The effect of extracorporeal efferent detoxication (EED) methods inclusion in the severe community-acquired pneumonia (CAP) treatment

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Abstract

Purpose: To assess the clinical efficacy including of EED methods in the treatment of severe CAP with endogenic intoxication syndrome.

Material and methods: Severe CAP in patients (n=103, aged 18-60 years, male 89%) were randomly subdivided into the 4 comparable groups. The 1st group (n=30) was standard treated with antibiotics. The 2nd group (n=27) underwent additionally 3 courses of extracorporeal ultraviolet light-exposure (UVLE). The 3rd group (n=25) was co-treated with 3 courses of biospecific hemosorption (BSS). The 4th group (n=21) underwent 2 additional courses of BSS plus 3 courses of UVLE. The effectiveness of these schemes therapy was assessed by clinical and laboratory data.

Results: The additional application of EED methods led to faster disappearance of clinical symptoms, focal chest signs and the infiltrate resolution in chest X-ray (CXR) as compared with standard treatment. Mean time of the disappearance of fever and sweating was 2.2; 2.5; 2.0 days and 4.8; 5.0; 4.6 days in the 2nd, 3rd and 4th group respectively after EED courses vs 6.1 and 8.0 days in 1st group ($P<0.05$). The baseline elastase activity was elevated by 5 times in the 1st-4th groups vs the control (healthy) group and was decreased by 1.5; 2.1; 4.1; 6.6 times respectively ($P<0.05$) after treatment in these groups. The initial trypsin-like activity was increased about 5.5 times in all groups vs control and decreased after therapy by 2.1; 3.8; 6.4; 6.0 times ($P<0.05$) in the 1st-4th groups respectively. Small CXR residual changes persisted in 7, 4 and 5 patients from the 2nd, 3rd and 4th groups vs 12 patients in the 1st group. The spirometry data were normalized faster in the patients who underwent EED methods (by the 14th day) vs the 1st group.

Conclusions: Additional using of EED methods in severe CAP therapy is more effective (as compared with traditional management with antibiotics only) in term of faster improvement of patients general condition, reduced time of inflammatory infiltrate resolution and hospitalization by 3-4 days. It has been shown that EED methods correct the main pathogenic mechanisms of severe CAP. Our results indicated on the EED methods as an attractive supportive therapy for the empiric antibiotics treatment of this disease.

Key words: community-acquired pneumonia, extracorporeal efferent detoxication, elastase, trypsin-like activity, oxidative stress.

Introduction

CAP is a common acute illness. Its incidence in different population has ranged from 2 to 15 cases per 1 000 persons per year [1]. CAP is potentially fatal if not managed appropriately. Thus, CAP mortality rate has ranged from 5% to 15% among hospitalized patients [2]. This figure rises to >50% for patients with severe CAP that requires treatment in intensive care unit (ICU) [3].

Insufficient effect of antibacterial therapy of this disease with severe endogenic intoxication syndrome demands the search of new and more effective methods of treatment. Efforts to improve the efficacy of treating patients with CAP have been focused predominantly on improved schemes of empiric antibiotics therapy. EED methods (EUVE or BSS) have been successfully used in the therapy of acute pancreatitis [4,5] and other severe pathologic conditions [6,7]. However, their clinical efficacy as a supportive therapy to antibiotic treatment of severe CAP has not been studied as of yet.

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For the successful management of severe CAP patients are necessary not only drugs, having the anti-inflammatory effect, but also the abilities to the normalization of microcirculation and oxidation-reduction balance and to the improvement of ventilation as well. One of such a method is the autotransfusion of UVLE blood. The bactericidal and oxygenic effects of UVLE have been known since a long time [8]. Recently the interest in this method has been increased. It was promoted by the high observable costs of long antibiotics therapy as well as suppression of immunity, dysbacterioses and toxic liver lesion.

In an effort to provide clinicians with the better management of severe CAP, we would like to increase the efficacy of this pathology treatment. Thus, we conducted the prospective randomized controlled trial to investigate the hypothesis that the additional treatment of severe CAP with EED methods would result in a better outcome as compared with the conventional scheme as well as to ensure that there is no an increase in the adverse events from such an intervention. The present studies aimed at determining whether treating of severe CAP patients with the addition of EED methods is superior to the standard therapy with antibiotics alone.

Material and methods

Patients

We examined 103 inpatients (11 female, 92 male) with severe CAP (aged from 18 to 60 years, who were admitted and treated in ICU of the 1st, 2nd and 10th Minsk large public hospitals. These patients fulfilled the inclusion criteria and were randomized to this trial between 2000-2003 years. Dominated men (89%), among them there were 70% smokers. 7% of these patients were taken β-lactams prior to the hospital admission during 1-2 day. 90% of the patients were admitted to the hospital within 1-3 days of severe CAP onset. This diagnosis was defined by the new focal signs and symptoms of the lower respiratory tract infection (complaints of cough, expectoration, dyspnoea, chest pain) as well as by clinical history, physical examination of chest on admission. The results of initial biochemical analyses (hematocrit, leucocytes count, renal function, sodium and potassium values and arterial blood gases), laboratory (including respiratory tract microbiology) examination, CXR findings (new pulmonary infiltrate that were not attributable to other causes) and associated pathologies were considered.

Severe CAP was considered if one or more of the following criteria were present: hemodynamic instability – systolic BP<90 mmHg or diastolic BP<60 mmHg, heart rate (HR) >100 beats/min; new onset of mental impairment; increased respiratory effort (respiratory rate – RR>30/min); multilobar involvement; presence of significant pleural effusion; acute renal failure; leucopenia (<4000/μl) or severe leucocytosis (>30000/μl); anemia; hypoalbuminemia or bacteriemia.

The inclusion criteria for the study were established before the trial and strictly followed. These inclusion criteria were: >18 and ≤60 years old, clinical and laboratory signs of severe CAP, confirmed new lung infiltration by CXR (compared with old radiographs if available) and disease onset outside of hospital. Exclusion criteria were: pulmonary infiltrates due to other forms of pneumonia (nosocomial or due to large-volume aspiration and against the background immune deficiency status); age of the patients >60 years; presence of an infiltrate on CXR typical for the pleural effusion; presence of severe coexisting diseases – cancer (in previous 5 years), diabetes mellitus, lung tuberculosis and chronic obstructive pulmonary disease as well as chronic diseases of heart (coronary artery disease or congestive heart failure of the III-IV grade according to NYHA), liver (preexisting chronic hepatitis, cirrhosis), pancreas (chronic pancreatitis), kidneys (preexisting chronic renal failure with documented abnormal serum creatinine level >180 μmol/L outside of pneumonia episode); immunosupression (receiving chemotherapy or treatment by immunosuppressive drugs).

This study was approved by the Human Studies Committee of the Belarusian State Medical University and informed consent has been obtained from these patients.

Procedures

The ultraviolet light exposure (UVLE) of blood was performed with the apparatus "Nadezda" in the one-time polymeric cannula in the oscillating regimen. The patient's blood was exposed to ultraviolet light twice: at taking blood and then during returning blood to the body. The volume of UV exposed blood was 2-2.5 ml/kg of body mass at one procedure. The rate of blood taking made up 18 ml per min. The normal saline solution (NaCl 0.9%) was a blood stabilizer with addition of heparin in a dose of 50-70 units per kg of the body mass. The course of blood photomodification in addition to the standard treatment included 3 procedures of autotransfusion of UV-radiated blood in the 2nd and 4th groups. We performed one ultraviolet photomodification of blood daily with an interval of one day.

The biospecific hemosorption (BSS) with antiprotease hemosorbent "Ovosorb" (containing ovomucoid, which could bind the serum proteinases) [9,10] by using of a peristaltic pump was performed during the first days on admission. This procedure was used after the preliminary heparinization of the body by intravenous administration of heparine on the basis of 150±25 units per kg of the patient's body mass. The vein-venous type of connection was used. The rate of perfusion was 50-60 ml per min and the time of perfusion – from 60 to 90 min. The course of treatment consisted of 3 manipulations (with additional using of BSS) in the 3rd group and 2 procedures in the 4th group. BSS was done by single sorption daily with an interval of a day.

The therapy effectiveness was assessed by clinical, commonly used laboratory tests and CXR data, including severity assessment – by the clinical severity index (CSI) [11] and by the scale PORT [12].

The study design

All the patients were initially divided into 4 comparable groups according to: sex (χ^2=0.01; P>0.05); age (χ^2=6.88; P>0.05); class (χ^2=0.58; P>0.05) and clinical severity index (χ^2=1.16; P>0.05 among these groups); baseline CXR as well as host immune status, concomitant chronic diseases and alcohol consumption. There were no significant differences in antimicrobial treatment regimens (including time of receiving the first antibiotic delivery and door-to-drug delivery time) among the patients of these groups. The physicians in charge received no

Table 1. **Distribution of patients from the 1st-4th groups according to age**

Age (years)	Groups			
	1st n=30	2nd n=27	3rd n=25	4th n=21
<20	1	3	1	1
21-30	8	6	6	5
31-40	3	6	6	4
41-50	11	7	4	6
51-60	7	5	8	5
Mean age	40.5±2.4	37.5±2.3	40.5±2.6	39.9±2.8

The difference in mean age among these groups was not significant (P>0.05)

Table 2. **Distribution of patients in the 1st-4th groups according PORT (Fine score)**

Severity class (scores)	Groups			
	1st n=30	2nd n=27	3rd n=25	4th n=21
IV (91-130)	25	23	21	19
V (>130)	5	4	4	2
Mean score	108.5±3.8	106.7±3.8	103.1±3.6	104.9±3.8

The difference in the mean scores among these groups was not significant (P>0.05)

information on the objectives or specific target variables of this trial, although they could not be completely blinded. We did quasi randomized trial to compare four schemes of therapy. Thus, on admission the patients were randomly assigned to one of the four groups according to the therapy schemes depending on No of case record.

