 134)
Systolic blood pressure (Hgmm)	109 (72 – 128)
Diastolic blood pressure (Hgmm)	72 (64 – 88)
Respiratory rate/min	30 (22 – 46)
SpO2 (%)	82 (76 – 89)
O2 partial pressure (arterial) (Hgmm)	79 (68 - 89)
CO2 partial pressure (arterial) (Hgmm)	39 (32 – 47)
Blood glucose level (mmol/l)	10.2 (6.8 – 13.6)
Serum urea-nitrogen (mmol/l)	14 (9.6 – 18.8)
White blood cell number (G/l)	13.6 (10.2 – 17.0)
Blood culture positivity	21

Table 3. Differences showed on chest X-ray records in CAP leading to the development of sepsis (N=160)

Unilateral, involvement of one lobe pulmonis	n=20
Unilateral, involvement of more lobes pulmonis	n=69
Bilateral, involvement of more lobes pulmonis	n=81
Full unilateral coverage	n=29
Existence of pleural fluid	n=59
Cavitation	n=28
Progressive radiological differences	n=29

Table 4. Disposing (comorbid) basic diseases in CAP leading to the development of sepsis (n=160)

Cardiovascular origin	n=29
Chronic alcoholism	n=6
COPD	n=39
Malignant basic disease	n=12
Diabetes mellitus	n=8
Chronic liver disorder	n=9
Chronic renal disease	n=6
Neurological disease	n=10
Previous steroid treatment	n=12

The B-lymphoid cells (NK=natural killer cells) being active due to antigen-recognition of the pathogens participate in the specific humoral and cell-mediated immunity by their immunoglobulin secretion [1].

Type 1 helper cells (Th1) from the T-lymphoid cells are proinflammatory cytokines (TNF-, IL-1), while the Th2 helper cells (CD4+) perform secretion of the anti-inflammatory cytokines (IL-4, IL-10) [1,9]. During sepsis fundamental changes go on in the balance situation of the *procoagulant-anticoagulant system* of the organism. Due to the expression of the tissue factor the coagulation “cascade” system is activated in the damaged and activated endothelium, and as a result, disseminated arterial thromboses develop, and the interaction between fibrine and the thrombocytes results in the development of microvascular thromboses [1]. Reduced or inhibited operation of the anticoagulant factors (protein-C, protein-S, antithrombin III) further increase the predisposition of the thrombosis [1]. The diffuse thromboses developing in the microvasculature of the vital organs significantly contribute to the development of multi-organ functional disorder [1,3,5]. Those clinical symptoms (Table 5) can be derived from the pathogenesis of the sepsis whose recognition in good time and beginning of the goal-directed therapy (at least within 6 hours) significantly improve the life chances of the patients [2,9]. In case of goal-directed therapy used at the beginning of the sepsis lethality is between 10–15 %, in severe sepsis it is 20-30 %, while in septic shock it is between 40 and 70% [9].

Profound suspicion of the development of sepsis can be considered in case of each patient, who have high fever (more rarely hypothermia), tachypnoea, tachycardia, hypotension and decreased consciousness [1,3,9].

In case of elderly and malaise patients decreased consciousness may be the single clinical “indicator” symptom in sepsis (Table 5) Out of the laboratory values (Table 5) the increased CRP, leucocytosis, (more rarely leukopenia), immature myeloid precursors in peripheral blood and in the granulocytes the presence of toxic granulation and thrombocytopenia can be outlined. Often proteinuria can be noticed in the urine, in the beginning period of the sepsis respiratory alkalosis, then metabolic acidosis develops together with arterial hypoxaemia, icterus and renal function disorder. In majority of the patients moderate increase is characteristic in the blood glucose, in patients suffering from diabetes mellitus severe metabolic disorder may develop [1,3,4,9].

Arterial hypoxaemia, renal function damage, metabolic acidosis, mental disorder, hyperglycaemia, icterus symptom group can be evaluated as the sign of multi-organ disorder (MODS) [4,8-10].

By determining plasm procalcitonin we can separate systemic bacterial infection from local infections, and other, non-infectious diseases with fever (autoimmune diagnoses). In sepsis, especially high plasm procalcitonin level can be measured; the gradually decreasing value indicates effectiveness of the treatment [3,4,6,8-10].

In determination of the severity of the sepsis and in respect of the prognosis of the process mainly APACHE I-II (Acute Physiology and Chronic Health Evaluation) score and SAPS I-II (Simplified Acute Physiology Score) are used, which determine very detailed respiratory, renal, hepatic, cardiovascular, haematologic and neurologic clinical symptoms and laboratory values [16-19]. Determination of the severity (risk) grade of pneumonias (CAP) is very important, because the doctor performing the first examination of the patient can decide on treatment of the patient at home or about the required medical treatment in the hospital. Further analysis of the risk factors helps in deciding whether treatment at the intensive care department is

needed. In case of considering the factor of severity the chances of developing progressive forms of the disease can be answered with good probability, thus the prognosis and mortality may also be concluded [1,3,4,5,8].

