ENDOTHELIAL DYSFUNCTION IN COVID-19 PATIENTS AND CLINICAL APPLICATION OF LASER THERAPY

Kochetkov AV1 2, Ponomareva NV2, Kadnikova NG2, Mitkovskiy VG3 4, Yampolskaya EN1, Lazarev VV2

1 Academy of Postgraduate Education FNSC FMBA of Russia, Moscow, Russia
2 Central Clinical Hospital for the Rehabilitation of FMBA of Russia, Sokolchnogorsk District, Moscow Region, Russia

This review covers the published papers describing endothelial dysfunction pathogenesis and molecular mechanisms behind the effect of low-level laser therapy on regulation of the said pathogenesis. Herein, we present the current experience of using laser therapy to prevent development of endothelial dysfunction in the context of post-COVID-19 rehabilitation, as well as the accumulated data on the methods of combination of external or intravenous laser blood therapy and influence on the immunocompetent. We provide justification for practicing personalized approach at various stages of post-COVID-19 rehabilitation and treatment. The basis allowing greater efficacy of post-COVID-19 rehabilitation, including protocols making use of laser therapy, is the analysis of single-nucleotide polymorphisms of genes that determine adaptation processes, peculiarities of the immune response to infectious pathogens, predisposition to the development of respiratory distress syndrome, severe pneumonia, sepsis, multiple organ failure, development of endothelial dysfunction, thrombotic complications, the analysis that allows identification of patients running higher risk of critical conditions.

Keywords: COVID-19, endothelial dysfunction, rehabilitation treatment, laser therapy, personalized approach, genotyping

Author contribution: AV Kochetkov — idea, data analysis and interpretation; NVU Ponomareva — literature analysis, manuscript drafting; NG Kadnikova — laser therapy technique application, data collection; VG Mitkovskiy — research organization task setting; EN Yampolskaya — research results analysis and interpretation; VV Lazarev — selection of patients for application of the technique, analysis of the results.

Correspondence should be addressed: Andrey V. Kochetkov
Volokolamsko street, 91, Moscow, 125371; kotchetkov@inbox.ru

Received: 09.11.2020 Accepted: 24.11.2020 Published online: 18.12.2020

DOI: 10.47183/mes.2020.024

The global COVID-19 pandemic caused by the SARS-CoV-2 coronavirus is a challenge for the entire mankind, but the first to search for solutions thereto are scientists and doctors that are tasked with finding ways to curb incidence, effectively treat and rehabilitate COVID-19 patients and minimize the associated complications and mortality.

One of the many features of COVID-19 is the pronounced non-specificity of the observed pathological processes and its capacity to damage both organs and tissues and functional regulatory systems. At the same time, development of endothelial dysfunction can be named a factor that largely unites various disorders. There is an opinion gaining popularity that vascular endothelial damage is the cornerstone of organ dysfunction in severe SARS-CoV-2 infection cases [1].

The patients that died from respiratory failure resulting from COVID-19 had diffuse alveolar injury with perivascular T-cell infiltration as a specific histological pattern registered in the peripheral lung. The lungs of these patients have distinctive vascular features: severe endothelial damage associated with intracellular presence of the virus and fragments of destroyed cell membranes. Histological analysis of pulmonary vessels of COVID-19 patients revealed widespread thrombosis and microangiopathy. COVID-19 patients had alveolar capillary micro clots 9 times more often than influenza patients (p < 0.001). All this indicates that the disease also translates into a severe endothelial dysfunction [2].

Endothelial dysfunction (EnD) — a complex multifaceted process typically seen in the context of cardiovascular,
metabolic and immune disorders — is a current and serious challenge for clinical practitioners, even when considered outside of connection to COVID-19 [3]. And with a developing viral infection in the background, exploring the means to prevent this pathology is of paramount importance.