The 1st group comprised of 30 patients (27 men and 3 women), receiving the standard empirical treatment within the first hours of admission, which included antibiotics. This treatment began with intravenous β-lactamase-stable or third-generation cephalosporin alone or their combination with intravenous macrolide. Mostly patients received their first dose within 8 h (if no clinical effect was detected, intravenous "antipneumococcal" fluoroquinolone were taken), acetic acid derivates, mucolytics as well as (under the indications) physio- and oxygen therapy were given. The 2nd group was formed by 27 patients (24 men and 3 women), who underwent additionally UVLE courses. The 3rd group included 25 men (22 men and 3 women) treated in addition with procedures of BSS. Twenty one (19 men and 2 women) patients (the 4th group) were additionally treated with courses of UVLE plus BSS. No deaths occurred among the patients of these groups during treatment.

The control group for the biochemical parameters was formed by primary blood donors (16 healthy men and 5 women; with mean age 38.6±2.5 years).

Methods

Bedside spirometry was measured in the upright position at a fixed time (9:00) using a computered portable spirometer "Spirovit SP-10" ("Shiller"). The best FEV_1 and FVC after three reproducible measurements were used in the analysis.

We used the two levels principle of the immune status estimation. We regarded to the tests of 1st level the following tests: calculation of leucocytic formulas, detection of T-lymphocytes, immunoglobulins (Ig) and nonspecific resistance of the body (phagocytosis). We specified the lesion localization of the link of subpopulations T-lymphocytes by the second level tests – T-helpers (CD^{+4}) and T-supressors (CD^{+8}).

The quantitative and functional states of the immune system were determined in dynamics: on admission, by the 12--14th day and by the 21st day. The number of T-B lymphocytes with method of spontaneous rosset-formation T-helpers and T-supressors by the method of immunefluorescention with monoclonal antibody receptors were done [13]. The levels of serum immunoglobulins (Ig) were performed by Mancini's method of radial immunodiffusion [14]. Complement level (by 50% haemolysis of sensitized erythrocytes), circulating immune complexes, leukocyte phagocytary activity and leucocytic intoxication index were estimated [13,14].

The measurements of elastase [15] and trypsin-like activity, α_2-macroglobuline (α_2-MG) as well as α_1-antitripsine (α_1-AT) level by the complex method [16] and level of the peptide substances belonging to a group of "middle molecules" (MM) [17] were carried out.

The activity of catalase [18] and superoxide dysmutase (SOD) [19] as well as the level of malondialdehyde (MDA) [20] were assessed in the erythrocytes, as the indicators of the "oxidative stress".

Statistical analysis

The data are shown as mean ± SEM unless otherwise indicated. The paired and unpaired t-test was used to test the significance of baseline characteristics of the 1st-4th groups as well as the treatment effects within the groups and between them. All P values were two tailed. The group comparison used the Student's t test for quantitative variables and χ^2 method Fisher's exact test for qualitative variables. The χ^2 or Fisher exact test was used to compare categoric variables. The non-parametric Mann-Whitney U test was used to compare the difference between unpaired samples. The results of study were further corrected using the Bonferroni method where necessary. The significance level was set at $P \leq 0.05$.

Results

The 1st group did not differ according to the age and gender from the 2nd-4th groups additionally treated with supportive EED methods. Severe CAP was more often (29%) observed in the patients ranging from 41-50 years (*Tab. 1*). Periodic alcohol abuse (>80 g of calculated absolute ethanol per day at least during last year) without signs of dependence in history was detected in 1/3 of these patients. Two third of the patients have had a cold preceding this CAP onset. The work was connected to stay outside in 1/5 of these patients.

All the patients were stratified for the prediction of risk

Table 3. **Baseline selected clinical features of patients admitted to ICU**

Clinic signs	Groups				χ^2
	1st n=30	2nd n=27	3rd n=25	4th n=21	
Body temperature:					
38.1-39°C	7	8	6	5	1.96; P>0.05
>39°C	20	16	18	15	
Respiratory rate:					
21-29 breaths per min	23	22	19	14	1.44; P>0.05
≥30	7	5	6	7	
Heart rate:					
<109 beats per min	15	12	16	11	7.21; P>0.05
110-124	10	8	7	6	
BP systolic <90 mm Hg	9	8	4	5	6.99; P>0.05
Weakness	19	18	18	17	2.02; P>0.05
Productive cough	25	19	18	13	3.03; P>0.05
Haemoptysis	8	6	4	5	0.93; P>0.05
Pleural pain	17	13	16	16	4.19; P>0.05
Dullness (at percussion)	16	19	20	13	4.72; P>0.05
Respiration (at auscultation):					
bronchial	7	6	7	8	
hard	5	8	4	4	3.77; P>0.05
weaked	18	13	14	9	
Crackles,	22	20	19	18	1.26; P>0.05
crepitation,	11	10	12	9	0.94; P>0.05
pleural murmur	10	12	11	10	1.30; P>0.05
Pleural effusion	5	4	4	2	0.58; P>0.05

classes and evaluation of the pneumonia severity according to the scale PORT (*Tab. 2*) and CSI (it made up 4.0, 4.2, 4.1 and 4.2 conventional units in 1st-4th groups respectively). The statistical analysis did not detect any difference between the patients of these groups according to these tests.

The acute clinical symptoms and signs of these patients on admission are presented in *Tab. 3*. So, this disease development was sharp in 2/3 of patients in contrast to its gradual development in 1/3 of patients. Constant high fever and single chill were detected before the admittance to hospital in most patients. We observed the severe endogenic intoxication syndrome in most patients, resulting in the development of additional symptoms and vital signs abnormalities (that were associated with severe CAP): high fever (92%), chills (75%), weakness, hypotension (25%), disorders of mental status (17%), hypo- or adynamia (28%), septic shock (6%), vomiting (6%), convulsive syndrome (4%), syncope (8%), negative reaction from another body's systems (toxic hepatitis, nephropathy, myocardial dystrophy and collapse). One third of the patients had various arrhythmias. All the patients had an abnormal CXR (unilobar or multilobar alveolar infiltrate). The baseline radiological features were similar in all groups. Chest radiographic patterns were the following: bilateral transient non-malignant infiltrate was marked in 1/3 of patients (2 lobes in 25% of them and more than 2 lobes in 8%), unilateral infiltrate was noted in 67% of patients. Severe CAP was located in the right and left lung in 57% and 43% of the patients respectively. Pleural effusion was detected in 15% of these patients (*Tab. 3*).

The normal count of leucocytes was detected in the peripheral blood only in 10% patients on admission and leucopenia was observed in 5% of them. The mean leucocytes count made up $12.3\pm0.9x10^9$/L; 12.2 ± 1.2; 12.1 ± 1.3 and 13.1 ± 1.4 in the 1st-4th groups respectively (P>0.05 among these groups). Leucocytosis was marked in 85% of the patients (in intervals of: 10.1–15.0x10^9/L in 59% and >15.0x10^9/L in 21% of patients). Shift to the left of neutrophils was detected in 85% of the patients and toxic neutrophils granularity – in 36% of them. The leucocytosis and shift to the left were accompanied by significant increase of ESR as well as leucocytic index of intoxication. The latter was achieving 6.4 ± 1.8; 7.2 ± 2.0; 6.0 ± 0.7 and 4.0 ± 0.5 conventional units in 1st-4th groups respectively (P>0.05 among these groups). The mean ESR value made up: 42 ± 3; 39 ± 2; 45 ± 3 and 40 ± 3 mm/h in 1st-4th groups respectively (P>0.05 among these groups). Thus, increase of ESR >20 mm/h was observed in 95% of the patients.

Severe CAP on admission was verified by the changes of the biochemical tests too. Thus, increase of fibrinogen level (>4.5 g/L) and C-reactive protein (CRP) were detected in 93% and 89% of patients respectively. Transitory significant increase of AST and ALT was revealed in 35% of the patients. Some of the patients had toxic nephropathy in the first week of hospitalization. Thus, increased blood level of urea (due to intensification of catabolic processes) and transitory proteinuria were detected in 26% and 38% of patients respectively.

In all patients, the sputum and blood microbial investigations were done: the first sputum Gram stain (as a guide to the initial therapy), the sputum culture and the estimation of its sensitivity to antibiotics. The responsible pathogen was isolated only in 21% of these patients. Thus, *S. pneumoniae* (59%), mixed infections (14%; with *S. pneumonia* as the most commonly involved agent), *S. aureus* (14%), *Klebsiella pneumoniae* (9%) and *Pseudomonas aeruginosa* (4%) prevailed among detected causative pathogens.

