Coronavirus disease (COVID-19): rheumatological prospects/relevance.

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CORONAVIRUS DISEASE 2019 (COVID-19): A RHEUMATOLOGIST'S THOUGHTS
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In December 2019, an outbreak of a novel infection under the working name 2019-nCoV was registered in Wuhan (the Hubei Province located in China's central region), which has quickly spread throughout almost the entire world and become pandemic. The World Health Organization (WHO) proposed a new name coronavirus disease (COVID-19) for this disease, whereas the International Committee on Virus Taxonomy renamed 2019-nCov as SARS-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus-2). The development of the COVID-19 pandemic is not only of great social importance, but also draws the attention of a medical community to the fundamentally new clinical and fundamental problems of the immunopathology of human diseases that are yet to be formulated. The unique experience gained in rheumatology from studies of the pathogenetic mechanisms and pharmacotherapy of immune-mediated inflammatory rheumatic diseases (IMIRDs) can be of great importance for deciphering the nature of the pathological processes that underlie the severe, potentially fatal complications of COVID-19, and may assist in improving their therapy. As for prospects in patients with IMIRDs, although the development of COVID-19 in the presence of IMIRDs has not yet fortunately been described, infection with SARS-CoV-2, like other viruses, can be assumed to cause an exacerbation of the pathological process, whereas severe immune system pathology and comorbidities can worsen the course of infection. Since, according to the current concepts, it is the «hyperimmune» response, and not just the effect only of the virus itself, that underlies lung damage and deaths from COVID-19, special attention is drawn to the effects of antirheumatic therapy that includes glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), biological agents, and targeted DMARDs, which can have a multidirectional effect on the course of COVID-19. There are significant theoretical prerequisites for the repurposing of some drugs widely used in rheumatology for the treatment of COVID-19 and its complications. Consideration is given to the prospects of studying the immunopathology of COVID-19 and to the theoretical justifications for the use of antimalarial 4-aminoquinolines, anti-cytokine monoclonal antibodies (mAbs), and Janus kinase inhibitors for the prevention of complications and for the treatment of COVID-19.

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Coronaviruses (Coronaviridae – CoV) – is a family of large RNA viral genome, causing disease in humans and animals; the name coronavirus is derived from Latin Corona based on characteristic appearance of the virus under electronic microscope reminding solar crown [1]. Four genera of coronaviruses have been described: Alpha-, Beta-, Gamma-, and Delta-coronavirus. Humankind encountered two epidemic outbreaks caused by Beta-coronavirus during last 20 years, the first was associated with SARS-CoV virus (severe acute respiratory syndrome – SARS), causing atypical pneumonia (2002 y) [2], the second – with MERS-CoV virus, the pathogen responsible for Middle East respiratory syndrome (2015 y) [3]. New outbreak of infection caused by a novel virus under operating name 2019-nCoV was documented in December 2019 in Wuhan (Hubei province in the central region of China) [4]. The virus has spread quickly to almost every country on Earth giving rise to pandemic [5–8]. In February 2020 the World Health Organization (WHO) suggested a new name – coronavirus disease – COVID-19 [5], while the International Committee on Taxonomy of Viruses (ICTV) has renamed the 2019-nCov as SARS-Cov-2 (severe acute respiratory syndrome coronavirus-2) [9].

The outbreak of COVID-19 pandemic does not only raise significant social and economic implications for health services and medicine, but also indicates the emergence of essentially new clinical and fundamental problems in immunopathology of human diseases, which are yet to be formulated. However, it is already obvious that the unique experience in pathogenetic mechanisms and pharmacotherapy of immune-mediated inflammatory rheumatic diseases (IMIRDs) accumulated in rheumatology, can be of great importance for interpretation of the nature of pathological processes underlying all severe, and potentially fatal complications of COVID-19, and may contribute to improving their therapy. As for IMIDs patients, although fortunately not a single case of COVID-19 infection has not yet been described in them, it can be assumed that contraction of SARS-CoV-2 (or any other virus) can provoke an exacerbation of the pathological process [10,11], while severe immune system disorders and concurrent diseases can aggravate the course of infection.

In accordance with the current concept that the "hyperimmune" response, not only the SARS-CoV-2 itself, causes lethal lung injury and death in COVID-19, the specific effects of "antirheumatic" drugs, including, glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs), biologics, and targeted DMARDs, are in the focus of attention. Moreover, there are significant theoretical prerequisites for repurposing some of them [13] for treatment of COVID-19 and its complications.

Relevant information on epidemiology, diagnostics, clinical manifestations and laboratory features of COVID-19, as well as therapeutic approaches is presented in a series of original publications [14–19], numerous reviews [20–24], and is widely covered in the media. Therefore, it seems appropriate to briefly consider practical approaches to COVID-19 prevention and diagnosis essential for daily clinical practice of each rheumatologist, starting from doctor-patient interaction, but also to focus on future COVID-19 clinical and scientific research.