Endothelium is a cardiovascular endothelial organ that, in critical situations, enables communication between blood and tissues [4]. It acts as a barrier between the blood and the vascular wall, helps adaptation to changing environmental conditions through local regulation of vascular tone, vascular wall integrity protection etc. Normally, endothelial cells, following alterations in blood flow rate, exposure to mediators or neurotransmitters, react by increasing the synthesis of substances that cause relaxation of the vascular wall’s smooth muscle cells (nitric oxide (NO) and other relaxants). They also work to prevent thrombogenesis by blocking platelet aggregation, oxidizing low density lipoproteins, expressing adhesion molecules, “sticking” monocytes and platelets to the vascular wall, producing endothelin etc. Compensatory mechanisms are activated under the influence of a damaging factor. In case of prolonged exposure to such a factor (hypoxia, intoxication, inflammation, hemodynamic overload, etc.), compensation fades and a pathological process develops. Endothelial dysfunction is an imbalance between biologically active substances synthesized by endothelial cells (potentially protective NO, endothelial hyperpolarization factor, prostaglandins) and damaging substances (endothelin-1, thromboxane A2, superoxide anion etc.) [5]. It is the genotype that shapes all these normal and pathological molecular mechanisms of endothelium’s adaptive response to normal or excessive influences. Currently, there are over 1500 genes established to have an association with multifactorial human diseases.

The human genome investigation efforts in the context of the Human Genome Project, Hap Map project, The 1000 Genomes projects, The SNP Consortium, have revealed mutations and single nucleotide polymorphisms (SNP) in genes encoding protein molecules of the body’s regulatory systems. Their associations with various pathologies were either confirmed or refuted [6–9].

For example, the public Mendelian Inheritance in Man database (OMIM) [10] and the single nucleotide polymorphisms database contain more than 3.5 million SNP markers [11].

One of the studies investigating the significance of polymorphism of various genes considered possible contributors to the development of cardiovascular diseases (CVD) identified 105 genes that most likely support pathophysiology of CVD [12]. The researchers focus on genes that determine endothelium’s properties, its role in the development of local vasospasm/vasodilation, hemostasis, inflammation, atherosclerosis, angiogenesis, etc [13–14].

Long before the COVID-19 pandemic, significant individual characteristics of critical conditions observed dynamically triggered the analysis of the results of geno-phenotypic examinations of IC patients [15–19]. These studies presented comorbid conditions gene diagnostics, identified SNP markers associated with an increased risk of community-acquired and nosocomial pneumonia, risk of development of an acute respiratory distress syndrome, CVD-related thrombotic complications. The results of the analysis of identified gene polymorphisms the products of which shape regulation (hemostasis, renin-angiotensin system regulation, immune system regulation, i.e. individual response to infectious pathogens and production of cytokines, drug metabolism) provide justification to screening patients running a high risk of development of life-threatening conditions. Such patients need non-standard treatment approaches in critical situations.

Personalized approach is a strategy popular at various stages of rehabilitation. In particular, patients in cardio- and neurorehabilitation undergo genotyping enabled by various SNP panels [20–25]. In clinical practice, molecular markers of individual susceptibility to various patterns of CVD development (the most important of which is endothelial dysfunction) allow predicting sudden death of a patient or the development of catastrophic multiple organ complications, as well as choosing the most effective therapies, which may be pharmacotherapy and non-drug methods [26–27], including laser therapy.

It was observed that patients with different phenotypes respond to laser therapy differently. In particular, low level laser therapy (LLLT) was more effective in patients that exhibited domination of reactions of the sympathetic nervous system than in whose parasymathetic responses were stronger [28]. The peculiarities of the endothelial function were found to be behind this difference. The said function is genetically determined by the cooperation of gene regulatory networks [26–27]; it needs to be studied further, same as the collagen of geno- and phenotypical characteristics and individual responses to various therapies.

Concomitant diseases can synergistically activate pathophysiological pathways. Thus, inflammation activates vascular pathology through pro-inflammatory cytokines, endothelin-1 and nitric oxide, which contributes to long-term damage to fatty acids, proteins, DNA, and mitochondria. Dysfunctional energy metabolism (impaired production of mitochondrial ATP, the formation of amyloid-β), development of endothelial dysfunction and violation of the blood-brain barrier lead to the cerebral blood flow reduction and chronic cerebral hypoperfusion with oxygen and nutrient deficiency, metabolic and synaptic disorders, neurodegeneration and white matter atrophy, cognitive dysfunction and development of Alzheimer’s disease [29]. Identification and assessment of the entire complex of pathogenetic mechanisms driving inflammation form basis for targeted therapies designed to remedy the reduced cerebral blood flow and hypometabolism.

