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Evolution of Approaches to Therapeutic Prevention and Treatment of the New Coronavirus Infection

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Abstract—The means of drug intervention for the prevention and treatment of new coronavirus infection (COVID-19) are discussed. Changes in approaches aimed at the main links of pathogenesis and capable of positively influencing the course and outcome of the disease that have been implemented after the appearance of the results of numerous randomized trials are presented. Some aspects of the ongoing study of the problem are characterized.

Keywords: new coronavirus infection, COVID-19, prevention, treatment

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In the two years that have passed since the onset of the spread of the new coronavirus infection (COVID-19), ideas about the pathogenesis of the disease and optimal approaches to its prevention and treatment have been continuously refined. It quickly became clear that the main mechanisms of pathogenesis in COVID-19 include the penetration and replication of the virus with damage to many organs and tissues, activation of the immune response and inflammation (in many cases, excessive, turning into the main cause of the unfavorable course of the disease), and the associated excessive thrombus formation in small and larger vessels (in situ thrombosis and “macrovascular” thrombi) [1, 2].

Initially, approaches to the prevention and treatment of the new coronavirus infection were based on a very incomplete understanding of its pathogenesis, as well as on extrapolation of previously obtained data from similar patient populations. Later, specialists began to accumulate and systematize the results of everyday medical practice. However, such data give no confidence that the effect is associated specifically with the intervention analyzed since the groups of patients under comparison inevitably turn out to be

unbalanced in many factors that can affect the result. Attempts to balance comparison groups by known risk factors using mathematical approaches are far from always successful, can introduce additional distortions, and do not account for indicators that are not recorded during data collection. In a retrospective study, these ambiguities are exacerbated by the possible incompleteness of information and the lack of strict criteria for assessing the presence and severity of the indicators under study. Therefore, the results of the analysis of prospective nonrandomized studies are always only a hypothesis, which should be tested during randomized controlled clinical trials. The results of the latter have been published actively since the second half of 2020. Considering these results, as well as the accumulation of clinical experience, ideas about optimal approaches to the prevention and treatment of COVID-19 have also changed. In our country, their evolution can be traced according to the interim methodological recommendations of the Ministry of Health of Russia *Prevention, Diagnosis, and Treatment of the New Coronavirus Infection (COVID-19)*, which are regularly updated as new facts of practical importance appear (the 14th version of this document of December 27, 2021, is currently in force) [3].

Vaccination. Since the very beginning of the pandemic, vaccination has been considered the most effective way to prevent severe manifestations of the new coronavirus infection, and this position has been repeatedly confirmed. The number of publications on the role of vaccination in COVID-19 is huge, and con-

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sideration of them is beyond the scope of this article. The organization of mass vaccination requires significant organizational efforts. On the basis of the National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Health of Russia (according to Order of the Ministry of Health of Russia no. 198n dated March 19, 2020, On a Temporary Procedure for Organizing the Work of Medical Organizations to Implement Measures on Preventing and Reducing the Risks of the Spread of the New Coronavirus Infection COVID-19 (as amended of December 4, 2020, no. 1288n), a Federal Remote Consultative Center was created. Standard operational procedures were developed, including a flexible matrix for the placement of medical personnel to optimize the throughput of vaccination points. An interactive educational module was created for doctors. Additional professional advanced training programs on vaccination of the adult population were developed. A hotline for the population and a Telegram channel "All about vaccination" were organized. The interim methodological recommendations *Procedure for Vaccination against the New Coronavirus Infection (COVID-19)* were developed and updated (the 7th version of this document dated December 22, 2021, is currently valid) [4].

To study the features of the immune status of people vaccinated against the SARS-CoV-2 virus, a prospective observational study is being conducted at the National Medical Research Center for Therapy and Preventive Medicine, involving more than 2000 people who have not been sick with COVID-19 and have not been vaccinated against it. We are analyzing data on the level of IgG to the S-protein before vaccination, before the injection of the second component of the vaccine, and on the 42nd day after the introduction of the first component. According to the preliminary data, the level of antibodies to the S-protein 42 days after the introduction of the first component of the Gam-COVID-Vac vaccine is significantly higher than when using the CoviVac vaccine, while an increase in the IgG level by the 42nd day was observed in both groups. When assessing the state of plasma hemostasis using the integral thrombodynamics test, no statistically significant differences were found either when comparing the Gam-COVID-Vac-vaccinated and the CoviVac-vaccinated or when comparing the initial indicators with those obtained 42 days after the first dose of these vaccines. To assess the humoral response of B cells to the introduction of vaccines against the SARS-CoV-2 virus, it is planned to conduct a study on the comparative evaluation of the reactogenicity and immunogenicity of heterologous vaccination regimens against COVID-19 starting from January 2022.

