Medicina Clínica Práctica 5 (2022) 100346

MEDICINA CLINICA PRÁCTICA

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Original

Clinical protocol for early treatment of COVID-19 in a real-world scenario: Results of a series of patients

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ARTICLE INFO

Article history:
Received 10 July 2022
Accepted 11 September 2022
Available online 22 September 2022

Keywords:
COVID-19
Treatment protocol
Ivermectin
Corticosteroid
Anticoagulant

ABSTRACT

Introduction: Despite the advance in vaccination, the SARS-CoV-2 infection remains a challenge for the medical community. Outpatient and hospital therapy for COVID-19 are still improving. Our study aimed to report the results of a series of patients with COVID-19 who participated in an outpatient treatment protocol since the first clinical manifestation.
Methods: A case series report of individuals aged ≥18 years with clinical symptoms and a confirmed test for COVID-19 submitted to a treatment protocol. Patients were enrolled between May and September 2020 and followed for at least 15 days. The assessed clinical outcomes were the need for hospitalization, admission to the intensive care unit, orotracheal intubation, and death.
Results: We studied a 116 patients. The mean age was 48 ± 14 years. Females formed 53%. The main comorbidities wereobesity (15.5%), systemic arterial hypertension (10.3%) ,type II diabetes (6%), and lung diseases (6.0%). Temperature >37.7 °C (51.7%), cough (55.2%), myalgia (37.1%), headache (37.9%), and fatigue (34.5%) were the most frequent signs and symptoms. According to different disease staging, the most administered drugs were: azithromycin, ivermectin, corticosteroid, antibiotics, and anticoagulants. There was no death, and hospitalization accounted for only 8.6% of the patients (1 in ICU); none required orotracheal intubation. The mean length of hospital stay was 5.8 days.

Protocolo Clínico para el Tratamiento Precoz de la COVID-19 en un escenario real: resultados de una serie de pacientes

Palabras clave:
COVID -19
Protocolo de tratamiento
Ivermectina
corticoide
anticoagulanteducción

RESUMEN

Introducción: a pesar del avance en la vacunación, la infección por SARS-CoV-2 sigue siendo un desafío para la comunidad médica. La terapia ambulatoria y hospitalaria para COVID-19 sigue mejorando. Nuestro estudio tuvo como objetivo informar los resultados de una serie de pacientes con COVID-19 que participaron en un protocolo de tratamiento ambulatorio desde la primera manifestación clínica.
Métodos: estudio prospectivo con reportes de casos de personas ≥ 18 años con síntomas clínicos y pruebas confirmadas de COVID-19 en protocolo de tratamiento. Los pacientes se trataron consecutivamente entre mayo y septiembre de 2020 y se les dio seguimiento durante al menos 15 días. Los desenlaces clínicos evaluados fueron: la necesidad de hospitalización, la unidad de cuidados intensivos, la intubación orotraqueal y la muerte.
Resultados: se estudiaron 116 pacientes. La edad media fue de 48 ± 14 años. Las hembras formaron el 53%. Las principales comorbilidades fueron obesidad (15,5%), hipertensión arterial sistémica (10,3%), hipertensión arterial sistémica (10,3%), diabetes tipo II (6%), y enfermedades pulmonares (6,0%). Tos (55,2%), temperatura > 37,7 °C (51,7%), cefalea (37,9%), mialgia (37,1%) y fatiga (34,5%) fueron los signos y síntomas más frecuentes. Según los diferentes estadios de la enfermedad, los fármacos más administrados fueron: azitromicina, ivermectina,

Abbreviations: M, Male sex; Obesity 1, Class I obesity; Obsesity 2, Class II obesity; BMI, Body Mass Index; AH, Arterial Hypertension; DM, Diabetes Mellitus; ICU, Intensive care unit; CW, Covid ward; NWF O2, Nasal high-flow O2; LOS, Length of stay.

https://doi.org/10.1016/j.mcpsp.2022.100346

corticoides, antibióticos y anticoagulantes. La hospitalización representó solo el 8,6% de los pacientes (uno en UCI); ninguno requirió intubación orotraqueal y ningún fallecimiento. La estancia hospitalaria media fue de 5,8 días.