Molecular-cellular and physiological mechanisms of vascular homeostasis regulation

The key manifestations of EnD are abnormal bioavailability of nitric oxide (NO), the main vasodilator, which results from suppression of endothelial NO synthase (NOS), with the NO synthesis decreasing consequently [30]. Under normal physiological conditions, there is a balance between vasoconstrictors secreted by the endothelium and vasodilators. Any violation of this balance leads to a local spasm and vascular tone growth. As a result, the compensatory capacity of endothelium deteriorates gradually, which translates into breakdown of a rather complex regulation of the natural vascular bed expansion and shrinking mechanisms [13]. Endothelium plays a key role in maintaining vascular homeostasis since it releases biologically active substances (Table 1), but is also susceptible to the effects of external regulators [31–33]:

– mast cells that release heparin and histamine;
– platelets containing vascular endothelial growth factors and blood coagulation factors, etc;
– hormones and neuropeptides (adrenaline, acetylcholine, histamine, bradykinin, etc).

Despite the fact that the regulation mechanisms are known (see Table 1), the ways to remedy endothelial dysfunction pharmacologically require further comprehensive study and
Physiologically active substances, regulators of the circulatory system, synthesized in the endothelium

**Table 1. Physiologically active substances, regulators of the circulatory system, synthesized in the endothelium**

<table>
<thead>
<tr>
<th>Vascular wall tone regulators</th>
<th>Vasodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin I-II</td>
<td>Nitric oxide (NO)</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Prostaglandin E₂ (PGE₂)</td>
</tr>
<tr>
<td>Thromboxane (TXA₂)</td>
<td>Endothelial hyperpolarizing factor (EDHF)</td>
</tr>
<tr>
<td>Prostaglandin H₂ and G₂</td>
<td>Bradykinin</td>
</tr>
<tr>
<td><strong>Regulators of hemostasis and antithrombosis</strong></td>
<td>C-natriuretic peptide Adrenomedullin</td>
</tr>
<tr>
<td><strong>Prothrombogenic factors</strong></td>
<td>Endothelin III</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF) tissue plasminogen activator inhibitor (PA-I)</td>
<td>Tissue plasminogen activator (t-PA)</td>
</tr>
<tr>
<td>Von Willebrand factor (coagulation factor VIII)</td>
<td>Prostacyclin (PGI₂)</td>
</tr>
<tr>
<td>Angiotensin IV</td>
<td><strong>Antithrombogenic factors</strong></td>
</tr>
<tr>
<td>Endothelin I</td>
<td></td>
</tr>
</tbody>
</table>

**Leukocyte adhesion regulators**

<table>
<thead>
<tr>
<th>Stimulants</th>
<th>Inhibitors of myocyte migration and proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin-I</td>
<td>NO</td>
</tr>
<tr>
<td>Angiotensin-II</td>
<td>Prostacyclin (PGI₂)</td>
</tr>
<tr>
<td>Superoxide radicals</td>
<td>C-natriuretic peptide</td>
</tr>
<tr>
<td>Growth factors: fibroblast, platelet, insulin-like, transforming growth factor β (bFGF, PDGF, IGF, TGFβ)</td>
<td></td>
</tr>
</tbody>
</table>

**Stimulants**

<table>
<thead>
<tr>
<th>Tumor necrosis factor α (TNFα)</th>
<th>Superoxide radicals (O₂⁻, OONO⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein kinase C</td>
<td><strong>Inhibitors</strong></td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

**Primary and secondary mechanisms of the biomodulating action of low-level laser therapy (LLLT)**

The current understanding of the biomodulating action of LLLT, which agrees with the clinical practice of laser therapy use, has the thermodynamic triggering of Ca²⁺ dependent processes as the primary mechanism. Once the various intracellular components have absorbed photon energy (laser light), the intracellular calcium store is activated, Ca²⁺ ions are released and the concentration in the form of two waves with half periods of 100 and 300 s is increased, which is followed by the cascade of responses on all levels, from cells to the entire body: activation of mitochondria, cellular metabolism and proliferation, normalization of the immune and vascular systems, inclusion of the autonomic and central nervous system into the process, etc (Fig. 1) [35–37].

Versatility and high efficacy of laser therapy, which is unique type of physiotherapy, relies on the action at cellular level, with the maximum frequency of optical band electromagnetic waves and laser light coherence (monochromaticity).

**Influence of LLLT on the vascular homeostasis regulation factors and immunity**

It is well known that almost all of the above regulators (Table 1) are, to a certain degree, associated with changes in Ca²⁺ concentration; we will cite only a few reviews [38–39].

