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INTENSIVE CARE OF SARS-COV-2 PATIENTS: OUR EXPERIENCE

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ІНТЕНСИВНА ТЕРАПІЯ ПАЦІЄНТІВ SARS-COV-2: НАШ ДОСВІД

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Ми проаналізували 45-денний досвід роботи в COVID-лікарні на базі хірургічного центру. Більше 30% пацієнтів потребували ШВЛ. Найбільш важкі пацієнти старше 80 років (13,5%) та з ІМТ> 40 кг / м^2 (21,8%). При лікуванні використовувалися рекомендації МОЗ РФ. 17,9% пацієнтів отримували неінвазивну штучну вентиляцію легенів (NIMV), 33,9% – високопоточних назальний кисневу терапію (HFNOT). 69% були переведені на механічну вентиляцію, з них 19,8% – шляхом накладення трахеостоми. Госпітальна летальність склала 4,8%. (жінки 55%, чоловіки 45%, пацієнти з ожирінням – 36,8%, пацієнти старечого віку – 45% від усіх летальних випадків). Продемонстрували ефективність послідовне використання різних методів лікування респіраторних захворювань, методів «fast track» при МВ і використання екстракорпоральних методів лікування «цитокинового шторму».

Ключові слова: *коронавірус, інтенсивна терапія, ШВЛ, екстракорпоральні методи.*

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We have analyzed 45-day experience of work in the COVID-hospital, based on a surgical center. Over 30% patients required mechanical ventilation (MV). The most severe patients over 80 years old (13,5%) and with BMI > 40 kg/m^2 (21.8%). Russian Federation Healthcare Ministry guidelines were used during the treatment. 17,9% of patients were on non-invasive mechanical ventilation (NIMV), 33,9% – on

high-flow nasal oxygen therapy (HFNOT). 69% were leaned from the MV, 19,8% of them leaned through tracheostomy. Hospital mortality rate was 4,8%. (female 55%, male 45%, obese patients – 36,8%, senile patients – 45% from all lethal cases). Effectiveness of consecutive use of different respiratory care methods, "fast track" methods during MV and extracorporeal methods of "cytokine storm" treatment had shown their effectiveness.

Key words. *coronavirus, intensive care, mechanical ventilation, extracorporeal methods.*

Introduction. During SARS-Cov-2 pandemia, A.V.Vishnevsky National Medical Research Center of Surgery was converted to covid-19 hospital.

It is known, that covid-19 starts as an upper respiratory airway infection. Attacking endothelial cells via ACE-2 receptors, virus releases proinflammatory cytokines, that increase adhesion and blood coagulation, and if massive contamination occurs, it can cause so called "cytokine storm" with high levels of TNF-α, interleukins, Granulocyte-macrophage colony-stimulating factors, chemokines[1].

Hyperinflammatory response, microcirculation and blood-circulation system alteration lead to fulminant manifestation of polyorganic insufficiency. 93% and 25% of patients need basic and expanded cardio-protective therapy, 20% required renal therapy, 5% – neurological therapy, and 0,4% required liver-protective therapy. [2]. Troponin rise is associated with 5-fold risk of MV requirement and death – it required expanded hemodynamic monitoring; preventive renal support care improves survival rate; aggressive antithrombotic treatment; can reduce pulmonary embolism rate; at least 25% of patients have cognitive and psychological disorders and have low physical exercise tolerability, so they need early neuro-protective treatment. That's why we consider SARS-Cov-2 as a multisystem clinical syndrome and we were actively searching for other organs involvement apart from respiratory system.

Analysis of our experience is the main goal of this article.

Methods. 150 specialized beds (with oxygen supply) were established in 4 departments, as well as 28 intensive care beds, with the access to the use of mechanical ventilation (MV), non-invasive mechanical ventilation (NIMV) and high-flow nasal oxygen therapy (HFNOT). Besides that, intensivists have been working in the admission room to regulate patients' triage according to the severity of their condition. Totally 414 patients were treated in our center, 156 (37,7%) of them were treated in ICU. Male – 89 (57,05%); female – 67 (42,9%). Mean age – 69±11,3 [min 24 max 97] years. Senile patients >80 years – 21 (13,5% of all ICU patients). Patients with BMI>40 kg/m^2 – 34 (21,8%) [min 128 kg; max 183 kg]. Severity of patient's condition was evaluated with National Early Warning Score (NEWS) score: 6,9±2,7 [min 4, max 9], in the ICU Sequential Organ Failure Assessment (SOFA) score was also evaluated: 8,1±3,1 [min 3, max 16]. Prolonged MV was carried out in 84 cases (20,3% of all patients, or 50,6% of all ICU patients) CT-4th grade pneumonia was diagnosed in 94 patients (60,2%). After admission to the hospital polymerase chain reaction (PCR), CT-scan, ECG, lab tests (blood test, urine test, and acid-base test, troponin I, D-dimer, C – reactive protein, creatinine, coagulation profile, and blood culture test). All patients were receiving triple antiviral treatment (lopinavir/ritonavir + hydroxychloroquine+azithromycin), 78% of them started this treatment before hospitalization; ascorbic acid 0,1 g/kg; paracetamol up to 4g/day; different vitamins, including D3; H-blockers; Enoxaparin sodium. While on MV, unless