Background

COVID-19 was the name chosen for a severe acute respiratory syndrome caused by a new coronavirus (SARS-COV-2) identified in Wuhan, China, in 2019 for the first time.[1] Frequent symptoms and signs are fever, dry cough, headache, anosmia, ageusia, sore throat, myalgia, tremors, dyspnoea, and in more severe cases, pneumonia.[2] Despite this, most patients remained asymptomatic; unfortunately, a small percentage with this highly contagious disease has a virulent curse, leading to mass deaths.[3–5]

Regrettably, despite disease knowledge advances and how to better avoid contamination by a coronavirus, we have not had vaccines or drugs scientifically approved to treat this disease in May 2020. There were already 514 200 cases of COVID-19, and 29 314 (5.7%) individuals died due to COVID-19 in Brazil at the end of May 2020.[6] At that time, feelings of frustration, hope, and sadness led to anecdotal interventions.[7] Yet, it is supposed that the infection by the new coronavirus interconnects several mechanisms, i.e., inflammation, coagulation disturbances, and thrombotic phenomena.[1,8–12] These processes occur in different stages of the pathophysiology of COVID-19 as they initiate with the virus invasion or early infection (stage I), followed by the pulmonary phase (stage II), and the hyper inflammation phase (stage III).[13,14] As Siddiqi and his co-author demonstrated in fig. 1 of their paper, these stages are potential therapeutic targets.[14] In addition, other clinical complications due to these pathological mechanisms, such as opportunistic infections and the involvement of other organs, have been observed.[4,15,16] Therefore, studies concerning early interventions with hydroxychloroquine and azithromycin were published.[17,18] However, due to low efficacy and possible cardiac complications, the administration of hydroxychloroquine was almost abandoned.[19] Instead, following the approval of FDA-USA, ivermectin was used to inhibit viral replication.[20–24] Shortly, we faced several randomized clinical trials (RCTs), even systematic revisions with associations between medicines, including antivirals, "immunomodulators and corticosteroids".[25] Nevertheless, despite the number of studies, we are still waiting for robust and well-designed RCTs or reliable and non-biased systematic revision with meta-analysis.[17,26–30]

Objective

We aimed to report the results of a structured clinical protocol for early treatment of COVID-19 (CPET-COVID-19) in patients with symptoms of the disease and specific complementary exams that proved the disease.

Rationale

We expected to take action in the first 2 stages of the disease, combining the available repurposed drugs to reduce hospitalizations and deaths.

Patients and methods

Study design

A case series of patients treated based on a structured protocol.

Inclusion criteria

Individuals aged ≥ 18 years, symptomatic (symptoms started up to 7 days before the first consultation), with a positive test for COVID-19 (RT-PCR or serology for COVID-19) between May and September 2020 and submitted to the CPET-COVID-19.

Symptomatic patients

For the present study, symptomatic patients had one or more signs or symptoms: fever, dry cough, odynophagia, anosmia, ageusia, headache, myalgia, dyspnea, delirium, and diarrhoea.

Exclusion criteria

We excluded patients who disagreed with joining the study, those with a dubitable or subsequent negative test for COVID-19, and those who lost follow-up.

Place of study

The principal author and F.P. evaluated most patients in their office as an outpatient protocol. They also recruited all potential cases admitted to the Hospital da Cidade (H.C.) emergency rooms, Salvador-Brazil. Patients were admitted to this hospital when necessary.

Medical care

The first author of this study or F.P. examined and submitted every patient to the following laboratory exams and thorax imaging according to timing and symptoms of the disease process: hemogram, C-reactive protein, creatine phosphokinase, coagulation tests, liver transaminases, creatinine, urea, D-dimer, and thorax computed tomography or thorax X-ray. Based on the medical literature, we considered critical test values, for example, D-dimer 3 times the normal value; C-reactive protein >20; substantially reduced number of lymphocytes; Substantially elevated CK and CT scan of the chest with more than 50% ground-glass involvement, as well as acute renal dysfunction.

In addition, most cases were followed up daily through remote queries by the *Zoom Platform or the WhatsApp application*. Furthermore, we monitored oximetry and temperature at least 3 times a day. In addition, we have strictly monitored patients with comorbidities such as diabetes, obesity, and hypertension. Clinical complications received particular support, such as investigation, suitable treatment, and evaluations at the H.C. emergency department, as necessary (Fig. 1).

Early clinical treatment protocol

CPET-COVID-19 uses the COVID-19 pathophysiology stages as therapeutic targets, as shown in Fig. 1.

Consultations

The authors obtained the opinions of G.M. (pulmonologist) regarding thorax image and AB (neurologist) concerning neurological complaints.