Clinical manifestations

Airborne (with virus loaded droplets) and contact transmissions were confirmed for SARS-Cov-2; the incubation period lasts usually 2–5 days, being sometimes associated with "common cold" symptoms. COVID-19 clinical presentation varies from asymptomatic carrier status and up to development of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) (Table 1). Usually symptoms at the onset include fever (not in all patients), fatigue, chest tightness, nasal congestion, sneezing, dry cough, shortness of breath, sore throat, myalgia, chills, headache, diarrhea, and are hard to distinguish from symptoms of other common respiratory infections. However, by the end of the first week some patients develop severe complications, such as pneumonia, ARDS, pathology of kidneys, gastrointestinal, heart, and central nervous system, that are sometimes lethal. Lung pathology in COVID-19 is characterized by massive infiltration with "immune" cells "[25,26]. ARDS as a rapidly progressive form of respiratory failure is characterized by severe hypoxia, which often requires intensive care, including mechanical ventilation and extracorporeal membrane oxygenation (ECMO) [6,27,28]. Most severe cases occur in comorbid (or multi-morbid) elderly people [29,30]. Data from meta-analysis of a large group of patients with COVID-19 (p=46248) indicate that most severe disease was associated with arterial hypertension (OR=2.36, 95% CI 1.146–3.83), diabetes mellitus, cardiovascular diseases (OR=3.42, 95% CI 1.88–6.22), and respiratory system diseases (OR=2.46, 95% DF 1.76–3.44). In general, the incidence rate of fatal complications in hospitalized patients ranged from 3% to 11%, and the overall mortality rate reaches 3%. High incidence of cardiometabolic [31,32] and pulmonary comorbidities [33,34] should be emphasized specifically in IMRDs patients, as in case of COVID-19 contraction their prognosis would be inevitably worse, while severe course of any SARD itself makes it difficult to diagnose the infection. Our data collected from 200 patients with rheumatoid arthritis (RA) (mean age 55 years) within international **CORRONA** study (**CO**nsortium of **R**heumatology **R**esearchers **O**f **N**orth **A**merica) indicates that arterial hypertension was present in 60%, and coronary heart disease – in 21% of them [35].

Diagnosis

Differential diagnosis of COVID-19 includes other potential etiologies of respiratory disease, i.e., respiratory viruses (influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, and other coronaviruses), Mycoplasma, Chlamydia, and bacterial infections, and such differentiation is really difficult in the absence of specific for COVID-19 clinical manifestations or lab parameters tested in routine practice [36]. As there's currently no treatment specifically approved for COVID-19, early diagnosis of COVID-19 is essential for immediate isolation of the infected individual in order to prevent further spread of infection. When COVID-19 is suspected, presence of abovementioned non-specific symptoms (however, many patients remain asymptomatic), but, most importantly, patient's history indicating that the patient or his/her contacts were visiting countries with announced COVID-19 epidemic, should be taken into account.

Laboratory abnormalities in COVID-19 are also non-specific, but important for the assessment of patient's prognosis [37]. In "severe" cases requiring intensive care, as compared to patients who do not require hospitalization, there is a more pronounced (1.5–3-fold) increase vs normal values of the following parameters: leukocytes, neutrophils (accompanied by relative and absolute lymphopenia), alanine and aspartate transaminases (ALT/AST), total bilirubin, creatinine, cardiac troponin D-dimer, and procalcitonin. It should be emphasized, however, that increased concentration of procalcitonin indicates the presence of bacterial infection, not the persistence of virus. Presumably, new sepsis-specific biomarkers in COVID-19 are important for early diagnosis of concomitant bacterial infection and assessment of the risk of death [38,39].

An association was found between lethality and altered blood coagulation, including prolongation of prothrombin time, increased concentrations of D-dimer and fibrin/fibrinogen degradation products [40.41], as well as thrombocytopenia [42]. Importantly, disseminated intravascular coagulation syndrome was documented in 2/3 of the deceased patients, but only in 6% among the survivors [41]. Therefore, assessment of coagulation parameters should be included in monitoring standards for COVID-19 patients.

Specimens obtained from nasopharyngeal or oropharyngeal smears are used for real-time polymerase chain reaction (PCR) in combination with reverse transcription PCR (RT-PCR) to identify SARS-Cov-2 RNA and confirm the COVID-19 infection. [43.44]. Specific challenges associated with collection and transportation of specimens, and varying PCR positivity (30–60%) at the onset of COVID-19 infection limits the use of this test for early diagnosis of the disease [45]. It should be mentioned that insufficient "sensitivity" (i.e. "false negative" results) makes impossible early diagnosis of COVID-19 infection on one hand, but quite possible – premature patient's discharge from the hospital on the other; while insufficient specificity ("false positive' results) leads to overdiagnosis, i.e. undesirable identification of several quite harmless seasonal coronaviruses causing only mild upper respiratory tract disease.

There is a growing evidence that high-resolution computed tomography (HRCT) can detect typical radiographic changes in pulmonary tissue (such as "ground glass" opacity, multifocal consolidation, and/or peripheral interstitial involvement) in many patients with COVID-19 [46], including those with negative PCR tests [47–52]. Meanwhile, interpretation of HRCT scans can become a real challenge in IMIRDs patients developing COVID-19 infection against underlying background lung disease, as it was mentioned above, the majority of them have such comorbidities.

For rheumatologists it is especially important that manifestations associated with COVID-19 might mimicking typical clinical and laboratory features of IMRSs, including arthralgia, myalgia, lymphopenia, thrombocytopenia, acute interstitial pneumonia/diffuse alveolar damage, myocarditis, impairment of renal function, macrophage activation syndrome (MAS), venous thrombosis, increased levels of acute phase proteins, and, possibly antiphospholipid and antinucler antibodies.