Table 4. **Immune parameters of the patients on admission**

Parameter	Patient's groups				
	Control n=21	1st n=30	2nd n=27	3rd n=25	4th n=21
Lymphocytes, %	31± 1	16±2*	15±2*	15 ±2*	15± 2*
Lymphocytes×10^9/L	1.7±0..2	1.7±0.2	1.6±0.1	1.5± 0.1	1.9± 0.2
T-lymphocytes, %	60.7±0.9	61.0±2.2	64.0±2.4	63.3±2.6	61.0±2.9
T-lymphocytes×10^9/L	1.14±0.02	1.08±0.11	1.16±0.11	0.98±0.10	1.11±0.12
active T-lymphocytes, %	25.5±0.6	29.8±2.2	26.1±2.3	26.4±2.3	27.6±2.4
active T-lymphocytes × 10^9/L	0.45±0.01	0.50±0.05	0.46±0.05	0.41±0.05	0.50±0.06
B-lymphocytes, %	6.1±0.3	6.1±0.6	7.1±0.6	6.0±0.6	7.1±0.7
B-lymphocytes ×10^9/L	0.17±0.02	0.11±0.02*	0.13±0.01	0.09±0.01*	0.13±0.02
CD^{+4}	54.7±1.2	46.3±2.0*	44.9±2.5*	40.1±3.5*	46.6±2.2*
CD^{+8}	13.9±0.9	18.4±1.2*	19.5±1.6*	18.2±2.0*	17.8±1.5*
Ig G, g/L	10.9±0.7	15.7±1.5*	14.6±1.0	17.8±1.7*	14.3±1.9
Ig A, g/L	3.2±0.2	4.6±0.4*	4.3±0.4*	4.4±0.4*	4.8±0.6*
Ig M, g/L	0.7±0.1	1.9±0.2*	1.6±0.2*	1.9±0.2*	1.6±0.2*
CH_{50}, hemolytic U.	53.0±0.7	59.3±3.6	56.5±3.8	62.3±2.7	56.8±4.9
Immune complexes, conv.U	7.7±1.3	8.1±1.2	7.1±0.9	8.4±1.0	7.6±1.5
Leucocytes phagocytic activity, %	58.9±2.2	62.4±3.2	54.1±3.3	56.4±3.5	57.4±2.3
Phagocytosis (latex-test), conv. U	1.16±0.05	1.10±0.02	1.10±0.02	1.11±0.02	1.11±0.02

* – P<0.05 vs the control; conv. U – conventional units

The baseline changes of immune status concerned both cellular (mostly) and humoral links (*Tab. 4*). These data were verified by the expressed and various disorders of immune response of severe CAP patients during first days of disease onset both on mean values and number of the patients with deviation from the control. Thus, relative lymphopenia, deficiency of absolute count of B-lymphocytes were detected before treatment in these patients. Though the level of peripheral blood T-lymphocytes in these patients did not differ from the control (as compared with the mean value), the initial decrease (<1.0x10^9/L) of the count of these cells was marked in: 57%, 37%, 57% and 38% of patients the 1st-4th groups respectively (χ^2=1.32; P>0.05). The count of T-lymphocytes exceeded 1.2x10^9/L in 33%, 48%, 28% and 52% of patients from the 1st-4th groups respectively (χ^2=1.79; P>0.05 among these groups).

Although, the baseline relative count of active T-lymphocytes in these groups did not significantly differ from the control one, the deficiency of active T-lymphocytes (<0.4x10^9/L) was observed in 40%, 48%, 52% and 40% of patients from the 1st-4th groups respectively (χ^2=0.50; P>0.05). Meanwhile, the increase of active T-lymphocytes count (>0.5x10^9/L) was marked in 40%, 37%, 28%, 48% patients of the 1st-4th groups respectively (χ^2=0.89; P>0.05 among these groups). Deficiency of T-helper (CD^{4+}) cells and an increase in the mean number of T-suppressors (CD^{8+}) were observed in these patient's groups in contrast to the control. Thus, we detected the low baseline of CD^{+4} level as well as the high its level in 20, 19, 16, 14 and in 7, 6, 3, 6 patients of 1st-4th groups respectively. The high initial count of CD^{8+} cells was detected in 19, 17, 13, 10 patients of 1st-4th groups respectively.

The changes of humoral response have been shown by an increase in the serum levels of IgG, M, A in all patients groups as compared with the control one. Thus, the high initial level of IgA as well as the low its level were observed in 20, 14, 15, 13 and 3, 12, 6, 5 patients from 1st-4th groups respectively. The high baseline levels of IgG and IgM were marked in 17, 16, 17, 7 and 21, 15, 22, 15 patients of 1st-4th groups respectively.

The complement titer was low (<50 hemolytic units) in 13%, 8%, 8%, 14% of patients of 1st-4th groups respectively (χ^2=0.81; P>0.05 among these groups). Meanwhile, an increase of the complement titer (>55 hemolytic units) was marked in about 70% patients of all groups. The leucocyte phagocytic activity in patients from all groups did not differ from the control one. Thus, its decrease (<1.09 conventional units) was observed (*Tab. 4*) in 53%, 38%, 52% and 38% of 1st-4th patients groups respectively (χ^2=0.72; P>0.05 among these groups).

The balance of the lipids peroxidation (LP) and an antioxidant defense in the blood was characterized by a significantly increased baseline level of MDA – the main toxic product of LP membranes (by about 30%) as well as activity of SOD (by about 1.7 times) in all groups as compared with the control one (P<0.05). On the contrary, initial catalase activity was decreased (by about 10%) significantly in all groups vs the control one (*Tab. 5*).

A predominant part of the patients on admission had some imbalance in the system of proteinase-inhibitors. Thus, data showing a significant increase in serum elastase activity (by about 5 times in all groups vs the control one) and trypsin-like activity (by about 5.5 times in all groups vs the control one) against a background of α_1-AT and α_2-MG deficiency are listed in *Tab. 6*. So, an increase of elastase activity (>12.6 μmol/h/L) was detected in 93%, 100%, 92 % and 95% of the 1st-4th patient's groups respectively (χ^2=0.05; P>0.05 among these groups).

The enhancement of trypsin-like activity was revealed in 87%, 74%, 88% and 95% of the 1st-4th patient's groups respectively (χ^2=0.37; P>0.05 among these groups). α_1-AT

Table 5. **Condition of system of lipids peroxidation/antioxidant defense in patient's groups on admission**

Parameter		Patient's groups				
		Control n=21	1st n=30	2nd n=27	3rd n=25	4th n=21
SOD	U/ml of blood	508±27	841±35*	841±45*	799±39*	843±54*
	U/mg of Hb	4.1±0.2	7.6±0.4*	7,3±0.4*	7.3±0.5*	7.9±0.8*
Catalase	μmol H_2O_2/μL x min	10.4±0.3	9.1±0.4*	9.3±0,3*	9.3±0.3*	8.9±0.4*
MDA	μmol/ml of hemolysate	3.5±0.2	4.3 ±0.2*	4.3±0.2*	4.3±0.2*	4.4±0.2*
	μmol/mg of Hb	1.01±0.05	1.29±0.06*	1.29±0.04*	1.37±0.09*	1.36±0.09*

* – P < 0.05 vs the control; U – units; μL – microlitr; μmol – micromol

Tab. 6. **Condition of system proteases-inhibitors in patient's groups on admission**

Parameters	Patient's groups				
	Control n=21	1st n=30	2nd n=27	3rd n=25	4th n=21
Elastase, mmol/h x L	9.8±1.3	55.7±4.7*	49.8±3.0*	49.8±6.3*	49.1±4.6*
Trypsin-like activity, nmol/sec x L	28.7±3.6	154.7±33.1*	157.0±30.9*	159.8±34.0*	158.3±39.4*
α_1-AT, μmol/sec x L	7.7±0.4	3.2±0.7*	3.3±0.7*	2.8±0.7*	2.8±0.7*
α_2-MG, μmol/ sec x L	0.92±0.04	0.41±0.06*	0.51±0.07*	0.46±0.06*	0.43±0.08*
Middle molecules, g/L	0.38±0.03	0.96±0.05*	1.08±0.05*	1.12±0.06*	1.07±0.07
Total protein, g/L	70.7±1.3	64.2±1.6*	60.8±1.2*	62.1±0.7*	62.8±1.6*

* – P < 0.05 vs the control; μmol – micromol; nmol – nonamol

level before treatment was decreased by 2.4; 2.2; 2.8; 2.9 times (p<0.05 vs the control group) in the 1st-4th groups respectively. Thus, the deficiency of α_1-AT was observed in 83%, 85%, 88% and 90% of the patients from of 1st-4th groups respectively (χ^2=0.05; P>0.05 among these groups). The mean baseline level of α_2-MG was reduced by about 2 times in all groups vs control one (P<0.05). A decrease of α_2-MG level was marked in 83%, 74%, 80% and 81% of the 1st-4th patient's groups respectively (χ^2=0.09, P>0.05). We detected also a significant increase in the level of MM and the lower concentration of total protein as compared with the control group. Thus, a decrease of albumin level (<35 g/L) was observed in 27%, 33%, 20% and 24% of the patients from 1st-4th groups respectively (χ^2=0.74; P>0.05 among these groups).