Another important task solved by the health authorities is the organization of medical care for those who have not escaped infection. Its main areas are prevention of the entry and replication of the virus,

elimination of excessive immune response and inflammation, and antithrombotic therapy.

Prevention of virus entry and replication. For the treatment of the new coronavirus infection, many drugs with various mechanisms of action have been proposed (and temporarily approved) to inhibit the entry and/or replication of the SARS-COV-2 virus in the body. However, the results of clinical trials of some of them were disappointing. In particular, chloroquine/hydroxychloroquine seemed promising for the treatment and postexposure and even preexposure prophylaxis of the new coronavirus infection. The results of numerous randomized trials have not confirmed the effectiveness of this drug in any of these scenarios [5–11]. In addition, chloroquine/hydroxychloroquine is known to have cardiac toxicity and may prolong the QT interval¹ and lead to life-threatening arrhythmias. Hence, its use requires observing a number of precautions, accounting for numerous contraindications and restrictions, monitoring the level of potassium in the blood, and performing ECG re-registration. Obviously, in a pandemic, all this is practically not feasible for outpatients. As a result, chloroquine/hydroxychloroquine was excluded from the above-mentioned interim methodological recommendations of the Russian Ministry of Health [3].

Outpatients with COVID-19 at increased risk of adverse disease (PRINCIPLE randomized open trial; $n = 2265$) and inpatients (RECOVERY randomized open trial; $n = 7763$) showed no evidence of benefit from the antiviral and anti-inflammatory antibiotic azithromycin [12, 13]. The antiviral drug lopinavir/ritonavir has also shown no benefit in hospital treatment (randomized open trials SOLIDARITY and RECOVERY; $n = 5499$ and 1616, respectively) [11, 14]. It is known that it interacts adversely with drugs necessary for the treatment of COVID-19. As a result, azithromycin and lopinavir/ritonavir were also excluded from the interim methodological recommendations of the Russian Ministry of Health [3].

In treating outpatients with risk factors for severe disease, the results of randomized placebo-controlled trials indicate the benefit of remdesivir (when treatment was started within the first 7 days after the onset of COVID-19 symptoms (PINETREE study; $n = 562$) and molnupiravir (when treatment was started within the first five days after the onset of the symptoms (MOVE-OUT study; $n = 1433$) [15, 16]. In a study of patients hospitalized with signs of lung disease and requiring respiratory support for the most part, faster recovery was observed in the remdesivir group (randomized placebo-controlled trial ACTT-1,

¹ The QT interval is an electrocardiogram measurement used to assess the electrical properties of the heart. It is calculated as the time from the beginning of the Q wave to the end of the T wave and approximates the time elapsed from the moment when the cardiac ventricles begin to contract until the moment when they finish relaxing.

$n = 1062$) [17]. The result of subgroup analysis in randomized trials suggests that in hospitalized patients who do not require intensive respiratory support, a decrease in mortality can be expected with the use of remdesivir [11].

At the beginning of treatment in the first 5 days after the onset of symptoms in unvaccinated patients with risk factors for a severe course of the disease, a decrease in the number of cases of hospitalization or death was noted when using a combination of two drugs: nirmatrelvir, which prevents the reproduction of the SARS-CoV-2 virus, and ritonavir, which prolongs the action of nirmatrelvir due to the inhibition of its metabolism by cytochrome P450 3A isoenzymes (randomized placebo-controlled study EPIC-HR; $n = 2246$) [18].

The viral load can be quickly reduced by intravenous administration of monoclonal virus-neutralizing antibodies. Currently, there is evidence of the effectiveness of this approach in postexposure prophylaxis, in outpatients with risk factors for a severe course of the disease, and in certain categories of hospitalized patients [19, 20]. However, it is not yet clear how the spread of new strains of the SARS-COV-2 virus will affect the clinical effectiveness of this approach.