Potential use of anti-inflammatory drugs

Since, as already noted, no specific antiviral drugs for COVID-19 are available [53,54], patient management is based on symptomatic and empirical antiviral therapy (its effectiveness has not been proven), and use of intensive treatment, when necessary. At the same time, high mortality rates in COVID-19 patients due to severe lung injury and MODS turned attention to specific role of immune mechanisms in the development of coronavirus-associated complications [12,55], and potential benefits of anti-inflammatory drugs in their prevention and treatment. In current context these are primarily 4-aminoquinolines and GCs.

Just to remind, that chloroquine and hydroxychloroquine (4-aminoquinolines), synthetic derivatives of quinine, have been used in clinical practice for more than 70 years, initially for treatment of malaria, and later – for a wide range of SARDs [56]. 4-aminoquinolines of action at the molecular level include local alteration of intracellular pH in phagocytic cells, interference of lysosomal activity and autophagy with destabilization of biomembranes, and modulation of several signaling pathways' and activity of transcription factors. At the cellular level, these drugs, due to a variety of insufficiently studied mechanisms (including those listed above), inhibit the function of "immune" cells: dendritic and antigen-presenting cells (monocytes, macrophages, B cells). Specific immune effects of 4-aminoquinolines are associated with downregulated expression of the class II MHC (major histocompatibility complex) molecules, presentation of antigens, immune activation (downregulation of CD154 expression on the T-cell membrane), synthesis of "pro-inflammatory" cytokines, including interleukin (IL)1β, tumor necrosis factor (TNF)α, interferon (IFN)γ, interference with signaling pathways induced by toll-like receptors (TLR) 7 and TLR9, and finally, inhibition of GMP-AMP synthase (cyclic GMP – AMP synthase-cGAS) activity. It's reasonable to remind that cGAS stimulates the IFN gene (stimulator of interferon genes – STING), while STING mediates type I IFN immune response which plays a crucial role in development of IMRDs [57]. Of notice is the demonstrated capability of 4-aminoquinoline drugs to suppress development of fungal and viral infections, including a wide range of RNA-viruses, human immunodeficiency virus, and SARS-CoV-1 alongside with antimalarial and immunomodulatory effects [58–60]. Potential mechanisms of 4-aminoquinolines antiviral activity are summarized in the review [59]. Available evidence substantiates the repurposing of 4-aminoquinoline drugs for the prevention and treatment of COVID-19 [61–65], but there's also preliminary data on 4-aminoquinolines effectiveness already summarized in a systematic review of 6 studies that can be taken into account [65]. It turned out that chloroquine therapy leads to faster resolution of fever and improvement of lung function (based on HRCT data), resulting in shorter recovery period compared to the control group. The optimal dosage regimen and duration of therapy are yet unknown, but most likely do not go beyond regimens generally accepted in rheumatology, except very high starting dose of 4-aminoquinolines. Although 4-aminoquinolines' have very good safety profile, nevertheless potential adverse drug reactions (ADRs) include nausea, vomiting, diarrhea, myopathy, cardiac arrhythmia and conduction disorders (especially QT interval prolongation), and retinopathy. However, such ADRs occur mainly after long-term (10–25 years) administration of high doses (>5 mg/kg), or due to persistence of high cumulative dose of the drug (> 6000–1000 g) in patients with severely compromised renal function.

The relevance of glucocorticoids (GCs) use in COVID-19 is not clear [28.66.67]. Rheumatology has accumulated huge positive experience with GCs, especially in management of life-threatening complications in IMRDs patients [68.69]. This is due to an extremely wide range of their anti-inflammatory and immunomodulatory effects [70], although potential ADRS, especially with long-term administration of high doses, limits the clinical use of GCs [71]. It's worth mentioning, that GCs block synthesis of a wide range of "pro-inflammatory" mediators, responsible for most unfavorable prognosis in COVID-19 patients, as their increasing concentration results in "cytokine storm "(see below) with subsequent development of ARDS and sepsis [14]. Available data from published meta-analyses and systematic reviews indicate a favorable effect of short-term therapy with low-to-medium GCs doses on the course of septic shock and ARDS with refractory hypoxemia, including those associated with SARS-CoV and MERS-CoV [72–75]. At the same time, there's also evidence that GCs use in MERS-CoV infection does not improve mortality rates, but increases patients' viral load, therefore slowing down MERS-CoV RNA clearance [66,76], and moreover, GCs potentially increase mortality in patients with influenza-associated pneumonia [67]. However, it should be emphasized that viral load does not correlate with increasing severity of illness [14,77], and that excessively high GCs doses were used in most studies reporting negative results. Currently, an RCT is being designed to evaluate the effectiveness of short-term therapy with low / median GCs doses in COVID-19 patients [78]. However, actual WHO guidelines do not support standard use of GCs for ARDS treatment in COVID-19 patients [79]

Potential development of "hyperimmune" response resembling the "cytokine storm" is of special interest in the context of COVID-19 immunopathology [80.81] (Table 2). Secondary hemophagocytic lymphohistiocytosis (HLH) in adults [82], macrophage activation syndrome (MAS) [83,84], and cytokine release syndrome (CRS) following CAR-T-cell (Chimeric Antigen Receptor T-Cell) therapy in cancer patients [85] represent pathogenetic variants of this syndrome. MAS should be mentioned as a well-known severe complication of IMRDs in children and adults, occurring in patients with systemic juvenile idiopathic arthritis (SJIA), adult Still's disease, as well as systemic lupus erythematosus (SLE), spondyloarthritis, and others [80]. The main clinical and laboratory manifestations of these pathological conditions are intermittent fever, cytopenia, hyperferritinemia, and lung injury (including ARDS).