The assessment of pulmonary function was available only in 78 patients and it showed mainly a restrictive ventilation disorders of various degree severity. This testing was impossible in remaining 22 patients due to expressed chest pain or intoxication psychosis. Analysis of pulmonary function detected abnormal lung function indices. Thus, we revealed decrease of FVC (<85% from norm) in: 84%, 83%, 91% and 87% of patients from the 1st-4th groups respectively (χ^2=0.06; P>0.05). 36%, 39%, 48 % and 67% of the patients from the 1st-4th groups respectively had reduced FEV_1 (<80% from norm; χ^2=3.30; P>0.05 among these groups) (*Tab. 7*).

We also estimated the dynamics of basic clinical features before-post carrying out EED methods as well as just after ending the first procedure. All used EED methods (better BSS plus UVLE) reduced the endogenic intoxication signs (decrease of HR, RR, BT and CSI) just after using of one procedure. Treatment with EED methods was associated with shorter time of fever resolution as compared with the conventional therapy.

Table 7. **Bedside spirometry of patient's groups on admission**

Parameters	Patient's groups			
	1st n=25	2nd n=24	3rd n=23	4th n=15
VC, %	70±3	74±3	71±3	69±5
FVC, %	64±3	65±4	64±3	65±4
FEV_1,%	74±4	71±4	71±4	70±5
FEV_1/FVC	88±4	90±3	92±3	88±4
FEV_{25},%	71±7	68±6	76±7	59±5
FEV_{50},%	74±5	68±5	72±5	65±6
FEV_{75},%	77±6	67±6	71±5	67±7

Differences among these groups were not significant (P>0.05)

Thus, high fever (BT>38°C) and low grade fever were observed in 61% and 39% of patients from 4th group before carrying out BSS plus UVLE. Significant decrease of BT (accompanied with the improvement of general health status) was observed in 58% of these patients (from those in 3 patients BT was normalized) just after finishing carrying out a single UVLE plus BSS procedure. BT did not change just after using BSS only in 42% of patients. Normalization of BT was observed in dynamics (in 10 hours) in 86% of patients of the 4th group and a day later in remaining 14%. Thus, BT made up 36.8+0.1°C (P<0.05 vs the initial data) following day. Dynamics of BT decreasing did not differ significantly after single using of UVLE, BSS and UVLE plus BSS (*Tab. 8*).

Tachypnoea (>25 breaths per min) was decreased by 22% in patients (vs the baseline data) after carrying out single BSS plus UVLE procedure. Thus, 43% of these patients noted significant relief of breathlessness in the early postsorption period. Initial

***Table 8*. Dynamics (before-after the procedure) of basic clinical parameters after single carrying out of UVLE, BSS and BSS plus UVLE**

Parameter	UVLE		BSS		BSS plus UVLE	
	Before/after		Before/after		Before/after	
BT°C	38.3±0.6	37.8±0.5*	38.0±0.1	37.5±0.1*	38.4±0.2	37.2±0.1*
RR, breaths/min	26.4±0.6	25.7±0.3*	25.7±0.7	23.7±0.6*	26.1±0.5	20.3±0.3*
HR, beats/min	110±2	103±2*	112±1	107±2*	114±2	102±2*
Systolic BP, mmHg	111±2	113±2	112±3	114±2	109±3	112±2
CSI, conv.U	4.2±0.2	3.7±0.1*	4.1±0.2	3.8±0.2*	4.2±0.1	3.5±0.2*

* – P<0.05 vs the initial level

breathlessness at rest and during conversation was marked in 5 patients of the 4th group. After the BSS plus UVLE procedure it disappeared and these patients could start to move independently within the nearest 10 hours. The rest 57% of patients have felt a reduction of breathlessness and a relief of breath within a day.

Single application of BSS plus UVLE caused a more significant decrease of RR, than the separate using of these procedures. Thus, RR in a day after using single combination of BSS plus UVLE also decreased by 10% and made up 18 breaths per min (P<0.05 vs the initial level and the similar values in the 2nd-3rd groups).

The positive influence of BSS plus UVLE procedure has concerned HR too (it was decreased by 11% after this manipulation). Thus, HR in patients of 4th group in a day decreased by 5% (made up 97 beats per min; P<0.05 vs the initial value, but P>0.05 vs the similar parameter of the 2nd and 3rd groups). While, HR decreased by 6% and 4% during single application of UVLE or BSS.

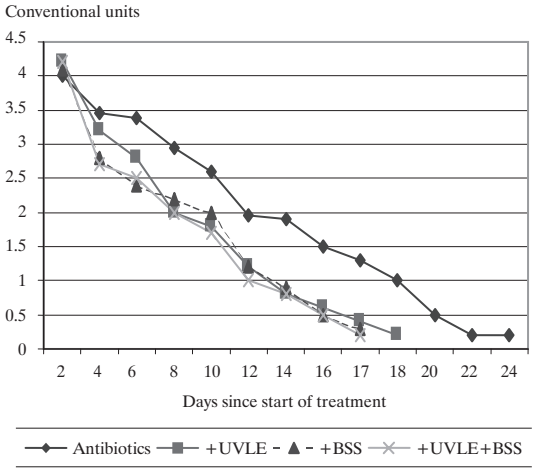
Systolic BP did not significantly change in all groups just after finishing a single EEDM procedure. Systolic BP every other day exceeded (by 11%) the initial level in the 4th group and made up 122 mmHg (P<0.05 vs the initial data; but P>0.05 vs similar value in the 2nd and 3rd groups).

86% of patients noted reduction of weakness after a single application of BSS plus UVLE. Productive cough appeared instead of dry cough in 38% of these patients as well as disappearance of cough was detected in 14%. Out of 16 patients who initially had a pleural pain, its reduction was noted in 4.

CSI just after a single application of BSS plus UVLE was decreased by 17%. CSI every other day was reduced by 3% and made up 3.4±0.2 conventional units (P<0.05 vs the initial value; but P>0.05 vs the similar value of the 2nd and 3rd groups). CSI was decreased (*Fig. 1*) by 2.5 times by the 10th day of treatment (P<0.05) in patients who were treated with the application of BSS+UVLE.

Further decrease of CSI (by 2 times) was marked by the 14th day of therapy. CSI made up 0.23±0.01 unit in the 4th group by the 17th day. Comparison of CSI values has not revealed the significant difference in different terms of treatment of patients who were applied the other EED methods. Meanwhile, decreasing of CSI was slower after traditional therapy. Thus, CSI was decreased by 1.5 times by the 10th day (made up 2.6±0.1 units; p<0.05 vs the value in the 4th group) and CSI has achieved value 0.53±0.04 unit only by the 22 day of conventional management.

***Figure 1*. Dynamics of CSI during standard treatment as well as the additional courses of UVLE, BSS and UVLE plus BSS**



The analysis of immune response in the period of using different schemes of severe CAP therapy showed that the similar dynamics of leukocytes count was observed in various terms of treatment in all groups. Nevertheless, leukocytosis (leukocytes count >9.0x10^9/L) persisted in 6 patients from the 1st group by the 21st day of therapy, in 2 from the 2nd group and in 1 patient from the 3rd group. Meanwhile, such leukocytosis was not observed in patients from the 4th group (χ^2=9.08; P<0.05).

Baseline relative lymphopenia was observed in patients of all groups on admission. A significant increase of lymphocytes level was noted in all groups just by the 12-14th day as compared with the initial level. The relative mean number of rosset-formated and active T-lymphocytes as well as rosset-formated B-lympocytes and complement titer in patients of all groups did not significantly change during treatment. But, qualitative analysis showed, that the normalization of low baseline level of T-lymphocytes (%) was detected in 6, 5, 7, 9 patients of the 1st-4th groups respectively. From the patients with the high baseline level of B-lymphocytes (%) as well as the low level, its normalization was detected in 6, 6, 6, 8 and 9, 6, 7, 7 patients of the 1st-4th groups respectively.

The additional using of EED methods eliminated an imbalance of T-helpers/T-supressors ratio by increasing of T-helpers level and by decreasing of T-supressors level just by the 12-14th day. Thus, T-helpers level increased (by 16% and 10%; P>0.05

vs the initial level) by the 22th day of therapy in the 2nd and 4th groups, while it was increased more in the 3rd group (by 28%; P<0.05 vs the initial data). Among the patients with initially low levels of T-helpers, their normalization was noted in 4, 12, 7, 6 patients of 1st-4th groups.

Deficiency of T-helpers persisted during the whole period of standard antibiotic treatment (pre-post – 46.3±2.0 and 43.8±1.6). The baseline mean level of T-supressors was replaced by it's normalization in all groups by the 12-14th day of therapy. Thus, high initial level of T-supressors was replaced by it normalization in 14, 13, 9, 7 patients of 1st-4th groups respectively.

The level of IgG remained increased (by 37%, 32%, 39%, 42%; P<0.05 vs the control) in patients of the 1st-4th groups respectively by the 12-14th day of therapy. On the whole, IgG content had the tendency to normalization to the end of treatment in all groups. Thus, its high baseline level was normalized in 11, 11, 15, 5 patients of 1st-4th groups.