superinfection signs were present (procalcitonin<0,5 ng/ml) dexamethasone 0,1 mg/kg was also used. Consecutive respiratory support was used: first of all, active pronation to the right/left side, to the back and the abdomen every 2 hours with arterial and venous blood gas testing. If respiratory parameters were low, high-flow oxygenation was used, if this technique was ineffective, non-invasive ventilation was used, if none of these measures were useful, then patient underwent trachea intubation and mandatory mechanical ventilation. Weaning from the ventilator was made in reverse sequence.

Results and discussion. Totally 393 patients (94,9%) were discharged from our hospital. Average ICU-stay for survived patients was 9,4±3,9 [min 2, max 34] days. 58 patients (69%) were weaned from ventilator, excluding those who died or was transferred to other hospital. All patients on MV were also in a prone-position. Protective MV in SIMV+PC mode was used with FiO2 <70%, 70% Pi ≤ 25cmH2O; PS 20-22 cmH2O; Peep ≤12cmH2O; respiration rate depended on CO2 levels. 31 patients (19,8%) underwent tracheostomy in 6,7 days[min 3, max 11]. 28 patients were on non-invasive ventilation, later they were converted to MV. 53 patients were on high-flow oxygenation (33,9%; 21 of them (39,6%) were later converted to MV). ESICM suggests using oxygen delivered through the nasal catheter with high-flow (HFNC) as a first line therapy for COVID-19 patients with acute hypoxic respiratory failure instead of NIPPV / CPAP, although CPAP can be used with "careful monitoring for a short period of time". Studies from China show that HFNC is the most frequent used respiratory support technique.

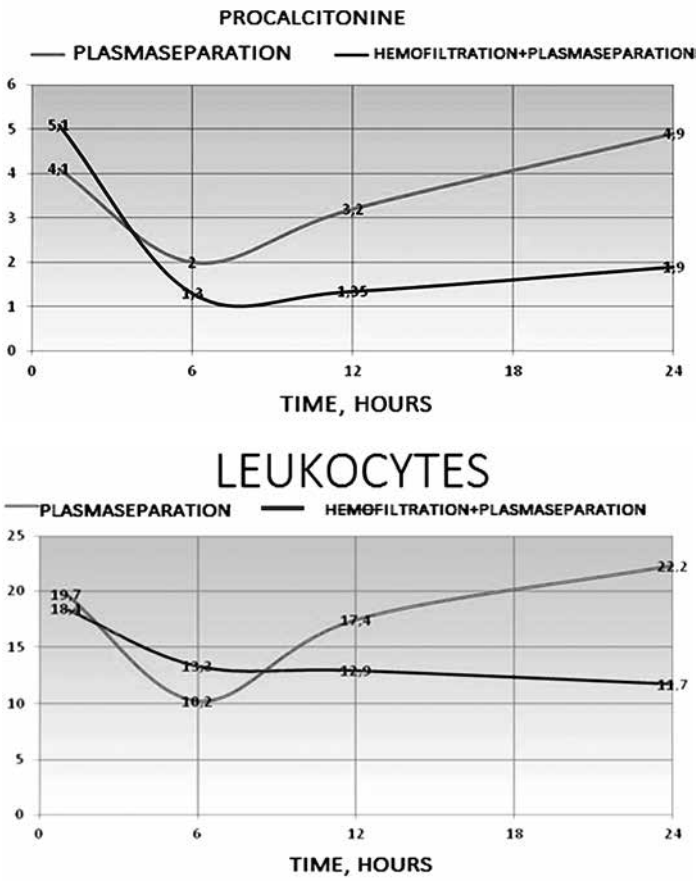
Based on the fact, that cytokine storm – is a hyperimmune reaction, we applied our own treatment and prevention strategies that we usually use for systemic inflammatory response syndrome during long-standing cardio-pulmonary bypass, graft rejection or septic shock. [5] Combined techniques were mostly used, because stand-alone procedures allow neutralizing shock and stabilizing hemodynamics. 48 extracorporeal procedures were conducted in 27 patients (30 hemodiafiltrations and hemodialysis, 18 cytosorbtion in different variations – hemoperfusion and plasmasorbtion). Duration of these procedures was 6 hours min till 64 hours max. Indications were following:

- Septic shock/ cytokine storm – 17 (10,9% in ICU or 4,1% amongst all patients)
- Chronic renal failure/ acute renal failure – 5 (3,2% in ICU, or 1,2% amongst all patients)
- Hyperhydration/acute respiratory distress syndrome– 5 (3,2% in ICU)

In 4 cases (2,6% of all ICU patients) at unstable hemodynamics because of vasoplegia (septic shock) – positive results were sustained by glucocorticoid pulse-therapy, 40-50 ml/kg hydration with following hemofiltration and/or forced urine output (1 death (25%)). (pic. 1).

In 36 cases (23,1% of all ICU patients) when "cytokine storm" started (high fever, desaturation, increased lung damage on CT-scan) tocilizumab was used. 3 patients got this medication twice. One lethal case in this group (2,7%). Results varied depending on initial fever level. In 76% cases there was a positive trend according to clinical signs (decrease in fever level, lover lung involvement on CT-scan), 12% got worse lab tests, and 12% got better lab tests. In latter group there also was a lower ventilation time. Hence tocilizumab has very narrow therapeutic range for patients in critical condition and it can be used for patients with hyperactive reaction in short-term period.

Triple antiviral therapy was used in 100% ICU patients, but different length of treatment before admission. Significant positive clinical signs were not registered, but from

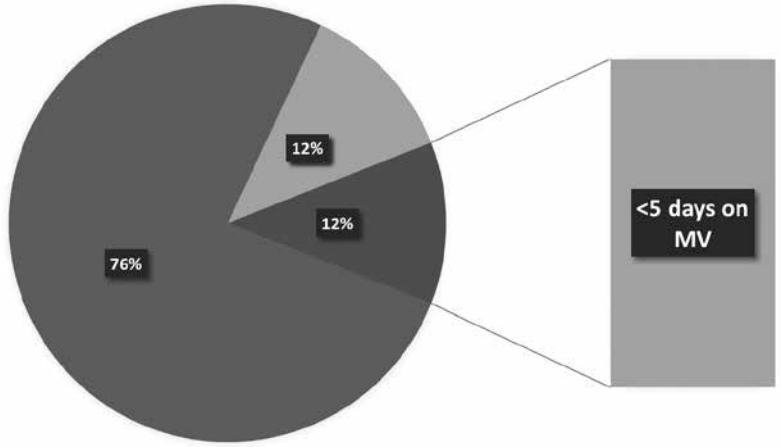


Picture 1. Changes in inflammatory response markers during stand-alone and combined procedures.

Note. Plasma filtration (Evaclio EC-2C20) – duration 6 h; Hemofiltraion (Filtryzer BK-U) – duration 24 h; WBC x109; procalcitonine ng/ml.

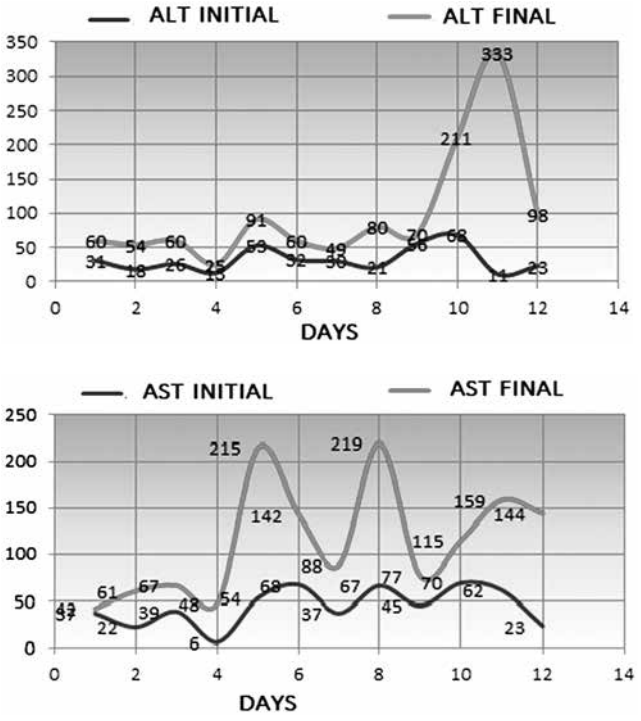
the 5th day there was an exponential increase in cytolysis signs and clinical manifestation of liver and intestine malfunction (jaundice, indigestion), after which treatment was discontinued. (pic.3). Allergic reaction, often recognized as a skin manifestation of COVID-19 in 4 cases (2,6%) were gone after discontinuation of antiviral treatment.