Elimination of excessive immune response and inflammation. Immune inflammation is the central link in the pathogenesis of the new coronavirus infection. Initially, there were concerns about the use of drugs that suppress inflammation, especially in the early stages of the disease. However, later it turned out that such an approach is quite safe and can significantly improve the clinical course and prognosis. In particular, in hospitalized patients with severe enough manifestations of the disease (needing oxygen therapy), the effectiveness of the use of corticoids has been proven. Thus, intravenous or oral administration of dexamethasone reduced mortality in those receiving oxygen therapy or those on mechanical ventilation and did not benefit patients who did not need respiratory support (RECOVERY randomized open trial; $n = 6425$) [21]. In more severe cases, stronger anti-inflammatory drugs are used: interleukin-6 inhibitors and Janus kinase inhibitors [22, 23].

In outpatients with COVID-19 with severe risk factors and symptom duration of less than 14 days, the use of the inhaled corticoid budesonide for two weeks accelerated recovery (PRINCIPLE randomized open trial; $n = 1856$). There was also a trend towards lower cumulative rates of hospital admissions or death [24].

Colchicine is a promising and readily available agent that can reduce the severity of inflammation. Published data indicate no positive effect on the clinical course and mortality when administered in a hospital (RECOVERY randomized open trial; $n = 11\,340$), but do not exclude benefit in the treatment of outpatients with a confirmed diagnosis (COLCORONA, a randomized placebo-controlled trial that included

4488 patients with risk factors for a severe course of the disease) [25, 26]. However, the data are still insufficient to determine the feasibility of using colchicine in COVID-19 on a broad basis [27]. Active study of its effectiveness continues. In particular, an international multicenter randomized controlled trial involving outpatients and hospitalized patients is being conducted in the Russian Federation [28] (495 patients participated as of early December 2021).

Antithrombotic therapy. It soon became clear that thrombosis plays an important role in the pathogenesis of the new coronavirus infection. With an increase in the severity of the disease, the frequency of both venous and arterial thrombotic complications increases, which, according to aggregate data, in severe patients in a hospital can reach 30 and 5%, respectively [29]. Initially, antithrombotic therapy was aimed at the prevention and treatment of “macrovascular” thrombosis. However, as evidence accumulated, thrombus formation at the level of small vessels began acquiring great importance; such thrombus formation is largely determined by the severity of the infectious process and immune inflammation. Therefore, antithrombotic therapy will hopefully reduce the risk of the disease progressing to more severe forms and the frequency of adverse outcomes. The experience of everyday medical practice and the analysis of the results of prospective randomized trials indicate that anticoagulants (preferably heparin preparations) should be a mandatory component of the treatment of COVID-19 in a hospital.

At the same time, the results of randomized trials comparing different doses of anticoagulants published in 2021 completely changed the vision of the optimal doses of heparin preparations based on knowledge of the pathogenesis of the disease and analysis of the results of everyday medical practice: it was previously believed that the more severe the patient, the more reason for the use of high doses of anticoagulants, while the results of randomized clinical trials demonstrate that high (therapeutic) doses of heparin preparations should be used in patients who do not need to stay in the intensive care unit, and with an increase in the severity of the disease, prophylactic doses of parenteral anticoagulants have an advantage (Table 1) [30–35].

It is still unclear whether it is appropriate to use anticoagulants in the outpatient treatment of COVID-19. The first experience of using prophylactic doses in this category of patients was unsuccessful. The intake of these drugs did not affect the course of the disease, and the frequency of clinically significant thrombosis was so low that the widespread prophylactic use of antithrombotic drugs seemed unjustified [36, 37]. Accordingly, the existing recommendations for the selective (not universal!) use of low (prophylactic) doses of anticoagulants in patients with moderate manifestations of the disease who are treated at home

Table 1. Comparison of doses of anticoagulants in the hospital in the treatment of the new coronavirus infection: The main results of randomized controlled trials