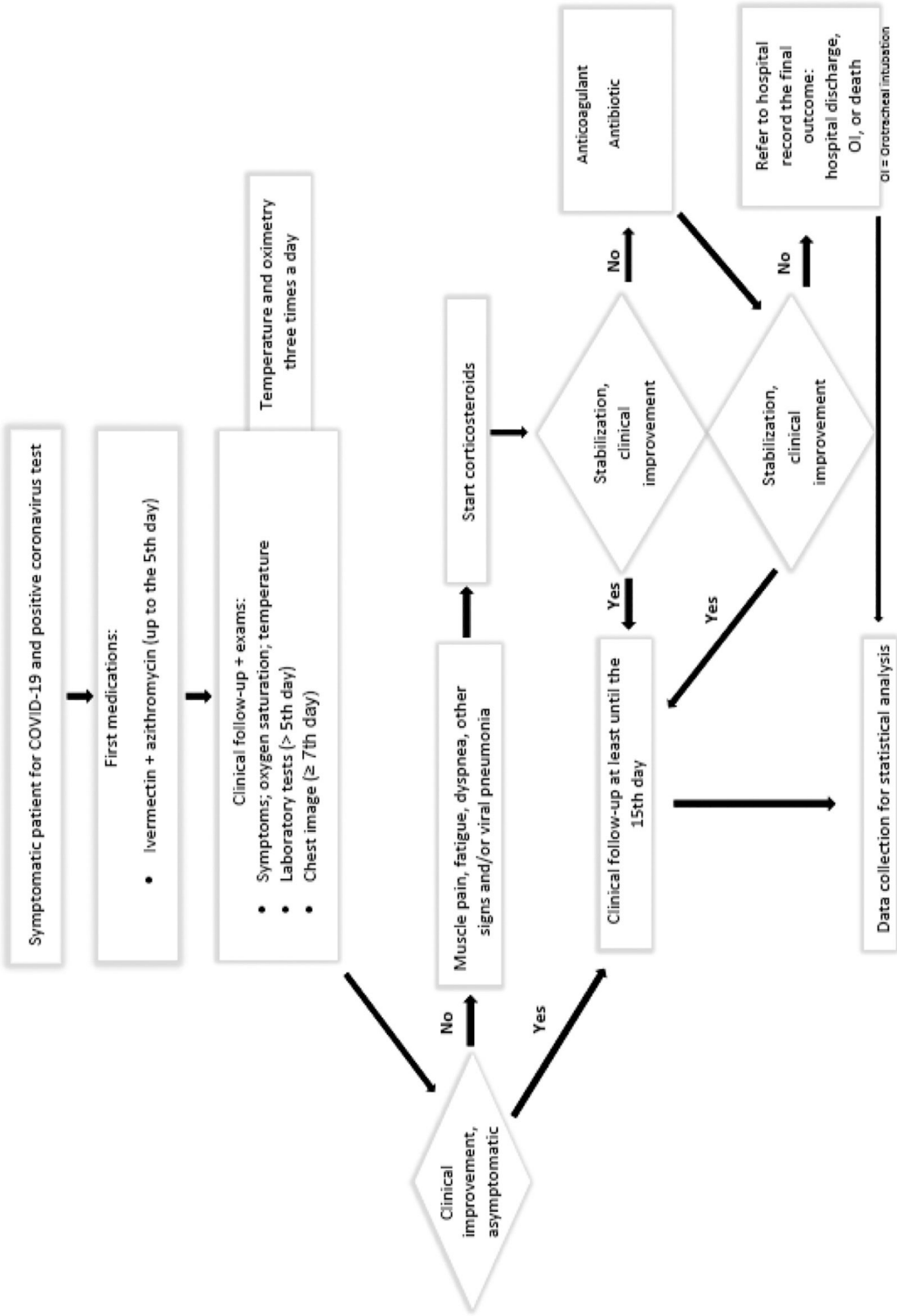

Fig. 1. The algorithm of the Clinical Early Treatment Protocol for COVID-19.

Drugs

According to disease staging and patient characteristics, the principal author prescribed the following drugs: ivermectin, azithromycin, prednisolone, rivaroxaban, enoxaparin, antibiotics, and paracetamol or dipyrone.

Outcomes

The assessed clinical outcomes were the need for hospitalization, admission to the intensive care unit, orotracheal intubation, and death.

Statistical analysis

We ran Statistical Package for the Social Sciences (SPSS for Windows version 20.0) program; IBM, Armonk, NY, USA), 844052 Software: R Program, version 3.6.1 and Microsoft Excel, version 2016 (16.0.6769.2017). We used the mean and the standard deviation to describe quantitative variables with normal distribution. In addition, we expressed categorical variables in absolute numbers and percentages.