The pathogenetic basis of the syndrome involves hyperproduction of a wide range of "pro-inflammatory" cytokines and chemokines that characterize activation of innate immunity, Th1 and Th17 types of immune response, namely: IL1, IL2, IL6, Il7, IL8, Il9, IL10, IL12, Il17, IL18, granulocyte

colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF, interferon (IFN) γ induced protein 10, IFNα and IFNβ, monocyte chemoattractant protein (MCP-1/CCL2), macrophage inflammatory protein (MIP) – 1α, chemokines (CCL1, CCL3, CCL5, CXCL8, CXCL9, CXCL10, and others). It is noteworthy that similar profile of cytokine and chemokine hyperproduction was documented in severe COVID-19 cases associated with unfavorable prognosis [14]. Increased counts of highly "pathogenic" CCR4+CCR6+Th17 cells in the peripheral blood of COVID-19 patients confirm the activation of the TH17 type of immune response [86.87]. Previously, biomarkers of the TH17 type of immune response were found in MERS-CoV, SARS-CoV. and influenza [88–90]. Other studies involving severe SARS-CoV-2 infection associated with lung injury demonstrated accumulation of "pathogenic" T cells in peripheral blood synthesizing GM-CSF, which induces production of IL6 and other "pro-inflammatory" mediators via activation of CD14+CD16+ "inflammatory" monocytes [91]. From clinical point of view increased concentrations of IL6, as well as ferritin and D-dimer, (laboratory biomarkers of the "cytokine storm") correlate with the severity of COVID-19 infection and risk of death [92,93]. Therefore, the "cytokine storm" should be considered as an important pathogenetic component of life-threatening complications developed in patients with COVID-19.

Provided evidence allows to discuss innovative approaches to anti-inflammatory therapy of severe COVID-19 infection, using both innovative drugs, and drugs (biologics agents) already widely used in IMRDs patients. Documented improvement in survival after blocking "pro-inflammatory" IL1 cytokine with recombinant human interleukin 1 receptor antagonist (Anakinra) in patients with sepsis [94] and secondary HLH [95] developing "hyperinflammation" serves as sound substantiation. Suppression of IL6 [96–99] and IL1 [100] by monoclonal antibodies (mAbs) is already considered as promising treatment of "cytokine release" syndrome occurring after CAR-T-cell therapy. Preliminary results are indicative of humanized mAb against IL6 receptors Tocilizumab (TCZ) effectiveness in patients with severe COVID-19 [101]. The study included 20 patients; following a single TCZ infusion 15 patients reduced the need for oxygen supplementation, resolved fever, normalized CRP concentration, and lymphocyte counts. A randomized placebo-controlled trial (RCT) TACOS (Tocilizumab vs CRRT in Management of Cytokine Release Syndrome in COVID-19; clinicalTrials.govr: NCT04306705) was initiated in patients with COVID-19-associated pneumonia and increased IL6 concentrations. Meanwhile preliminary recommendations for TCZ therapy in patients with severe COVID-19 and suspected "cytokine storm" syndrome have been provided. The main provisions of the document include the following: a multidisciplinary approach based on consensus of experienced intensivists, hematologists, infectious diseases specialists and rheumatologists; evidence of developing "hyperinflammation" based on increasing concentrations of IL6, ferritin, and high HScore (reactive hemophagocytic syndrome diagnostic score) *(http://saintantoine.aphp.fr/score)* that should be dynamically monitored; other infectious pathogens should be ruled out as potential cause, except for SARS-CoV2. The recommended weight-adjusted range of TCZ doses include: 400 mg (in patients with body weight 50–60 kg), 600 mg (>60–85 kg) and 800 mg (weight > 85 kg). Ferritin, fibrinogen, procalcitonin. CRP, and IL6 concentrations, platelet counts and AST/ALT levels should be monitored during treatment. The upcoming RCT (NCT02780583) is planned to assess effectiveness of Anakinra in pediatric and adult patients with "cytokine storm" syndrome. Beyond that, effectiveness of IL18 blockade was reported in children with a rare genetically determined autoinflammatory disease (NLRC4-associated inflammasomopathy), known to be associated with the "cytokine storm" syndrome [102]. FDA has already approved an anti-interferon γ mAb (anti-IFNγ mAB) for treatment of primary familial HLH, while anti-IFNγ mAb effectiveness in secondary HLH conditions is been evaluated in ongoing RCTs [103].