The mean level of IgA was normalized after the therapy in all patients' groups too. Thus, the high baseline level of IgA was replaced by it normalization in 14, 10, 12, 11 patients of 1st-4th groups.

The mean IgM level decreased to some extent, but persisted increased (P<0.05 vs control) after standard therapy in contrast to the significant reduction of it after the additional using of EED methods (by 18%; 31% and 24% in the 2nd-4th groups respectively). Thus, the high baseline level of IgM was normalized in 11, 11, 15, 5 patients of 1st-4th groups.

The level of immune complexes was decreased by 2 times in patients of the 2nd group (P<0.05 vs the initial level) by the end of therapy. Similar (but non-significant) dynamics of immune complexes level was observed in the 3rd-4th group in contrast to the absence of such positive changes during traditional management.

A significant increase of LPA (digested phagocytes activity) was already noted by the 12-14th day of treatment in patients of the 2nd-4th groups (by 26%, 33% and 23% respectively). Whereas, LPA did not significantly change during traditional therapy. Phagocytosis (according to the latex test) did not change in patients of all groups after the therapy.

Using of EED methods caused more significant positive changes of the proteinase inhibitors system (*Tab. 9*). Thus, the high baseline elastase level as well as trypsin-like activity were significantly decreased by 1.5; 2.1; 4.1; 6.6 times and by 2.1; 3.8; 6.4; 6.0 times (P<0.05) after finishing treatment in the 1-4th groups respectively. α_1-AT level was significantly increased by 1.8; 2.2; 3.0; 2.7 times in these groups after the therapy. The level of α_2-MG increased up to normal too in all groups by the end of management.

The baseline high elastase level in patients of the 4th group was decreased by 44% (vs the initial level) by the 12-14th day and still decreased by 72% by the 20-22th day. Similar dynamics of elastase level was marked in patients of the 3rd group too. An additional using of UVLE alone was less effective concerning the decrease of elastasemia (P<0.05 vs the data of the 3rd and 4th groups by the 20-22th day). *Tab. 9* shows, that the high level of elastasemia persisted by the 22th day in the patients who underwent standard therapy (P<0.05 vs other groups).

Using of UVLE alone did not influence the proteinase/ /antiproteinase system. Whereas, a single application of BSS or BSS plus UVLE caused significant decrease of the elastase and trypsin-like activity as well as the MM level. Thus, the elastase and trypsin-like protease activity was decreased by 58% and 61% (P<0.05 vs the initial level) just after the finishing of BSS plus UVLE procedure. We registered some an enhancement of proteinase activity in a day, but it did not reach an initial level. The elastase and trypsin-like activity in a day were increased by 28% and by 22% (P<0.05 vs the initial level) in patients of the 4th group.

The baseline high level of the trypsin-like activity in patients of the 4th group was decreased by 61% by the 12-14th day (p<0.05 vs the initial level) and by 56% by the 22th day (P<0.05 vs the data by the 12-14th day). The trypsin-like activity was normalized in patients from the 3rd and 4th groups by the 20--22th day; meanwhile its high level persisted in the patients who were conventional treated (mostly) or with the application of UVLE.

Using the combination of BSS plus UVLE promoted the increase of the proteinase inhibitors level by the 12-14th day. So, the maintenance of α_1-AT and α_2-MG was increased by 2 times (P<0.05 vs the initial level) and the levels of these proteases inhibitors were completely normalized by the 20-22th day. The contents of α_1-AT and α_2-MG did not significantly change just after the combined BSS plus UVLE procedure every other day too. Similar dynamics of this antiproteinase activity was observed in the 3rd group. While a slight increase of α_1-AT by the 12-14th day was observed in patients of the 1st and the 2nd groups with further enhancement of this level by 45% to the 20-22th day (P<0.05 vs the data by the 12-14th day) in the 2nd group and by 38% in the 1st group (P<0.05 vs the data by the 12-14th day). A significant increase of α_2-MG level was marked only by the 20-22th day in the patients underwent standard management.

The level of MM was decreased by 13% (P<0.05 vs the initial level) after using a single BSS plus UVLE procedure. Meanwhile, MM contents every other day did not change. The MM level was decreased by 2 times by the 12-14th day (P<0.05 vs the initial level) in the 4th group and later – by 1.6 times by the 20-22th day (P<0.05 vs the data by the 12-14th day). Similar changes of the MM content were detected in patients after a single using of BSS or UVLE. Thus, the level of MM was decreased by 2.5 times by the 22-th day after the application of UVLE in contrast to 1.9 times after standard therapy. MM level also significantly decreased by the 20-22th day during antibiotic management, however, it did not reach the control one.

The total protein level had the tendency to an increase in patients who were treated with the application of EED methods (mostly in the 2nd group). On the contrary, the total protein was further decreased in those patients receiving traditional therapy.

The high baseline SOD activity in all groups was significantly decreased in the course of treatment by 1.4 times and 1.6 times in the 1st and the 2nd-4th groups respectively (*Tab. 10*). The decrease of the SOD activity by 30%, 39%, 36% and 39% (P<0.05 vs the data by the 12-14th day) was detected by the 20--22th day in the 1st-4th patient's groups respectively. This reducing of SOD activity was more detected for this period according to recalculation of this value per mg of Hb (by 23%, 30%, 42% and 44% in the 1st-4th patient's groups respectively) (*Tab. 10*).

Table 9. **The condition of proteinase/proteinase inhibitors system in the course of standard antibiotics therapy and with the additional treatment using of EED methods**

Parameter	Control n=21	Standard therapy (ST) (days)			ST+UVLE (days)			ST+BSS (days)			ST+BSS+UVLE (days)		
		Before n=30	12-14th n=30	20-22th n=25	Before n=27	12-14th n=27	20-22th n=24	Before n=25	12-14th n=25	20-22th n=24	Before n=21	12-14th n=21	20-22th n=20
Elastase mmol/h x L	9.8 ±1.3	55.7 ±4.7*	59.2 ±6.1*	38.2 ±3.7*,▽	49.8 ±3.0*	41.7 ±3.8*,⊗,**	23.3 ±2.4*,⊗,**,▽	49.8 ±6.3*	28.4 ±2.3*,⊗,**	12.1 ±1.5⊗,**,▽	48.9 ±4.6*	27.4 ±4.1*,⊗,**	7.6 ±1.2⊗,**,▽
Trypsin-like activity nmol/s x L	28.7 ±3.6	154.7 ±33.1*	120.4 ±18.0*	72.5 ±16.3*	157.0 ±30.9*	107.3 ±26.0*	41.4 ±5.9**,▽	159.8. ±34,0*	60.0 ±10.0⊗,**	24.9 ±3.6⊗,**	158,3 ±39,4*	62.5 ±1.4.2*,**	27.2 ±3.5⊗,**
α_1-AT µmol/s x L	7.7 ±0.4	3.2 ±0.7*	3.6 ±0.8*	5.8 ±0.7**,▽	3.3 ±0. 7*	4.0 ±0.8*	7.3 ±0.7**,▽	2.8 ±0.7*	5.3 ±0.6**	8.3 ±0.6⊗,**,▽	2.77 ±0.7*	5.6 ±0.8**	7.4 ±0.7**
α_2-MG µmol/s x L	0.92 ±0.04	0.41 ±0.06*	0.57 ±0.05*	0.80 ±0.05**,▽	0.51 ±0.07*	0.90 ±0.06⊗,**	1.00 ±0.04**,⊗	0.46 ±0,06*	0.86 ±0.06⊗,**	0.90 ±0.04**	0.43 ±0.08*	0.87 ±0.07⊗,**	1.01 ±0.04⊗,**
Middle molecules g/L	0.38 ±0.03	0.92 ±0.05*	0.73 ±0.05*,**	0,51 ±0.05*,**,▽	1.08 ±0.05*	0.61 ±0.05*,**	0.43 ±0.03**,▽	1.12 ±0.06*	0.54 ±0.04*,⊗,**	0.36 ±0.03⊗,**,▽	1.07 ±0.07*	0.50 ±0.06⊗,**	0.31 ±0.02⊗,**
Total protein g/L	70.7 ±1.3	64.2 ±1.6*	62.1 ±1.0*	62.8 ±1.1*	60.8 ±1.2*	63.8 ±1.3*,**	65.8 ±1.3*,**	62.1 ±0.7*	63.5 ±0.7*	64.8 ±0.8*	62.8 ±0.6*	62.3 ±0.3*	63.5 ±1.5*

* – P < 0.05 vs control group; ⊗ –P < 0.05 vs standard treatment in the same period; ** – P < 0.05 vs data of this group on admission; ▽ –P < 0.05 vs data by the 12-14th day in this group

Table 10. **Dynamics of the parameters of lipids peroxidation and antioxidant defense in the course of standard antibiotic therapy and with the additional treatment using of EED methods**