Pneumonia severity index (PSI) has been used from the earliest. This considers simultaneous presence of comorbidity, physical status of the patient and the essential laboratory and radiological diagnostic reports (Figure 1). Based on the detailed data and the differences the patients with pneumonia can be enlisted into five severity classes [12,13]. Despite the fact that PSI is the most validated severity “score” in CAP cases [7] simpler determinations have become practical in the recent years: in addition to CURB (confusion, urea nitrogen, respiratory rate, blood pressure) CURB-65 supplemented with the age of 65, and the very easy CRB-65 [14,15] have become approved in the everyday clinical practice (Table 6). Some clinical examinations have been made about the comparison of the most accepted and used severity indices (PSI, CURB-65): and it can be seen from the summary table of the advantages and disadvantages (Table 7) that PSI has high predictive value mainly in case of the low-risk, low mortality CAP groups and CURB-65 has determining importance mainly in severe CAP cases of the old age group [8,12,13,15,20-23].

Table 5. Clinical symptoms and laboratory differences in sepsis

Clinical symptoms	Laboratory differences
High fever > 38.6°C	Leucocytosis > 12000/mm ³
Hypothermia < 36°C	Leukopenia < 4000/mm ³
Tachypnoea > 90/min	toxic granulation of granulocytes
Respiratory rate	thrombocytopenia
Hypotension:	KIDNEY: proteinuria
Systolic RR < 90 Hgmm	urea-nitrogen level [^]
Diastolic RR < 70 Hgmm	METABOLISM: blood glucose level [^]
Tachycardia > 90/min	metabolic acidosis
Heart rate	HAEMOSTASIS: acute DIC
	LIVER: icterus
	CRP and plasm procalcitonin [^]
	ARTERIAL HYPOXAEMIA

Table 6. Pneumonia risk groups according to the CURB severity grades (on the basis of Lim WS *et al.* [14], Capelastegui A *et al.* [15])

Characteristics	CURB Severity scores	CURB-65 severity scores	CRB-65 severity scores
Respiratory rate ≥ 30/min	1	1	1
Diastolic blood pressure ≤ 60 Hgmm	1	1	1
Systolic blood pressure ≤ 90 Hgmm	1	1	-
Altered mental status	1	1	1
Age	-	1	1

CURB=confusion, urea nitrogen, respiratory rate, blood pressure

Table 7. The advantages and disadvantages of the pneumonia severity index (PSI) and CURB-65 index based on the different examination results (Acc. to Niederman MS *et al.* [7] Capelastegui A *et al.* [15], Aujesky D *et al.* [13])

PSI	CURB-65
Advantage	
most often examined, validated	easy to use
high predictive value in characterizing	high predictive value in severe CAP
low risk CAP groups	cases of the old age group
Disadvantage	
underestimates CAP severity (in case of young people without comorbidity)	gives less consideration to the importance of comorbidity
does not consider the CAP-specific characteristics	
strongly scores age and comorbidity	
None of the severity indices consider the importance of social factors (e.g. homeless people)	

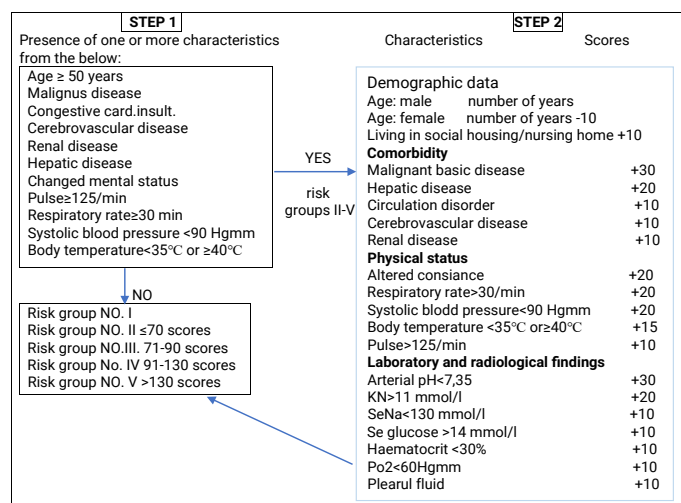


Figure 1. Pneumonia severity index (PSI) (according to Fine MJ *et al.* [12] and Aujesky D *et al.* [13])

CRB-65 score has the benefit that it gives very useful information about the severity of the patient with pneumonia at the first examination at home.

Based on the analysis of the diagnoses of our cases and on the data of the professional literature it can be stated that recognition of CAP in due time is of decisive importance in respect of providing efficient antibiotics for the patient the earliest possible [7,14,15,20]. Determination of the severity of pneumonia is recommended in case of each patient suffering from CAP (pneumonia-specific symptoms, circulation system, state of consciousness, age, comorbidity), providing for the most appropriate place for treatment of the patient and also the pneumonia patients in severe conditions, having septic clinical symptoms can receive the goal-directed treatment in due time (early goal-directed therapy) [1,2,7,21-24].

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