Janus kinase inhibitors with extremely wide range of anti-inflammatory activity are widely used for treatment of rheumatoid arthritis and other IMRDs [104,105] can also be considered as a rational pharmacotherapeutic approach in COVID-19 patients. It's time to recall that viral entry into the host cell occurs by receptor-mediated phagocytosis after initial SARS-Cov-2 attachment to angiotensin-converting enzyme (ACE) 2, expressed as receptor on membranes of respiratory epithelial cells, alveolar cells types I and II, kidneys, blood vessels, etc [106]. AP2-associated protein kinase 1 (AAK1) from NAK (Numb-associated family of protein kinases) family I is known as a regulator of endocytosis. Therefore its' inhibition blocks viral entry into the host cell, and intracellular mechanisms of virus assembly [107]. Baricitinib (JAK 1 and JAK2 inhibitor) binds the AAK1 and also binds the cyclin G-associated kinase, another regulator of endocytosis [108]. This dual inhibition capacity – of viral endocytosis and JAK-signaling of "proinflammatory" cytokines, coupled with favorable safety profile, already supported by strong evidence from rheumatology practice, designate Baricitinib as a very promising drug for the prevention and treatment of COVID-19 complications [109]. Moreover, data on effective and successful use of JAK-inhibitor Ruxolitinib in adult patients with secondary HFS look very promising [110].

There's a strong hope that accumulated in rheumatology unique knowledge on IMRDs immunopathology and pharmacotherapy will find relevant application and help to combat not only the fear of the unknown, but also the real life-threatening complications of COVID-19 infection posing a real challenge to all humankind.

Transparency of the research

The study had no sponsorship. The author is fully responsible for submitting the final version of the manuscript for publication.

Declaration of financial and other interests

The author designed the concept of this article and prepared the manuscript. The author did not receive any fee for the article.

REFERENCES

1. Richman DD, Whitley RJ, Hayden FG. Clinical Virology. 4th ed. Washington: ASM Press; 2016.
2. Chan-Yeung M, Xu RH. SARS: epidemiology. *Respirology*. 2003;8:S9-14. doi: 10.1046/j.1440-1843.2003.00518.x
3. Middle East Respiratory Syndrome Coronavirus. Available at: https://www.who.int/emergencies/mers-cov/en/ (accessed 16.02.2020).
4. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle. *J Med Virol*. 2020 Jan 16. doi: 10.1002/jmv.25678
5. WHO Coronavirus disease 2019 (COVID-19) situation report – 52. Available at: https://www.who.int/docs/default-source/coronaviruse/20200312-sitrep-52-covid-19.pdf?sfvrsn=e2bfc9c0_2
6. Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55(3):105924. doi: 10.1016/j.ijantimicag.2020.105924
7. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565-74. doi: 10.1016/S0140-6736(20)30251-8
8. WHO. Coronavirus disease (COVID-2019) situation reports. 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed 05.03.2020).
9. Gorbalenya AE, Baker SC, Baric RS, et al. Severe acute respiratory syndrome-related coronaviruses: the species and its virus – a statement of the Coronavirus Study Group. *bioRvxiv*. 2020 Feb 11. doi: 10.1101/2020.02.07.937862
10. Smatti MK, Cyprian FS, Nasrallah GK, et al. Viruses and autoimmunity: A review on the potential interaction and molecular mechanisms. *Viruses*. 2019;11(8). pii: E762. doi: 10.3390/v11080762
11. Joo YB, Lim YH, Kim KJ, et al. Respiratory viral infections and the risk of rheumatoid arthritis. *Arthritis Res Ther*. 2019;21(1):199. doi: 10.1186/s13075-019-1977-9
12. Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. *J Med Virol*. 2020;92(4):424-32. doi: 10.1002/jmv.25685
13. Kingsmore KM, Grammer AC, Lipsky PE. Drug repurposing to improve treatment of rheumatic autoimmune inflammatory diseases. *Nat Rev Rheumatol*. 2020;16(1):32-52. doi: 10.1038/s41584-019-0337-0
14. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506. doi: 10.1016/S0140-6736(20)30183-5
15. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020 (pub. online 2020 March 3). doi: 10.1007/s00134-020-05991-x
16. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet*. 2020;395(10223):P507-13. doi: 10.1016/S0140-6736(20)30211-7
17. Lei C, Huigo L, Wei L, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Chin J Tuberc Respir Dis*. 2020 Feb;43:E005.
18. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020 Feb 7. doi: 10.1001/jama.2020.1585
19. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020 Feb 24. doi: 10.1016/S1473-3099(20)30086-4
20. Adhikari SP, Meng S, Wu YJ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty*. 2020;9(1):29. doi: 10.1186/s40249-020-00646-x
21. He F, Deng Y, Li W. Coronavirus Disease 2019 (COVID-19): What we know? *J Med Virol*. 2020 Mar 14. doi: 10.1002/jmv.25766
22. Li LQ, Huang T, Wang YQ, et al. 2019 novel coronavirus patients' clinical characteristics, discharge rate and fatality rate of meta-analysis. *J Med Virol*. 2020 Mar 12. doi: 10.1002/jmv.25757
23. Yang Y, Peng F, Wang R, et al. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *J Autoimmun*. 2020 Mar 3:102434. doi: 10.1016/j.jaut.2020.102434
24. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, et al.; Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Electronic address: https://www.lancovid.org. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis*. 2020 Mar 13:101623. doi: 10.1016/j.tmaid.2020.101623
25. Xu Z, Shi L, Wang Y, et al. Pathological finding of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020. (Pub. Feb 18, 2020). doi: 10.1016/S2213-2600(20)30076-X
26. Tian S, Hu W, Niu L, et al. Pulmonary pathology of erarly phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol*. 2020. doi: 10.20944/preprints202002.0220.v2
27. Fung SY, Yuen KS, Ye ZW, et al. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. *Emerg Microbes Infect*. 2020 Mar 14;9(1):558-70. doi: 10.1080/22221751.2020.1736644
28. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers*. 2019;5(1):18. doi: 10.1038/s41572-019-0069-0
29. Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. *Circulation*. 2020 Mar 21. doi: 10.1161/CIRCULATIONAHA.120.046941
30. Yang J, Sheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systemic reviews and meta-analysis. *Int J Infect Dis*. 2020. doi: 10.1016/J.ijid.2020.03.017
31. Гордеев АВ, Галушко ЕА, Насонов ЕЛ. Концепция мультиморбидности в ревматологической практике. *Научно-практическая ревматология*. 2014;52(4):362-5. doi: 10.14412/1995-4484-2014-362-365
[Gordeev AV, Galushko EA, Nasonov EL. The concept of multimorbidity in rheumatologic practice. *Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice*. 2014;52(4):362-5. doi: 10.14412/1995-4484-2014-362-365 (In Russ.)].
32. Ferguson LD, Siebert S, McInnes IB, Sattar N. Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. *Nat Rev Rheumatol*. 2019;15(8):461-74. doi: 10.1038/s41584-019-0256-0
33. Arrossi AV. Pulmonary Pathology in Rheumatic Disease. *Clin Chest Med*. 2019;40(3):667-77. doi: 10.1016/j.ccm.2019.05.011
34. Antin-Ozerkis D, Hinchcliff M. Connective tissue disease-associated interstitial lung disease: evaluation and management. *Clin Chest Med*. 2019;40(3):617-36. doi: 10.1016/j.ccm.2019.05.008
35. Панафидина ТА, Кондратьева ЛВ, Герасимова ЕВ и др. Коморбидность при ревматоидном артрите. *Научно-практическая ревматология*. 2014;52(3):283-9. doi: 10.14412/1995-4484-2014-283-289
[Panafidina TA, Kondratyeva LV, Gerasimova EV, et al. Comorbidity in rheumatoid arthritis. *Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice*. 2014;52(3):283-9. doi: 10.14412/1995-4484-2014-283-289 (In Russ.)].

36. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus [2019-nCoV] infected pneumonia. *Mil Med Res.* 2020;7:4. doi: 10.1186/s40779-020-0233-6
37. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med.* 2020. doi: org/10.1515/ccim-2020-0198
38. Lippi G. Sepsis biomarkers: past present and future. *Clin Chem Lab Med.* 2019;57:1281-3. doi: 10.1515/cclm-2018-1347
39. Белов БС, Тарасова ГМ, Муравьева НВ. Роль биомаркеров в диагностике бактериальных инфекций при ревматических заболеваниях. *Научно-практическая ревматология.* 2019;57(3):333-8. doi: 10.14412/1995-4484-2019-333-338 [Belov BS, Tarasova GM, Muravyeva NV. Role of biomarkers in the diagnosis of bacterial infections in rheumatic diseases. *Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice.* 2019;57(3):333-8. doi: 10.14412/1995-4484-2019-333-338 (In Russ.)].
40. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med.* 2020 Mar 16. doi: 10.1515/cclm-2020-0188
41. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020 Feb 19. doi: 10.1111/jth.14768
42. Lippi G, Plebani M, Michael Henry B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta.* 2020 Mar 13. doi: 10.1016/j.cca.2020.03.022
43. Li T. Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0). *Emerg Microbes Infect.* 2020 Mar 14;9(1):582-5. doi: 10.1080/22221751.2020.1735265
44. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections – the state of the art. *Emerg Microbes Infect.* 2020 Mar 20:1-26. doi: 10.1080/22221751.2020.1745095
45. Lippi G, Simundic AM, Plebani M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). *Clin Chem Lab Med.* 2020 Mar 16. doi: 10.1515/cclm-2020-0285
46. Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology*. 2020. doi: 10.1148/radio.2020200230
47. Huang O, Liu T, Huang L, et al. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. *Radiology*. 2020. doi: 10.1148/radiol.2020200330
48. Xie X, Zghong Z, Zhao M, et al. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. *Radiology*. 2020. doi: 10.1148/radiol.2020200343
49. Tao Ai, Zhenlu Yang, Hongyan Hou, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology*. 2020;200642. doi: 10.1148/radiol.2020200642
50. Bai HX, Hsieh B, Xiong Z, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. *Radiology* 2020 Mar 10:200823. doi: 10.1148/radiol.2020200823
51. Yan Li, Liming Xia Coronavirus disease 2019 (COVID-19): Role of Chest CT in diagnosis and management. *Am J Roentgen: 1-7.* doi: 10.2214/AJR.20.22954
52. Han R, Huang L, Jiang H, et al. Early clinical and CT manifestations of coronavirus disease 2019 (COVID-19) pneumonia. *AJR Am J Roentgenol.* 2020 Mar 17:1-6. doi: 10.2214/AJR.20.22961
53. Liu C, Zhou Q, Li Y, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related coronavirus diseases. *ACS Cent Sci.* 2020. doi: 10.1021/acscentsci.0c00272
54. Dhama K, Sharun K, Tiwari R, et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. *Hum Vaccin Immunother.* 2020 Mar 18:1-7. doi: 10.1080/21645515.2020.1735227
55. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol.* 2017;39(5):529-39. doi: 10.1007/s00281-017-0629-x
56. Schrezenmeier E, DÖrner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol.* 2020;16(3):155-66. doi: 10.1038/s41584-020-0372-x
57. Насонов ЕЛ, Авдеева АС. Иммуновоспалительные ревматические заболевания, связанные с интерфероном типа I: новые данные. *Научно-практическая ревматология.* 2019;57(4):452-61. doi: 10.14412/1995-4484-2019-452-461 [Nasonov EL, Avdeeva AS. Immunoinflammatory rheumatic diseases associated with type I interferon: new evidence. *Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice.* 2019;57(4):452-61. doi: 10.14412/1995-4484-2019-452-461 (In Russ.)].
58. Rolain JM, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infection in the 21st century. *Int J Antimicrob Agents.* 2007;30:297-308.
59. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents.* 2020 Mar 11:105938. doi: 10.1016/j.ijantimicag.2020.105938
60. Boelaert JR, Piette J, Sperber K. The potential place of chloroquine in the treatment of HIV-1-infected patients. *J Clin Virol.* 2001;20:137-40. doi: 10.1016/S1386-6532(00)00140-2
61. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res.* 2020;30:269-71. doi: 10.1038/s41422-020-0282-0
62. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends.* 2020 Feb. doi: 10.5582/bst.2020.01047
63. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother.* 2020 Mar 20. doi: 10.1093/jac/dkaa114
64. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov.* 2020;6:16. doi: 10.1038/s41421-020-0156-0. eCollection 2020.
65. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care.* 2020 Mar 10. doi: 10.1016/j.jcrc.2020.03.005
66. Russell CD, Millar JE, Baillie JK. Clinical evidence does not suppot corticosteroid treatment for 2019-nCoV lung injury. *Lancet.* 2020;395:473-5. doi: 10.1016/S0140-6736(20)30317-2
67. Ni Y-N, Chen G, Sun J, et al. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care.* 2019;23:99. doi: 10.1186/s13054-019-2395-8
68. Strehl C, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-all-rounders tackling the versatile players of the immune system. *Front Immunol.* 2019 Jul 24;10:1744. doi: 10.3389/fimmu.2019.01744. eCollection 2019.
69. Hardy RS, Raza K, Cooper MS. Therapeutic glucocorticoids: mechanisms of actions in rheumatic disease. *Nat Rev Rheumatol.* 2020. doi: 10.1038/s415840020-0371-y
70. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol.* 2017. doi: 10.1038/nri2017.1