Parameter		Control n=21	Standard therapy (ST) (days)			ST+UVLE (days)			ST+BSS (days)			ST+BSS+UVLE (days)		
			Before n=30	12-14th n=30	20-22th n=25	Before n=27	12-14th n=27	20-22th n=24	Before n=25	12-14th n=25	20-22th n=24	Before n=21	12-14th n=21	20-22th n=20
SOD	U/ml blood	508 ±27	841 ±35*	802 ±38*	585 ±23**,▽	840 ±45*	910 ±44*,**	513 ±22**,▽	780 ±39*	914 ±20*,**,⊗	501 ±28**,▽	843 ±54*	940 ±51*,⊗	512 ±28**,▽
	U/mg Hb	4.1 ±0.2	7.6 ±0.4*	8.0 ±0.3*	6.6 ±0.2*,▽	7.2 ±0.3*	8.2 ±0.3*,⊗,**	4.8 ±0.3*,⊗,**,▽	7.2 ±0.6*	7.3 ±0.3*	4.2 ±0.3**,⊗▽	7.9 ±0.8*	7.9 ±0.5*	4.4 ±0.4⊗,**,▽
Catalase	µmol H_2O_2 µL x min	10.4 ±0.3	9.1 ±0.4*	9.3 ±0.4	7.6 ±0.3*,**,▽	9.2 ±0.3*	10.6 ±0.3⊗,**	8.0 ±0.4*,▽	9.4 ±0.4*	9.8 ±0.3	10.0 ±0.3⊗♦	8.9 ±0.4*	9.8 ±0.4	10.2 ±0.4⊗,♦
MDA	µmol ml hemolysate	3.5 ±0.2	4.3 ±0.2*	3.8 ±0.2	3.3 ±0.2**,▽	4.3 ±0.2*	4.6 ±0.2*,⊗	3,1 ±0.2**,▽	4.3 ±0.2*	4.3 ±0.2*	3.2 ±0.5**,▽	4.4 ±0.2*	4.3 ±0.2*	3.0 ±0.1**,▽
	µmol mg Hb	1.01 ±0.05	1.29 ±0.06*	1.33 ±0.05*	1.32 ±0.06*	1.29 ±0.04*	1.26 ±0.04*	1.07 ±0.09⊗,▽	1,37 ±0.09*	1.18 ±0.04	0.92 ±0.06**,⊗,▽	1.36 ±0.06*	1.26 ±0.07*	0.90 ±0.05⊗,**,▽

* – P < 0.05 vs control group; ⊗ – P < 0.05 vs the standard antibiotic treatment in the same period; ** – P < 0.05 vs the data of this group on admission; ▽ – P < 0.05 vs the data by the 12-14th day in this group;
♦ – P < 0.05 vs the 2nd group

Table 11. **Duration of basic clinical signs in patients who were standard treated and who underwent the courses of UVLE, BSS and BSS plus UVLE**

Signs	Mean duration (days)			
	Standard therapy (ST)	ST+UVLE	ST+BSS	ST+BSS+UVLE
Fever	**6.1±0.4** n=30	**2.2±0.3*** n=27	**2.5±0.3*** n=25	**2.0±0.3*** n=21
Tachycardia	**11.4±1.0** n=23	**6.7±0.5*** n=23	**6.8±0.5*** n=21	**5.7±0.5*** n=19
Sweating	**8.0±0.6** n=30	**4.8±0.4*** n=27	**5.1±0.5*** n=25	**4.6±0.4*** n=21
Weakness	**8.2±0.6** n=30	**5.6±0.4*** n=27	**5.9±0.4*** n=25	**5.1±0.4*** n=21
Cough	**13.3±0.7** n=30	**10.2±0.8*** n=27	**10.1±0.8*** n=25	**8.6±0.8*** n=21
Pleural pain	**8.3±0.4** n=17	**7.5±0.6** n=13	**8.1±0.6** n=16	**7.2±0.5** n=16
Breathlessness	**4.3±0.3** n=30	**2.4±0.2*** n=27	**2.8±0.2*** n=25	**2.2±0.2*** n=21
Dulness (at percussion)	**13.1±1.0** n=16	**9.6±0.9*** n=19	**10.0±0.9*** n=20	**8.8±0.8*** n=13
Normalization of vesicular breath	**17.1±0.8**** n=30	**14.4±0.6*,**** n=27	**12.8±0.7*,**** n=25	**10.2±0.6*** n=21
Disappearance of accessory respiratory murmur	**15.6±0.8** n=30	**12.9±0.6*** n=27	**13.0±0.8*** n=25	**11.4±0.5*** n=21
Unstable hemodynamics	**4.3±0.4** n=12	**2.7±0.3** n=12	**2.6±0.7** n=5	**2.2±0.4*** n=5

* – P<0.05 vs 1st group; ** – P<0.05 vs 4th group

The catalase activity had even decreased in the 1st group (by 18%; P<0.05 vs the initial level) after therapy, but did not change in the 2nd group and increased by 6% and 13% (P<0.05) in patients of the 3-4th groups (rising to the control level).

The baseline high MDA level was decreased by 17%; 33%; 30% (P<0.05) after using EED methods in the 2nd-4th groups, but did not differ in the 1st group. Thus, the normalization of MDA was detected by the 20-22th day of treatment by EED methods. While, the high MDA level (by recalculation of this value per mg of Hb) persisted in patients underwent traditional therapy.

As seen in *Tab. 11*, the application of EED methods promoted earlier disappearance of some signs of endogenic intoxication (fever, tachycardia, sweating, weakness) and focal chest signs (dullness, accessory respiratory murmus) in contrast to conventional management.

As a whole, using of EED methods caused earlier normalization of BT in comparison with treatment by antibiotics only (P<0.05). Thus, patients of the 2nd-4th groups became afebrile approximately on the 2.0; 2.2 and 2.5 days respectively as compared with 6 days in 1st group.

The application of BSS plus UVLE caused a decrease of HR (<90 beats per min) by the 5.7±0.5 day. Tachycardia persisted twice longer (P<0.05) in patients who were standard treated. A single using of BSS or UVLE also caused earlier normalization of HR, as compared with conventional therapy (P<0.05).

Weakness was observed within 5 days after the combined using of BSS plus UVLE. Meanwhile, patients who were standard treated marked weakness lasted (within 8.0±0.6 days; p<0.05 vs the data of the 4th group). Single introduction of BSS or UVLE into the therapy also promoted earlier disappearance of weakness in contrast to the standard treatment (p<0.05).

Sweating within 8.0±0.6 days was noted in patients of the 1st group. Sweating was marked for a shorter time (within 4.6+0.4 days) in patients from 4th group (P<0.05 vs the 1st one). Cessation of sweating was also noted earlier in the patients who were treated with the application BSS or UVLE (P<0.05), than in patients undergoing standard management.

On admission pleural pain was detected in 16 patients who were treated with the application of BSS plus UVLE. Out of this group, the significant reduction or disappearance of painful syndrome was marked in 44% of patients just after a single carrying out of these procedures. Pain arose again within 10 hours in a third of the patients, but it was not such intensive as before. After these manipulations, half of patients did not note changes in the pain syndrome. Pleural pain persisted 7.2±0.5 days after the combined using of BSS plus UVLE. *Tab. 11* shows, that pleural pain disappeared within the same period in patients of other groups (P>0.05).

Disappearance of cough and breathlessness after the including of EED methods in severe CAP treatment was noted to occur earlier than in patients of the 1st group (these patients complained of cough within 13.3±0.7 days). Thus, using of BSS plus UVLE caused earlier disappearance of cough (by the 8.6±0.8 day). Cough persisted a bit longer in patients with a single application of BSS or UVLE (10.1±0.8 and 10.2±0.8 day respectively; P<0.05). Breathlessness of a variable degree was observed in all patients on admission. Breathlessness persisted within 4.3+0.3 day during conventional therapy. The application of BSS plus UVLE caused earlier disappearance of breathlessness (by the 2.2±0.2 day; P<0.05 vs the 1st group). Similar dynamics of breathlessness was marked during a separate using of UVLE or BSS.

Dullness and accessory respiratory murmur disappeared quicker in patients who were treated with the application of BSS plus UVLE in contrast to who underwent standard management. Thus, dullness at lung percussion persisted 8.8±0.8 days during the BSS plus UVLE using. This dullness was detected till the 9.6±0.9 day of UVLE courses and a bit longer (till the 10.6±0.9 day) during including of BSS (both P<0.05 vs the conventional therapy).

Normalization of vesicular breath in patients of the 4th group was observed significantly quicker (by the 10.5±0.6 day) as compared with patients of the 1st-3rd investigated groups (by the 17.1; 14.4 and 12.8 days respectively). Disappearance of accessory respiratory murmur was observed by the 11.4±0.5 day in patients of the 4th group and longer (by the 15.6±0.8 day; P<0.05) in patients of the 1st group.

***Table 12*. Pre-post dynamics of spirometry tests during standard treatment as well as additional using of UVLE, BSS and BSS plus UVLE**

Parameter	Standard therapy (ST) (n=30)			ST+UVLE (n=27)			ST+BSS (n=25)			ST+BSS+UVLE (n=21)		
	Before	12-14th day	20-22th day	Before	12-14th day	20-22th day	Before	12-14th day	20-22th day	Before	12-14th day	20-22th day
VC, %	70±3	75±3	82±6**	73±3	89±3*	94±2*,**	70±3	84±2*,**	92±1**	66±5	88±3*,**	93±3**
FEV_1, %	74±4	78±3	81±3	71±4	86±3**	90±2**	71±4	81±3**	85±3**	70±5	83±3**	92±2**

* – P<0.05 vs the 1st group; ** – P<0.05 pre-post treatment

The stabilization of systolic BP was observed within 2.2±0.4 day in patients of the 4th group. Meanwhile, it normalization occurred later (by the 4.3±0.4 day) during traditional treatment. A single using of UVLE or BSS promoted shortening of the period of instable hemodynamics, however, significant differences vs the 1st group was not revealed.