Place of inpatient treatment	In the intensive care unit			Not in the intensive care unit		
Study	ATTACC, ACTIV-4a, REMAP-CAP (<i>n</i> = 1098) [30]	INSPIRATION (<i>n</i> = 562) [31]	HEP-COVID (<i>n</i> = 257) on oxygen, with D-dimer >4 times UNL or coagulopathy index ≥ 4 ; 34% in the ICU [32]	ATTACC, ACTIV-4a, REMAP-CAP (<i>n</i> = 2219) [33]	RAPID (<i>n</i> = 465) with elevated D-dimer [34]	ACTION (<i>n</i> = 615) with elevated D-dimer, mainly stable [35]
Anticoagulant	LMWH/UFH	LMWH/UFH	LMWH/UFH	LMWH/UFH	LMWH/UFH	Therapeutic: mainly rivaroxaban Prophylactic: LMWH/UFH
Main result	Therapeutic doses are not better than prophylactic doses	Intermediate doses are not better than prophylactic doses	Therapeutic doses are better than prophylactic or intermediate doses outside the ICU	Therapeutic doses are superior to prophylactic doses regardless of D-dimer levels	Therapeutic doses are better than prophylactic ones (trend, valid in terms of mortality)	Therapeutic dose up to the 30th day is not better than prophylactic doses of heparin in the hospital

UNL is the upper normal level for laboratory determination in a given medical institution; ICU is an intensive care unit; LMWH is subcutaneous injections of low molecular weight heparin; UFH is unfractionated heparin (subcutaneously in prophylactic or intermediate doses, intravenous infusion in a therapeutic dose).

and have an increased risk of venous thromboembolic complications still rely only on general ideas about the pathogenesis of the new coronavirus infection and on the extrapolation of the results of randomized controlled trials involving hospitalized nonsurgical patients before the onset of the pandemic [3].

In the second half of 2021, evidence appeared in favor of the use of prophylactic doses of anticoagulants in patients with COVID-19 after discharge from the hospital. In September, the results of the small-scale (320 participants) randomized open-label study MICHELLE were published, in which the use of the direct oral anticoagulant rivaroxaban at a dose of 10 mg once a day for 35 days led to a significant reduction in the risk of venous thromboembolic complications with clinical manifestations [38]. The criteria for selecting patients for this clinical trial were included in the updated version of the interim methodological recommendations of the Russian Ministry of Health for the treatment of the new coronavirus infection [3].

The role of antiplatelet agents as a treatment for COVID-19 remains unclear. The results of everyday medical practice indicate a possible reduction in mortality in patients who are prescribed low doses of acetylsalicylic acid, although the positive effect seems implausibly high (according to cumulative data, a risk reduction of 54% was noted) [39]. At the same time, in

the large-scale randomized open study RECOVERY, which included 14892 hospitalized patients, the use of acetylsalicylic acid at a dose of 160 mg per day did not reduce mortality, or the number of cases with a need for mechanical ventilation or the deaths of patients who initially did not need mechanical ventilation. The only positive effect of acetylsalicylic acid was a decrease in the duration of hospitalization by one day and an increase in the share of patients discharged in the first 28 days by 1%, which was achieved at the cost of a two-fold increase in the risk of major gastrointestinal bleeding, as well as more frequent occurrence of major bleeding requiring blood transfusion or surgery [40]. Unsuccessful results were also demonstrated by the ACTIV-4a randomized open trial involving 562 hospitalized patients, which was conducted to study the effect of P2Y₁₂ platelet receptor blockers—ticagrelor or clopidogrel in addition to a high (therapeutic) dose of anticoagulants in those who did not need to stay in the intensive care unit [41]. Evidence to date does not confirm the need for wide use of antiplatelet agents in addition to parenteral anticoagulant in patients hospitalized with COVID-19. Hopefully, antiplatelet monotherapy may be useful in earlier and/or sufficiently long-term treatment of the disease, in patients not receiving anticoagulants, and with a higher risk of adverse outcome and cardiovascular

complications, as well as in the use of lower doses of acetylsalicylic acid. However, all this does not remove the need for the use of antiplatelet agents in the presence of known indications for the drugs of this group in patients with cardiovascular diseases, as prescribed by the current clinical guidelines.

The data of a small placebo-controlled study indicate the possible benefit of using sulodexide in outpatients in the first 3 days after the onset of clinical manifestations of the disease (reducing the risk of hospitalization and the need for oxygen therapy) [42]. These effects are associated with the positive effect of sulodexide on the endothelium.