From the point of view of the subject researched, we should be primarily interested in nitric oxide, the synthesis and release of which is Ca²⁺ dependent [40]; therefore, it is not surprising that many studies confirm that LLLT can stimulate the release of NO, thus enabling regulation of the vascular homeostasis [41–47].

Moreover, there are studies demonstrating a direct relationship between intracellular Ca²⁺ concentration increase and NO release intensity and subsequent vasodilation [48–50]. Endothelial system normalization in children with bronchial asthma was confirmed by changes in various parameters of blood plasma, including endothelin-1 and nitric oxide [51–52]. The capacity of LLLT to effectively stimulate the release of PGE₂ has been proven both in experimental [53–55] and clinical studies [56–58].

In arterial hypertension patients, regimens of both external laser therapy (ELT) pulsed infrared LLLT and intravenous laser blood therapy (IVLBT) improve a number of biochemical, hemorheological and hormonal parameters (C-peptide, insulin, angiotensin, bradykinin, aldosterone, cortisol), and the improvements persist for at least 6 months [59–61].

Many researchers have shown the role of the kallikrein system in hemovascular regulation and the possibility of its correction through illumination of blood with red laser (wavelength of 635 nm) and/or incoherent ultraviolet (UV) light [62–65].

Current laser therapy techniques actively exploit the well-known anti-inflammatory effect of LLLT. Numerous studies have shown that LLLT can activate phagocytes (which absorb foreign particles of bacteria, viruses, and dying cells) and the synthesis of cytokines, including interferons (IFNs), which spearhead the first line of defense against viruses.
Fig. 1. Molecular-cellular mechanisms of the biomodulating action of LLLT and contribute greatly to the development of adaptive immunity. IFNa and IFNb, which are secreted by lymphocytes, macrophages, fibroblasts and some epithelial cells, stimulate the activity of macrophages and natural killer cells (NK). IFNg, secreted by T-cells and EK, regulates the immune response, has antiviral and antitumor effects. In addition, LLLT improves micro- and macrocirculation by increasing the saturation of damaged tissues with oxygen and improving their trophic supply by boosting metabolism and proliferation, thus initiating the development of recovery processes. These properties of LLLT make it an effective prevention and therapeutic tool that can be used to counter viral infection and its consequences and to prevent development of pulmonary fibrosis [37].

**Laser therapy techniques**

In the context of COVID-19 treatment, external laser therapy or intravenous laser blood illumination (ELD or IVLBT) are used...
Table 2. Zones exposed to laser light as a coronavirus disease prevention measure

<table>
<thead>
<tr>
<th>Emitting head type</th>
<th>Exposed area (Figure 2)</th>
<th>Exposure, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML-635-40</td>
<td>1 — left supraclavicular region</td>
<td>2</td>
</tr>
<tr>
<td>ML-904-80</td>
<td>2 — thymus</td>
<td>1</td>
</tr>
<tr>
<td>ML-904-80</td>
<td>3 — spleen</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. Parameters of the LLLT technique for prevention of coronavirus disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser light wavelength, nm (spectrum)</td>
<td>635 (red)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>904 (IR)</td>
<td>–</td>
</tr>
<tr>
<td>Laser operating mode</td>
<td>Pulse</td>
<td>Matrix emitting head, surface area 10 cm²</td>
</tr>
<tr>
<td>Light pulse duration, ns</td>
<td>100–150</td>
<td>–</td>
</tr>
<tr>
<td>Radiation power, W</td>
<td>35–40</td>
<td>635 nm</td>
</tr>
<tr>
<td></td>
<td>60–80</td>
<td>904 nm</td>
</tr>
<tr>
<td>Power density, W/cm²</td>
<td>4–5</td>
<td>635 nm</td>
</tr>
<tr>
<td></td>
<td>8–10</td>
<td>904 nm</td>
</tr>
<tr>
<td>Frequency, Hz</td>
<td>80</td>
<td>–</td>
</tr>
<tr>
<td>Exposure per zone, min</td>
<td>See Table 2</td>
<td>–</td>
</tr>
<tr>
<td>Number of exposed zones</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Localization</td>
<td>See Table 2</td>
<td>–</td>
</tr>
<tr>
<td>Method</td>
<td>Contact</td>
<td>Through the transparent tip</td>
</tr>
<tr>
<td>Number of procedures per regimen</td>
<td>2–3</td>
<td>Daily</td>
</tr>
</tbody>
</table>

Method 1: prevention

Before starting the procedure, it is necessary to remove the protective cover and mount the magnetostatic field (MF) tip. The tip should be subjected to preliminary chemical sterilization (disinfection).