Positive clinical dynamics was revealed after a combined using of BSS plus UVLE in 20 patients. Thus, we observed significant improvement of general health condition in the one patient and disappearance of breathlessness, but weakness, sweating and subfebrile BT (in the evenings) persisted. In dynamics (during the ensuing month), we revealed lung bacterial destruction in this patient.

Intermediate (by the 5th day) clinical benefits were detected in 21, 26, 24, 20 patients of 1st-4th groups respectively. The lack of positive clinical effect of standard therapy was detected in 9 patients (absence of positive changes – in 4 of patients and negative clinical dynamics – in 5) in contrast to only one patient in the 2nd-4th groups. We revealed the significant difference according these data among the 1st group on the one hand and the 2nd-4th groups on the other hand. Meanwhile significant difference has not been found between the patient's groups whose were treated by EED methods in all cases of the comparison.

Failure of CAP standard treatment was connected with development of lung destruction (abscess formation) and sacculated pleurisy. Thus, severe CAP was complicated by lung abscess in 5 patients of the 1st group in contrast to the 1 patient from the 2nd-3rd-4th groups. Meanwhile, the statistic analysis did not reveal the advantages of EED methods in contrast to the conventional management by prevention of development of lung abscess in these patients (χ^2=3.65; P>0.05 among these groups).

The destructive lung changes and infiltrative changes persisted both by the 21st day in 1 patient of the 4th group. The positive CXR dynamics took place in the rest patients of this group. Mean terms of infiltration disappears made up 17.7±0.7 days. Small residual CXR changes (mainly, intensification and deformation of pulmonary picture and pleural-diaphragmaticus adhesions) remained in 7, 4, 5 patients of the 2nd-4th groups as compared with 12 patients of the 1st group.

CXR signs of lung infiltration at control research disappeared only in 1 patient after conventional management. Thus, appearance of new infiltrates was detected in 3 patients, destructive changes – in 2 as well as lung abscess – in 3 patients. Reduction of infiltration (according to area and intensity) was noted in all other cases (in 70% patients of the 1st group). Lung infiltration did not detect by the 21st day in 68% of these patients. Radiological resolution of severe CAP begun by the 30th day of therapy (and later) in 5% of patients. Thus, the resolution came later (by the 22.2±0.7 day) after traditional treatment in contrast to the application of BSS plus UVLE (P<0.05).

Full CXR resolution and formation of residual changes were revealed in 13, 17, 20, 15 patients and in 2, 7, 4, 5 patients of 1st-4th groups respectively. Thus, radiological lung residual changes were marked in about half of 1st group patients during discharge from hospital and consist in the following: intensification and deformation of pulmonary picture (7 patients), thickening of the interlobular pleura (2 patients), formation of postpneumonic pneumosclerosis (2 patients) and development of pleural-diaphragmatical adhesions (2 patients). The qualitative analysis of the treatment effects on the residual CXR changes did not revealed significant advantages of any methods of severe CAP treatment (χ^2=6.1; P>0.05 among these groups). In our opinion, the initial radiographic involvement patterns have significant effects on the future resolution of severe CAP.

Efficacy of the treatment was estimated too by the terms of CXR resolution of severe CAP. For this purpose we built the cumulative curves and counted value of the logrange criterion (U_L). Considering the fact, that at the analysis resorted to the plural comparisons for calculation the significance, we accounted the Bonferroni correction as well as the Jets correction for compensation the influence of discrete. The analysis showed the higher efficacy of therapy with EED methods combination in contrast to traditional treatment. So, significant difference was revealed among the 1st group and 3rd group ($U_{L=}$10.62; z=3.76; P<0.05), between 1st and 2nd group (U_L =-8.46; z=2.78; P<0.05) as well as among the 1st and 4th group (U_L=-9.61; z=3.70; P<0.05). Any significant difference between the 2nd-4th groups has not been revealed.

The analysis of spirometry revealed the abnormal lung function indices (mainly restrictive disorders) in severe CAP patients on admission. The dynamics analysis of ventilation has shown its normalization in patients additionally treated with the application of EED methods already by the 12-14th day (*Tab. 12*). Thus, earlier normalization of spirometry parameters was revealed in the 4th group (P<0.05 vs the 1st group). Earlier normalization of spirometry tests was noted only during the additional using of UVLE or BSS. VC more increased (by 21%; P<0.05) after the application of UVLE or BSS. Thus, the FEV_1 of the 2nd group increased from 71±4% on day 1 to 90±2% by the 22th day

($P<0.05$). The same data were received in the 3rd-4th groups (none of the changes in VC, FEV_1 differed significantly among the 2nd-4th groups). Meanwhile significant decrease of VC persisted during using of standard therapy by the 22th day (even before discharge from hospital). VC rose from 70±3% on day one to 82±6% by the 22th day ($P<0.05$) in the 1st group.

Discussion

The central point of severe CAP pathogenesis is a microbial aggression against the background of immunodeficiency, hypoxia, systemic oxidative stress with degranulation of cytoplasmic membranes, going out of proteinases into the blood and the development of endogenic intoxication syndrome [21]. It is a generalized reaction of the body to the microbial pathogen with the involvement of the central nervous system, disorders of hemodynamics and all kinds of metabolism. The disturbances in the focal lung lesion, arising in severe CAP, lead to the blockade of antibiotic access into the pulmonary tissue, disorders of reparative processes, sharp increase of proteinases level and depression of local protective factors [22].

The beginning of an acute inflammatory injury of the lungs is initiated by a complex series of events with the development of disturbances of several systems. The outcome of the inflammatory response (progression or containment) depends within certain limits upon the balance between pro- and antiinflammatory mediators. Thus, we detected that the imbalance in the proteinase/antiproteinase system was defined by a decrease of the level of several natural inhibitors (α_1-AT and α_2-MG) against the background of increase of elastase and trypsin-like activity. This imbalance in the severe CAP was accompanied by an increase of MM level and a decrease of total protein concentration in blood.

The influence of the infectious-toxic factor and hypoxia as well as the presence of an inflammation in this disease set up the conditions for an increase of free radical oxidation of the lipids from cellular membranes. The intensification of PL is an important part of severe CAP pathogenesis [23-25] as well as the high MDA level is a natural process. Disorders in the system of LP/antioxidant defense were characterized by the increase of the contents of secondary of lipid peroxidation products (MDA) and decrease of catalase activity. Thus, the listed above various and significant disorders of different parts of homeostasis were not significantly eliminated by conventional treatment with antibiotics and required an additional correction by EED methods.

We revealed that severe CAP developed the background of various disorders of immune response, among which the relative lymphopenia, decrease of T-lymphocytes, deficiency of T-helpers as well as increase the contents of T-suppressors were mostly detected. The activation of immune parameters occurs in some patients was due to changes of quantity and increase of activity T-helpers and in others was due decreasing of quantity T-suppressors. Thus, EED methods did not simply change the level of T-lymphocytes, but led to the normalization of the helpers/suppressors ratio. The imbalance of the ratio of T-helpers/T-suppressors could warn against the development of lung autoimmune processes [24].

The initial disorders of immune response in these patients concerned mainly the cellular link. Thus, humoral immune status was characterized by the increase of IgM, IgA, IgG levels. The low level of B-lymphocytes against the background of the high level of Ig reflected a high functional condition of Ig. The significant increase of the levels of IgA, IgG, IgM confirmed the fact, that the immune protection of these patients was formed, mainly, by the humoral immune response.

Complex and heterogeneous pulmonary changes during severe CAP evolution, cause disorders of organs and systems function and demand including into its treatment the new methods which would stimulate the protectively-adaptive reactions and immune response as well as would have disintoxication action and ability to regulate the lipids peroxidation. EED methods can provide these effects.

The fluctuations of Ig levels led to the some normalizing influence on IgA, IgG (less IgM) values. It is possible to regard it as immune-correcting action of EED methods due to the activation of antibodies function and antibodies-formatted cells against the background of an acute lung inflammation.

The additional using of these methods promoted the increasing activity of the immune response by the 12-14th day of therapy with the subsequent tendency to normalization of these parameters against the background of clinical and radiological resolution of severe CAP. We revealed the positive dynamics of clinical and radiological signs in 96%, 91% and 95% of the 2nd, 3rd and 4th patient's groups respectively after finishing the treatment.

Three procedures of UVLE positively influenced the patient's immune response as well as the balance in the system of proteinase/inhibitors and stimulated the reduction of the terms of clinical and radiological resolution of this severe disorder in contrast to the standard management.

The complex positive effect of UVLE could be caused by a heterogeneous action: formation of photoproducts (as a result of loss of molecules of electrons, restructuring of molecules and their disintegration), UV rays action on cell membranes with the subsequent increasing of phagocytic activity, secretion of bactericidal proteins and interleukins; disintoxication and anti-inflammatory actions (direct bactericidal action due to the break of chemical communications and disorders of cell's structures); mediate influence due to the actions of the biologically active substance formed in the cells as well as antioxidant action (due to the stimulation of synthesis of antioxidants and increase the level of trap's substances of reactive oxygen species) and stabilization of PL [26].