Consequences of the new coronavirus infection. One of the consequences of COVID-19 is the so-called post-COVID syndrome. Clinical manifestations and features of the pathogenesis of this condition are being actively studied; no specific methods of prevention and treatment have been developed thus far [44]. Post-COVID complications and deviations are manifested in the activity of various organs and systems, primarily respiratory, cardiovascular, and nervous. Considering the high frequency and clinical significance of the manifestations of post-COVID syndrome, it is important to identify in a timely manner the changes and prevent the development of complications. This is envisaged by the program of in-depth medical examination. It started on July 1, 2021, and by the end of that year, one million people had completed it. NMIC TPM associates took an active part in its development. Research methods used during in-depth medical examinations allow timely detection of deviations in the functioning of organs and systems and possible complications after COVID-19. This screening is carried out in two stages. At the first stage, the physician or general practitioner evaluates the blood oxygen saturation at rest, the results of the test with a 6-min walk, spirometry data, general and biochemical blood tests, the concentration of D-dimer in the blood in patients who have had COVID-19 of at least moderate severity, and as the results of a chest X-ray (if it had not been done earlier in the year). At the second stage, if necessary, additional studies are carried out (echocardiography, computed tomography of the lungs, duplex ultrasound scanning of the veins of the lower extremities). Based on the results, indications for dispensary observation and rehabilitation are determined.

The prospective TARGET-VIP registry was formed at the National Medical Research Center for Therapy and Preventive Medicine, which included 1130 patients with COVID-19 and/or community-acquired pneumonia hospitalized during the first epidemic wave at the Pirogov National Medical and Surgical Center (headed by RAS Corresponding Member O.E. Karpov) [44]. According to the registry, within the epidemic wave, a weekly increase in the age of hospitalized patients with the new coronavirus infection was revealed, as well as the proportion of cases of con-

comitant cardiovascular diseases and/or chronic non-cardiac pathology. At the same time, the proportion of patients with a higher risk of developing fatal and non-fatal complications increased weekly (by 4%, on average) [45]. In the hospital, 4.9% of patients died; during the 12 months of the posthospital period, 2.4%. Repeat computed tomography after 12 months of follow-up after COVID-19 complicated by pneumonia (2–4 degrees of damage according to computed tomography during hospitalization in 2020) showed no residual changes in the representative sample of surviving patients in 91% of cases, and in 9% of cases, minor residual changes were recorded. No significant post-COVID changes were found. The dynamics of the results of computed tomography is planned to be reassessed after 24 months of follow-up.

The continuation of the TARGET-VIP registry was a personalized study of the condition of patients to reveal the frequency, structure, and severity of clinical manifestations that occur after COVID-19, as well as to develop personalized diagnostic and rehabilitation schemes.

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The most effective means of preventing a new coronavirus infection is vaccination. The choice of drugs for the treatment of this disease is a complex task that requires considering the phase of the infectious process, its severity, and the characteristics of a particular patient. During the pandemic, ideas about the optimal treatment of the disease were repeatedly refined and revised. Active exploration of new approaches continues. Although the properties of the SARS-CoV-2 virus are changing noticeably, understanding the common pathological processes that underlie the onset and progression of COVID-19 is essential to improve prevention and treatment methods.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. P. E. Marik, J. Iglesias, J. Varon, and P. Kory, "A scoping review of the pathophysiology of COVID-19," *Int. Immunopathol. Pharmacol.* **35**, 20587384211048026 (2021).
2. J. Leentjens, T. F. van Haaps, P. F. Wessels, et al., "COVID-19-associated coagulopathy and antithrombotic agents—lessons after 1 year," *Lancet. Haematol.* **8**, e524–e533 (2021).
3. S. N. Avdeev, L. T. Adamyan, E. I. Alekseeva, et al., *Prevention, Diagnosis, and Treatment of Novel Coronavirus Infection (COVID-19): Temporary Guidelines, Version 14 (December 27, 2021)* (Ministerstvo Zdravookhraneniya Rossiiskoi Federatsii, Moscow, 2021).