Fig. 2A and Fig. 2B show the zones (points) of application; Table 2 and Fig. 2C prescribe the type of emitting head and the exposure; Table 3 contains the parameters of the laser light.

Method 1: treatment

Before starting the procedure, it is necessary to remove the protective cover and mount the MF tip. The tip should be subjected to preliminary chemical sterilization (disinfection).

Fig. 2A and Fig. 2B show the zones (points) of application; Table 2 and Fig. 2C prescribe the type of emitting head and the exposure; Table 3 contains the parameters of the laser light.

Combined method 2

Combined method: external irradiation of zones 6-8 as shown on Fig. 2; type of emitting head and exposure as given in Table 4.

Table 4. Zones exposed to laser light in coronavirus patients

<table>
<thead>
<tr>
<th>Emitting head type</th>
<th>Exposed zone (Fig. 1)</th>
<th>Exposure, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML-635-40</td>
<td>1 — left supraclavicular region</td>
<td>2</td>
</tr>
<tr>
<td>ML-904-80</td>
<td>2 — thymus</td>
<td>1</td>
</tr>
<tr>
<td>ML-904-80</td>
<td>3 — spleen</td>
<td>1</td>
</tr>
<tr>
<td>ML-904-80</td>
<td>4 — liver</td>
<td>2</td>
</tr>
<tr>
<td>ML-635-40</td>
<td>5 — E36 (zu san li) — symmetrical</td>
<td>0.5 min per zone</td>
</tr>
<tr>
<td>ML-904-80</td>
<td>6–8 — lung injury projection (see Fig. 2 for localization example)</td>
<td>1.5 min per zone</td>
</tr>
</tbody>
</table>
Table 5. Parameters of the LLLT technique for treatment of coronavirus patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser light wavelength, nm (spectrum)</td>
<td>635 (red)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>904 (IR)</td>
<td></td>
</tr>
<tr>
<td>Laser operating mode</td>
<td>Импульсный</td>
<td>Matrix emitting head, surface area 10 cm²</td>
</tr>
<tr>
<td>Light pulse duration, ns</td>
<td>100–150</td>
<td>–</td>
</tr>
<tr>
<td>Radiation power, W</td>
<td>35–40</td>
<td>635 nm</td>
</tr>
<tr>
<td></td>
<td>60–80</td>
<td>904 nm</td>
</tr>
<tr>
<td>Power density, W/cm²</td>
<td>4–5</td>
<td>635 nm</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>904 nm</td>
</tr>
<tr>
<td>Frequency, Hz</td>
<td>80</td>
<td>Zones 1–5</td>
</tr>
<tr>
<td>Exposure per zone, min</td>
<td>See table 4</td>
<td>–</td>
</tr>
<tr>
<td>Number of exposed zones</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Localization</td>
<td>See table 4</td>
<td>–</td>
</tr>
<tr>
<td>Method</td>
<td>Contact</td>
<td>Through the transparent tip</td>
</tr>
<tr>
<td>Number of procedures per regimen</td>
<td>10–12</td>
<td>Daily</td>
</tr>
</tbody>
</table>

Laser light parameters as provided in Table 5. Next step: IVLBT-525 + LUVBI (Table 6; Fig. 3).

Thirty-one SARS-CoV2-induced pneumonia patients with comorbidities (CVD, metabolic syndrome, type 2 diabetes mellitus, COPD, etc.) received rehabilitation treatment in the Central Clinical Hospital for the Rehabilitation of FMBA of Russia. In this group, the degree of damage to the lung tissue varied from 25 to 92%. Both of the above laser therapy methods were used for the patients; they delivered good results in the treatment of COVID-19 patients with severe lung lesions.

Subjectively, all patients noted general condition improvement, relief of chest pain associated with coughing, better sputum discharge, less severe shortness of breath. Moreover, in all patients we registered better oxygen saturation (pulse oximetry data) with the mean improvement from 93 to 97%; stabilization of the external respiration function accompanied by the increase of the vital volume of lungs; improvements revealed by the repeated lungs computed tomography. It is important that in the process of rehabilitation, these patients had their psychoemotional status normalized and the number of asthenic and anxiety-depressive incidents decreased (as measured with the Beck Depression Inventory and the MPS test (multilateral personality study).