The only stay of blood outside of a vascular bed changes its properties (even during short time) and return blood to body is accompanied by the significant biological action. One of mechanisms of UVLE is connected with structurally functional changes of a surface of blood cells and entrance of the near-membrane components in a blood flow. The changes of cell glycocalix are accompanied by modifying of receptors activity of and the antigens which were localized on a cell surface [27,28]. It was complicate for us to verify this UVLE action because it supplemented the standard therapy of severe CAP.

The above mentioned mechanisms could: stimulate the metabolic and regeneration processes, modulating effect during

change of immune status parameters and PL processes; produce bactericidal and anti-inflammatory effects; improve microcirculation and reduce tissues hypoxemia [29-32]. We did not observe the exhaustion of a pool antioxidant defense during UVLE.

Just a single using of BSS significantly decreased the signs of intoxication as well as blood levels of elastase and trypsin-like proteases in severe CAP patients. The using of 3 procedures of BSS normalized some parameters of the immune response and imbalance of PL/antioxidant defense as well as reduced the terms of clinical and radiological resolution of this pathology in contrast to traditional treatment. The including of BSS in management of this pathology treatment provides more influence on the level of protease activity as compared with UVLE.

SOD, as well as catalase, participates in regulation of body oxidizing processes. Thus, the condition of antioxidant defense was characterized by a compensated significantly increasing activity of SOD. Meanwhile, catalase activity was significantly lower when compared with the control one in patients of all investigated groups. Such a reduction of catalase activity against the background increase of MDA should be regarded as the certain exhaustion of antioxidant defense. Similar data (expressed increase of free radical oxidation that was accompanied by the expressed reduction of antioxidant protection in severe CAP patients) was reported by Trubnikov [33]. Recent studies [21,29] have detected the absence of an adequate reaction from antioxidant defense enzymes in this disorder against a background of increase of LP products and reactive oxygen species from inflammatory cells. Decreasing of catalase activity could act as a risk factor of delaying the resolution of severe CAP [34,35]. Probably, the low level of LP products is the adverse prognostic sign in this pathology. The intensity of LP processes is the protective reaction [36] and do not require cessation of this process but only regulate its rate.

The significant increase of SOD activity as well as the small increase of catalase activity against the background of certain decrease of the baseline MDA level were observed in dynamics in patients who were treated with EED methods. The considerable improvement of the immune response in patients of the 2nd-4th groups after these procedures made it possible to consider that the antioxidant defense (supervising PL) makes the condition for the adequate immune response to the influence of the infectious agent. SOD activity and MDA level tended to reduce as well as to increase of catalase activity in patients who were standard treated by the 12-14th day.

The normalization of the imbalance of PL/antioxidant defense was noted in patients who underwent EED methods application by the 20-22th day. The normalization of functional catalase insufficiency was promoted by BBS or BSS plus UVLE additional using. These methods may decrease PL followed by the improvement of the patient's general condition.

The decreasing of the MDA level (the final product of PL) in patients who were treated with the using of EED methods, was testified by a more expressed stabilizing effect of UVLE, BSS and their combination upon the cellular membranes in contrast to the traditional treatment. During the latter a significantly higher MDA level was detected by the 20-22th day. The high level of products of PL as well as antioxidant defense persisted in patients who were standard treated till the moment of their discharge from hospital [29]. MDA, reacting with amino groups of proteins, could change the structure of elastic fibers in pulmonary tissue; break the function of aerohematic barrier as well as the intensity of pneumosclerosis processes during severe CAP [37].

The imbalance in the systems of proteinase/inhibitors as well as in PL/antioxidant defense develops in this pathology against the background increase of the MM level. The latter was seen naturally in this situation. These disorders were not sufficiently eliminated by antibiotics therapy only.

The condition of proteinase system was characterized by a significant increase of the elastase and trypsin-like activity against the background of expressed deficiency of the proteinases inhibitors (α_1-AT and α_2-MG) in severe CAP patients on admission. α_1-AT is the marker of acute inflammation and its level should be significantly increase during this disorder. Granulocytic elastase could cause the degradation of α_1-AT [38] as well as destroy all the basic lung structures (including of bronchi, alveoli and vessels). The low level of α_1-AT could explain by oxidizing denaturation of α_1-AT by various oxidizing agents [39]. The decrease of rate association between enzyme and inhibitor could allow the elastase activity to realize this destructive action during severe CAP [40]. Thus, the increase of serum protease activity in this pathology as well as accumulation of MM against a background of the small enhancement of α_1-AT and α_2-MG levels was reported by Egorshina [21].

Our results showed that the treatment with EED methods is effective in severe CAP with endogenic intoxication syndrome. Thus, a single using of BSS plus UVLE in these patients rendered the expressed positive influence upon the proteinase activity in blood. It was accompanied by the positive clinical dynamics (reduction of fever, weakness, breathlessness, tachycardia as well as an improvement of common health state).

The application of EED methods (better BSS plus UVLE) in CAP therapy is more effective (as compared with standard therapy only) for quicker improvement of the imbalance in oxidant/antioxidant and proteinase/antiproteinase systems. Even a single carrying out BSS and BSS plus UVLE caused the significant decrease of elastase and trypsin-like activity, as well as MM level. The latter is the marker of activation of endogenous proteolysis and the expressiveness of endogenic intoxication syndrome [26]. The high MM level could break microcirculation, reduce of erythropoiesis, stimulate development of a secondary immunodeficiency and reduce the synthesis of proteins as well as the level of tissue respiration [41-43].

The obtained data could be explained by the fact, that during procedures of BSS some exo-/endogenic metabolites from the patient's body were eliminated. Such positive dynamics was accompanied by decrease of the endogenic intoxication signs (reduced BT, HR, RR and CSI). These results were in accord with the concept of the key role of proteolysis hyperactivity in generation of endogenic intoxication syndrome [26].

We observed every other day the repeatedly increasing activity of proteinase, but it did not reach an initial level. It was caused by going out of proteases into a blood according to gradient of concentration against a background the decrease of microcirculation blockade [22]. A single carrying out UVLE did not influence the protease system, however, it was accompanied

by reduction of the endogenic intoxication signs too. The similar clinical benefits of a single application of UVLE were observed by other researchers [29,32,44]. Our results extend those of previous studies by showing greater reduction of endogenic intoxication syndrome by using of EED methods.

We revealed that these methods could provide the significant benefits, largely by reducing this syndrome. Thus, carrying out the BSS or UVLE courses (as their combination) led to the significant decrease of elastase and trypsin-like activity (by about 2 times) as well as MM level and to increase of antiproteinase level (by 2 times) by the 12-14th day. These parameters were subsequently normalized by the 20-22th day of treatment. Meanwhile, in the 2nd group the decrease rate of protease activity was notably lower and by the 20-22th day the high elastase activity level persisted against a background of normalization of other parameters.

Normalization of CSI and the radiological resolution of severe CAP were detected by the finishing treatment in majority of patients (95% of patients of the 3rd-4th groups). The time of this pathology radiological resolution in the 2nd group significantly did not differ from the 3rd and 4th groups.

Some increase of elastase activity against a background of small decrease of trypsin-like activity as well as MM level ($P<0.05$) and several enhancement the level of protease inhibitors was observed during standard therapy by the 12-14th day. The high levels of elastase and trypsin-like activity as well as MM were detected by the 20-22th day in patients who were conventional treated.

Those, who underwent such therapy, received a worse clinical dynamics. The dynamics of protease activity and MM level was accompanied by the later terms of CSI decrease and radiological resolutions, as compared with the patient's groups those were treated with using of EED methods.

Our data showed the favourable outcomes in severe CAP patients who were additionally early treated with EED methods vs conventional management only. Thus, the using of EED methods allowed decrease the length stay in ICU for this disorder in contrast to traditional treatment. The including of UVLE cut down therapy costs of this pathology by 14%, either BSS or BSS+UVLE by 18% in spite of additional application of these methods.

Conclusions

Our results suggest the innovative therapeutic options for severe CAP, which could improve the outcome. This trial has shown the benefit of EED methods including in traditional therapy of this pathology. Thus, EED methods improved the patients' general condition and treatment failure rate.

The introduction of BSS and UVLE into severe CAP therapy has significantly sped up the decrease of elastase and trypsin-like activity, the MM level, simultaneously the increase of α_1-AT and α_2-MG levels in contrast to the standard management. Positive dynamics of these laboratory parameters was accompanied with the significantly faster improvement of the patient's general condition (symptoms disappeared quicker in the 2nd-4th groups by 2-4 days vs the 1st group), the decrease of CSI as well as reduction of CXR terms resolution in comparison with traditional management of this pathology.

Combination of BSS plus UVLE improved treatment efficacy of severe CAP as well as provided the similar effect with single BSS using. But this combination quicker normalized vesicular breath in contrast to standard therapy and single application of BSS or UVLE. These two management strategies (BSS or UVLE) appear equally effective in this disorder treatment.

Thus, the use of EED methods in severe CAP therapy is more effective (as compared with the standard management only) for quicker improvement of patient's status as well as for decreasing the treatment period, which makes EED methods an attractive therapy option.

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