- https://стопкоронавирус.рф/ai/doc/1213/attach/vmr_COVID-19_V14_27-12-2021.pdf
4. O. M. Drapkina, A. Yu. Gorshkov, Yu. V. Yakimov, et al., *The Procedure for Vaccination against a New Coronavirus Infection (COVID-19): Temporary Guidelines*, Version Dated December 22, 2021 (Ministerstvo Zdravookhraneniya Rossiiskoi Federatsii, Moscow, 2021). https://www.consultant.ru/document/cons_doc_LAW_404645/
 5. D. R. Boulware, M. F. Pullen, A. S. Bangdiwala, et al., “A randomized trial of hydroxychloroquine as postexposure prophylaxis for covid-19,” *New Engl. J. Med.* **383** (6), 517–525 (2020).
 6. R. Rajasingham, A. S. Bangdiwala, M. R. Nicol, et al., “Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: A randomized trial,” *Clin. Infect. Dis.* **72** (11), e835–e843 (2021).
 7. B. S. Abella, E. L. Jolkovsky, B. T. Biney, et al., “Prevention and treatment of COVID-19 with hydroxychloroquine (PATCH) investigators. Efficacy and safety of hydroxychloroquine vs. placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: A randomized clinical trial,” *JAMA Intern. Med.* **181** (2), 195–202 (2021).
 8. R. V. Barnabas, E. R. Brown, A. Bershteyn, et al., “Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection: A randomized trial,” *Ann. Intern. Med.* **174** (3), 344–352 (2021).
 9. O. Mitjà, M. Corbacho-Monné, M. Ubals, et al., “A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19,” *New Engl. J. Med.* **384** (5), 417–427 (2021).
 10. RECOVERY Collab., “Effect of hydroxychloroquine in hospitalized patients with Covid-19,” *New Engl. J. Med.* **383** (21), 2030–2040 (2020).
 11. WHO Solidarity Trial Consortium, “Repurposed antiviral drugs for Covid-19—Interim WHO Solidarity Trial results,” *New Engl. J. Med.* **384** (6), 497–511 (2021).
 12. PRINCIPLE Trial Collab., “Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): A randomised, controlled, open-label, adaptive platform trial,” *Lancet.* **397**, 1063–1074 (2021).
 13. RECOVERY Collab., “Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial,” *Lancet* **397**, 605–612 (2021).
 14. RECOVERY Collab., “Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial,” *Lancet* **396**, 1345–1352 (2020).
 15. R. L. Gottlieb, C. E. Vaca, R. Paredes, et al., “Early remdesivir to prevent progression to severe Covid-19 in outpatients,” *New Engl. J. Med.* **386** (4), 305–315 (2022).
 16. A. J. Bernal, M. M. Gomes da Silva, D. B. Musungaie, et al., “Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients,” *New Engl. J. Med.* **386** (6), 509–520 (2022).
 17. J. H. Beigel, K. M. Tomashek, L. E. Dodd, et al., “Remdesivir for the treatment of Covid-19: Final report,” *New Engl. J. Med.* **383**, 1813–1826 (2020).
 18. J. Hammond, H. Leister-Tebbe, A. Gardner, et al., “Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19,” *N. Engl. J. Med.* **386**, 1397–1408 (2022).
 19. S. M. Pinna, T. Lupia, S. Scabini, et al., “Monoclonal antibodies for the treatment of COVID-19 patients: An umbrella to overcome the storm?,” *Int. Immunopharmacol.* **101**, Article no. 108200 (2021).
 20. D. M. Weinreich, S. Sivapalasingam, T. Norton, et al., “REGEN-COV antibody combination and outcomes in outpatients with Covid-19,” *New Engl. J. Med.* **385**, e81 (1–12) (2021).
 21. RECOVERY Collab., “Dexamethasone in hospitalized patients with Covid-19,” *New Engl. J. Med.* **384**, 693–704 (2021).
 22. E. Tharmarajah, A. Buazon, V. Patel, et al., “IL-6 inhibition in the treatment of COVID-19: A meta-analysis and meta-regression,” *J. Infect.* **82** (5), 178–185 (2021).
 23. S.-H. Lana, C.-K. Wang, S.-P. Chang, et al., “Janus kinase inhibitors for hospitalized patients with COVID-19: A meta-analysis of randomized controlled trials,” *Expert Rev. Anti Infect. Ther.*, No. 5, 773–779 (2021).
 24. L.-m. Yu, M. Bafadhel, J. Dorward, et al. (PRINCIPLE Trial Collab), “Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): A randomised, controlled, open-label, adaptive platform trial,” *Lancet.* **398**, 843–855 (2021).
 25. RECOVERY Collab., “Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial,” *Lancet Respir. Med.* **9**, 1419–1426 (2021).
 26. J.-C. Tardif, N. Bouabdallaoui, P. L. L’Allier, et al., “Colchicine for community-treated patients with COVID-19 (COLCORONA): A phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial,” *Lancet Respir. Med.* **9**, 924–932 (2021).
 27. A. Mikolajewska, A.-L. Fischer, V. Piechotta, et al., “Colchicine for the treatment of COVID-19,” *Cochrane Database Syst. Rev.* **10** (10), CD015045 (2021).
 28. Anti-coronavirus therapies to prevent progression of coronavirus disease 2019 (COVID-19) trial (ACTCOVID19). <https://clinicaltrials.gov/ct2/show/NCT04324463>
 29. M. B. Malas, I. N. Naazie, N. Elsayed, et al., “Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis,” *eClinical Medicine.* **29**, 100639 (2020).
 30. REMAP-CAP, ACTIV-4a, and ATTACC Collabs., “Therapeutic anticoagulation with heparin in critically ill patients with Covid-19,” *New Engl. J. Med.* **385**, 777–789 (2021).
 31. INSPIRATION Collab., “Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: The INSPIRATION randomized clinical trial,” *JAMA* **325**, 1620–1630 (2021).