The use of laser therapy for COVID-19 patients for the first time in the Central Clinical Hospital for the Rehabilitation of FMBA of Russia is mentioned as an example of the above promising non-drug therapies. As we gain experience, we shall report clinical data, more widely and in detail, with a statistical analysis of the results, evidence-based conclusions of the effectiveness of the method and personalized approaches in the complex treatment and prevention of complications.

CONCLUSION

This literature review demonstrates the capacities of laser therapy in the context of endothelial dysfunction treatment. The review cites positive experience of using laser therapy in the complex treatment and rehabilitation of patients with atypical pneumonia caused by various coronaviruses and the new SARS-CoV2.

LLLT is shown an absolutely safe, highly effective, simple and inexpensive method of prevention, treatment and rehabilitation of both chronic non-infectious cardiovascular and pulmonary pathologies and diseases caused by a viral infection, including COVID-19.

To enable personalized approach to rehabilitation of COVID-19 patients, it is necessary to search for informative biomarkers of genetic predisposition to endothelial dysfunction, hemostasis disorders, assess the individual characteristics of

Table 6. Parameters of the IVLBT 525 + LUVBI technique (basic)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser light wavelength, nm (spectrum)</td>
<td>365–405 (UV)</td>
<td>LUVBI</td>
</tr>
<tr>
<td></td>
<td>520–525 (green)</td>
<td>IVLBT-525</td>
</tr>
<tr>
<td>Laser operating mode</td>
<td>Continuous</td>
<td>–</td>
</tr>
<tr>
<td>Radiation power *, mW</td>
<td>1,5–2</td>
<td>At the outlet of the disposable light guide</td>
</tr>
<tr>
<td>Exposure, min</td>
<td>3–5</td>
<td>LUVBI</td>
</tr>
<tr>
<td></td>
<td>7–8</td>
<td>IVLBT-525</td>
</tr>
<tr>
<td>Localization</td>
<td>Vein ulnar median (v. mediana cubiti)</td>
<td>–</td>
</tr>
<tr>
<td>Method</td>
<td>Intravenously</td>
<td>Through the disposable sterile light guide KIVL-01 made by the Matrix R&amp;D Center (TU 9444-005-72085060-2008)</td>
</tr>
<tr>
<td>Number of procedures per regimen</td>
<td>10–12</td>
<td>Daily, alternating every other day IVLBT-525 and LUVBI</td>
</tr>
</tbody>
</table>
innate immunity and adaptive immune response to infection, risks of hyperreaction, cytokine storm, multiple organ failure, delayed manifestation of complications in a particular patient. Determination of the contribution of these individual (hereditary and environmental) factors, consideration of their mutual influences are crucial for application of the results of such complex examinations in real practice and indispensable for the development of individual diagnosis, prevention (primary and secondary) measures, targeted treatment regimens that, in particular, include LILT.

References


Литература


5. Александров А. А. База знаний по биологии человека. Раздел нарушения функции эндотеля и сердечно-сосудистые заболевания. Доступно по ссылке: https://humbio.ru/humbio/car_g/000b1acc.htm.


45. Brownlee M. The pathobiology of diabetic complications: a
42. Dabbous OA, Soliman MM, Mohamed NH, et al. Evaluation of
41. Dabbous OA, Soliman MM, Mohamed NH, et al. Evaluation of
40. Dabbous OA, Soliman MM, Mohamed NH, et al. Evaluation of
38. Dabbous OA, Soliman MM, Mohamed NH, et al. Evaluation of
37. Dabbous OA, Soliman MM, Mohamed NH, et al. Evaluation of
35. Dabbous OA, Soliman MM, Mohamed NH, et al. Evaluation of
34. Dabbous OA, Soliman MM, Mohamed NH, et al. Evaluation of
33. Brownlee M. The pathobiology of diabetic complications: a
32. Brownlee M. The pathobiology of diabetic complications: a
27. Brownlee M. The pathobiology of diabetic complications: a
5. Brownlee M. The pathobiology of diabetic complications: a
2. Brownlee M. The pathobiology of diabetic complications: a

89
пути коррекции их нарушений у больных бронхиальной астмой [диссертация]. Пермь, 1995; 21.