All patients with normal parameters of serum hemostasis hyperthrombocytosis was registered, as well as increase in D-dimer levels and hyperaggregation. Enoxaparin sodium, used subcutaneously in therapeutic dose, did not work properly mainly because of vasopressive drugs that have been used in this patients. As an alternative, we have been using IV administration on enoxaparin sodium 0,8 every 8 hours (based on half-life of this drug). Adequate hemostasis parameters were reached by triple anti-platelet therapy (including aspirin 100 mg and clopidogrel 75mg) with continuous IV heparin administration 10-25 IU/day under ACT control. Also in this terms, subcomoensated anemia correction is reasonable for maintaining adequate O_2 levels to the tissues. Decrease in hemoglobin levels (which, most commonly concurs with hyperthrombocytop-



Picture 2. Change in T° and percentage of lung tissue involvement on CT after tocilizumab.

Note: 76% – better clinical signs without any changes on CT, 12% light – 2 parameters got worse, 12% dark – 2 parameters got better.



Picture 3. Cytolisis rise depending on length of triple antiviral therapy.

Note. ALT – alanine aminotransferase, IU/L , AST – aspartate aminotransferase, IU/L.

athy) is caused by sludge-effect of blood cells in microcirculation, which requires use of angioprotectors, such as pentoxifylline.

Hospital-acquired infection was registered in 16 patients (10,25%) with their ICU-stay 14,5±5,1 days. Patients, who required respiratory care and have received azithromycin earlier, in case of bacterial pneumonia, were treated with cefaperazone/sulbactame + vancomycin or linezolid. After transfer to ICU all patients got bacterial culture test from tracheobronchial tree, blood and urine and after that according to antibiotic susceptibility treatment was administered. The most used combinations were cefaperzone/sulbactame+vancomycin (linezolid) – 72%, tigecyclin + colistin – 21%; meropenem+colistin – 7%. Considering hypercoagulation syndrome, we almost haven't used immune donor serum, despite its' popularity in several studies. There have been several randomized trials, showing its low effectiveness [6]

Analysis of lethal cases

20 lethal cases (4,8%). Mortality in ICU 12,8%. Male mortality – 9 (45% of all lethal cases, or 10,1% from all males), female mortality 11 (55%, or 16,4% of all females), although other authors report significantly higher mortality in males [7]. The majority of lethal cases are in senile patients (80+ years) – 45% and overweighed – 7 (36,8% of all deaths, all females). 5 patients (25%) had negative CoV-2 test and died because of the decompensation of their comorbidities (COPD, chronic heart failure, renal failure).

Organizational aspects

All staff members while in "red zone" were wearing full individual protective equipment (respirators FFP3, glasses, overalls), which allowed to minimize contact-associated contamination of the personnel. As a result from 98 staff members 1 (1,02%) had a mild case (CT-1), 2 (2,04%) had positive test results with no clinical symptoms. Triage with intensivists in the admission room allowed us not to overload ICU with mild patients. Forming several departments depending on severity of patients condition provided rational allocation of the personnel and division of recovering patients and incoming patients in critical condition. Additional ICU wards outside of reanimation department was also rational, with intensivists working there, providing non-invasive and mechanical ventilation, if transportation of the patients was impossible. Constant intensivist consultations of patients from different departments provided well-timed transfer to ICU. Inability to clean every day all wards was compensated by combination in one ward patients with similar bacterial flora.

Conclusion. Our experience allows us to assume that dividing COVID-19 patients according to their condition with opening at least 20% of ICU beds with the use of different techniques of respiratory support, participation of our intensivists in every stage of treatment, using modern techniques for "cytokine storm" reduction, including extracorporeal detoxication and immune-suppressive treatment, fast-track standards in weaning from ventilation, rational antibacterial medications minimize lethal cases and provide decent outcomes in quality of life for patients.

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