71. Oray M, Abu Samra K, Ebrahimiadib N, et al. Long-term side effects of glucocorticoids. *Expert Opin Drug Saf.* 2016;15(4):457-65. doi: 10.1517/14740338.2016.1140743
72. Heming N, Sivanandamoorthy S, Meng P, et al. Immune effects of corticosteroids in sepsis. *Front Immunol.* 2018;9:1736. doi: 10.3389/fimmu.2018.01736
73. Rygard SL, Butler E, Granholm A, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med.* 2018 Jul;44(7):1003-16. doi: 10.1007/s00134-018-5197-6
74. Meduri GU, Bridges L, Shih MC, et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med.* 2016;42(5):829-40. doi: 10.1007/s00134-015-4095-4
75. Chan ED, Chan MM, Chan MM, Marik PE. Use of glucocorticoids in the critical care setting: Science and clinical evidence. *Pharmacol Ther.* 2020;206:107428. doi: 10.1016/j.pharmthera.2019.107428
76. Arabi YM, Mandouran Y, Al-Hameed F, et al. Glucocosteroid therapy for critically ill parients with middle east respiratory syndrome. *Am J Resp Crit Care Med.* 2018;197L757-767. doi: 10.1164/rccm.201706-1172OC
77. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak or coronavirus-associated SARS pneumonia: a prospective study. *Lancet.* 2003;361:1767-72. doi: 10.1016/S0140-6736(03)13412-5
78. Zhou Y-H, Qin Y-Y, Lu Y-Q, et al. Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: protocol of a randomized controlled trial. *Chin Med J.* 2020. doi: 10.1097/CM9/ 0000000000000791
79. WHO. Clinical management of severe acute respiratory infection when novel coronavirus [nCoV] infection is suspected. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novelcoronavirus-[ncov]-infection-is-suspected (accessed 09.02.2020).
80. Behrens EM, Koretzky GA. Review: Cytokine storm syndrome: looking toward the precision medicine era. *Arthritis Rheum.* 2017;69(6):1135-43. doi: 10.1002/art.40071
81. Gupta KK, Khan MA, Singh SK. Constitutive inflammatory cytokine storm: a major threat to human health. *J Interferon Cytokine Res.* 2020;40(1):19-23. doi: 10.1089/jir.2019.0085
82. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, et al. Adult haemophagocytic syndrome. *Lancet.* 2014;383:1503-16. doi: 10.1016/S0140-6736(13)61048-X
83. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. *Front Immunol.* 2019 Feb 1;10:119. doi: 10.3389/fimmu.2019.00119
84. Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. *Front Immunol.* 2019 Jan 31;10:55. doi: 10.3389/fimmu.2019.00055
85. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer.* 2018;6(1):56. doi: 10.1186/s40425-018-0343-9
86. Wu D, Yang XO. Th17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor fedratinib. *J Microb Immun Infect.* 2020. doi: 1016/j.jmii.2020.03.005
87. Faure E, Poissy J, Goffard C, et al. Distinct immune response in two MERS-CoV-infected patients: can we go from bench to bedside. *PLoS One.* 2014;9:e88776. doi: 10.1371/journal.pone.0088716
88. Josset L, Menachery VD, Graliski LE, et al. Cell host response to infection with novel human coronavirus EMC predict potential antiviral and important differences with SARS coronavirus. *mBio.* 2013;4:e00165-00113. doi: 10.1128/mBio.00165-13
89. Bermejo-Martin JE, Ortiz de Lejarazu R, Pumarola T, et al. Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. *Crit Care.* 2009;13:R201. doi: 10.1186/cc8208
90. Zhou Y, Fu B, Zheng X, et al. Abberant pathogenic GM-CSF+T cells and inflammatory CD14+CD16+ monocyte in severe pulmonary syndrome patients of a new coronavirus. *bioRxiv.* 2020. doi: 10.1101/2020.02.12.945576
91. Liu T, Zhang J, Yang Y, et al. The potential role of interleukin 6 in monitoring severe case of coronavirus disesase. *MedRxiv.* 2020. doi: 10.1101/2020/03/01/20029769
92. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol.* 2020 Mar 17. doi: 10.1002/jmv.25770
93. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. *Crit Care Med.* 2016;44:275-81. doi: 10.1097/CCM.0000000000001402
94. Eloseily EM, Weiser P, Crayne CB, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheum.* 2020 Feb;72(2):326-34. doi: 10.1002/art.41103
95. Насонов ЕЛ, Лила АМ. Ингибиция интерлейкина 6 при иммуновоспалительных ревматических заболеваниях: достижения, перспективы и надежды. *Научно-практическая ревматология.* 2017;55(6):590-9. doi: 10.14412/1995-4484-2017-590-599 [Nasonov EL, Lila AM. Inhibition of interleukin 6 in immune inflammatory rheumatic diseases: achievements, prospects, and hopes. *Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice.* 2017;55(6):590-9. doi: 10.14412/1995-4484-2017-590-599 (In Russ.)].
96. Koch C, Barrett D, Teachey T. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. *Exp Rev Clin Immunol.* 2019;15:813-22. doi: 10.1080/1744666X.2019.1629904
97. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med.* 2019;24(6):739-48. doi: 10.1038/s41591-018-0036-4
98. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014 Oct 16;371(16):1507-17. doi: 10.1056/NEJMoa1407222
99. Giavridis T, van der Stegen SJC, Eyquem J, et al. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med.* 2018;24:731-8. doi: 10.1038/s41591-018-0041-7
100. Xu X, Han M, Sun W, et al. Effective treatment of Severe COVID-19 patients with tocilizumab. ChinaXiv (internet) 2020 Mar 5. Available at: https://ser.es/wp-content/uploads/2020/03/TCZ-and-COVID-19.pdf
101. Canna SW, Girard C, Malle L, et al. Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition. *J Allergy Clin Immunol.* 2017;139(5):1698-701. doi: 10.1016/j.jaci.2016.10.022
102. Lounder DT, Bin Q, de Min C, Jordan MB. Treatment of refractory hemophagocytic lymphohistiocytosis with emapalumab despite severe concurrent infections. *Blood Adv.* 2019 Jan 8;3(1):47-50. doi: 10.1182/bloodadvances.2018025858
103. Насонов ЕЛ, Лила АМ. Ингибиторы Янус-киназ при иммуновоспалительных ревматических заболеваниях: новые возможности и перспективы. *Научно-практическая ревматология.* 2019;57(1):8-16. doi: 10.14412/1995-4484-2019-8-16. Nasonov EL, Lila AM. Janus kinase inhibitors in immuno-inflammatory rheumatic diseases: new opportunities and prospects. *Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice.* 2019;57(1):8-16. doi: 10.14412/1995-4484-2019-8-16 (In Russ.)].
104. Schwartz DM, Kanno Y, Villarino A, et al. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov.* 2017;16(12):843-62. doi: 10.1038/nrd.2017.201
105. Zhao Y, Zhao Z, Wang Y, et al. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. Bio Rxiv. 2020 (pub. online Jan 26). doi: 10.1101/2020.01.26.919985

106. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020 (pub. online Jan 30). doi: 10.1016/S0140-6736(20)30251-8
107. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020 Feb 15;395(10223):e30-e31. doi: 10.1016/S0140-6736(20)30304-4
108. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020 Feb 27. doi: 10.1016/S1473-3099(20)30132-8
109. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. *Lancet Haematol*. 20192019;6(12):e630-e637. doi: 10.1016/S2352-3026(19)30156-5
110. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007 Feb;48(2):124-31. doi: 10.1002/pbc.21039
111. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheum*. 2014;66(9):2613-20. doi: 10.1002/art.38690

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