32. A. C. Spyropoulos, M. Goldin, D. Giannis, et al., “Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: The HEP-COVID randomized clinical trial,” *JAMA Intern. Med.* **181** (12), 1612–1620 (2021).
33. ATTACC, ACTIV-4a, and REMAP-CAP Collabs., “Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19,” *New Engl. J. Med.* **385** (9), 790–802 (2021).
34. M. Sholzberg, G. H. Tang, and H. Rahhal, “Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with Covid-19 admitted to hospital: RAPID randomised clinical trial,” *BMJ* **375**, n2400 (2021).
35. R. D. Lopes, P. G. M. de Barros e Silva, R. H. M. Furtado, et al., “Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): An open-label, multicentre, randomised, controlled trial,” *Lancet* **397**, 2253–2263 (2021).
36. J. M. Connors, M. M. Brooks, F. C. Sciruba, et al., “Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: The ACTIV-4B randomized clinical trial,” *JAMA* **326**, 1703–1712 (2021).
37. J. Ananworanich, R. Mogg, M. W. Dunne, et al., “Randomized study of rivaroxaban vs. placebo on disease progression and symptoms resolution in high-risk adults with mild COVID-19,” *Clin. Infect. Dis.*, ciab813 (2021).
38. E. Ramacciotti, L. B. Agati, D. Calderaro, et al., “Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): An open-label, multicentre, randomised, controlled trial,” *Lancet* **399**, 50–59 (2022).
39. J. W. Martha, R. Pranata, M. A. Lim, et al., “Active prescription of low-dose aspirin during or prior to hospitalization and mortality in COVID-19: A systematic review and meta-analysis of adjusted effect estimates,” *Int. J. Infect. Dis* **108**, 6–12 (2021).
40. RECOVERY Collab., “Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): A randomized, controlled, open-label, platform trial,” *Lancet* **399**, 143–151 (2022).
41. J. S. Berger, L. Z. Kornblith, M. N. Gong, et al., “Effect of P₂Y₁₂ inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: A randomized clinical trial,” *JAMA* **327** (3), 227–236 (2022).
42. A. J. Gonzalez-Ochoa, J. D. Raffetto, A. G. Hern, et al., “Sulodexide in the treatment of patients with early stages of COVID-19: A randomized controlled trial,” *Thromb. Haemost.* **121**, 944–954 (2021).
43. S. Lopez-Leon, T. Wegman-Ostrosky, C. Perelman, et al., “More than 50 long-term effects of COVID-19: A systematic review and meta-analysis,” *Sci. Reports* **11**, Article no. 16144 (2021).
44. O. M. Drapkina, O. E. Karpov, M. M. Luk’yanov, et al., “Experience in creating and first results of a prospective hospital registry of patients with suspected or confirmed coronavirus infection (COVID-19) and community-acquired pneumonia (TARGET-VIP),” *Profilakticheskaya Med.* **23** (8), 6–13 (2020).
45. M. M. Luk’yanov, S. Yu. Martsevich, A. A. Pulin, et al., “Dynamics of age indicators, the frequency of comorbid cardiovascular and non-cardiac diseases among patients hospitalized for COVID-19 during the epidemic wave (data from the TARGET-VIP register),” *Kardiovask. Terap. Profilak* **20** (8), 16–22 (2021).

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