Ethics

The ethical committee for human research of Hospital Ana Nery has approved this protocol. Therefore, the author registered this study in the Brazilian Platform for Research. Furthermore, all included patients have signed the informed consent document. The drugs used were: azithromycin, ivermectin, enoxaparin, prednisolone, and symptomatic (dipyrone or paracetamol).

Results

We enrolled a 122 symptomatic patients. Six patients were negative for coronavirus, and 116 patients were eligible as a case and included in the study. Most cases are the author's patients; others came from other physicians' referrals or the emergency rooms of H.C. As COVID-19 is a contagious disease, some patients were relatives living in the same home. In addition, 7 patients joined the protocol with routine laboratory tests already done. The mean age observed was 48 years (SD ± 14), and females were 62 (53%). The most common comorbidities were obesity (15.5%), systemic arterial hypertension (10.3%), type II diabetes (6.0%), and lung diseases (6.0%). Temperature >37.7 °C (51.7%), cough (55.2%), myalgia (37.1%), headache (37.9%), and fatigue (34.5%) were the most frequent signs and symptoms. The following drugs and their percentage of uses were: azithromycin (100%), corticosteroids (75.9%), anticoagulants (34.5%), antibiotics (10.3%), and ivermectin (99.1%). Table 1 shows the laboratory tests concerning most inflammatory and coagulation disorders related to COVID-19 and their percentage of abnormal results. We did not mention renal function as there was no abnormal result. The significantly higher complementary test was C-reactive protein, followed by leukogram and D-dimer (see table below). One patient developed Rhabdomyolysis, and another significantly increased liver enzymes (transaminases).

Table 1
The absolute number of patients and number of patients submitted to complementary exams and abnormal results in percentages.

Exams	Patients $n = 116$	Abnormal results
White blood cell count	109	19%
Lactate dehydrogenase (LDH)	88	11%
C-reactive protein (CRP)	109	42%
D- dimer	56	18%
Creatine phosphokinase (CPK)	83	18%
Prothrombin time (P.T.)	80	18%

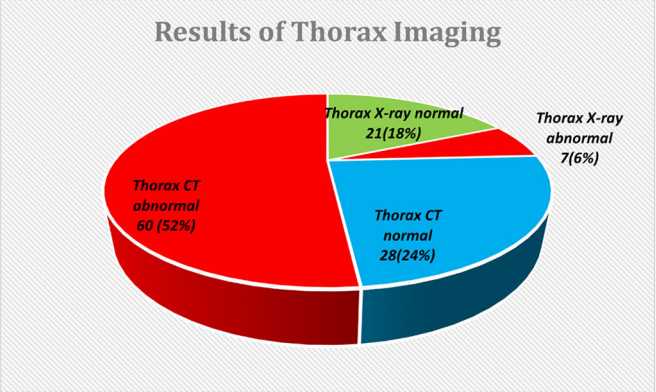

Fig. 2. The thorax imaging of 116 patients with COVID-19. CT = computed tomography. Eighty-eight patients submitted to thorax CT and 28 to thorax X-ray. In parenthesis, the percentual among the total number of patients.

Both recovered very well in 2 weeks. Fig. 2 demonstrates the results of imaging tests (abnormal percentages of computed tomography and chest X-rays).

Hospitalization accounted for 10 (8.6%) patients, and 90% were male. Table 2 shows the characteristics of inpatients. Most non-hospitalized patients reached the status of cured up to 15 days.

Seven patients (6%) entered the study with an average white blood cell count and normal C-reactive protein results. Most white cell disorders were lymphopenia.

Discussion

Despite the advance in vaccination, SARS-CoV-2 infection remains a challenge for the medical community. Therapy for COVID-19 has advanced, but it is already on the evolution curve. Our study reported a series of 116 cases of COVID-19 submitted to CPET-COVID-19. The theoretical protocol framework follows the disease's pathophysiological stages proposed by Siddiqi et al.[14] According to this protocol by Siddiqi, our patients entered the study at "stage 1" of that protocol.

We developed this protocol from May to September 2020, when the medical community's therapeutic recommendations for COVID-19, especially those of the early and outpatient phases, were under intense discussion[25] [31–34].

During this protocol period, COVID-19 devastated populations, so time and scientific rigour were competing [35]. Unfortunately, several reasons led to the scarcity of well-designed trials: the severity of COVID-19, different response to coronavirus infections among patients, physician concern of committing an unethical decision giving a placebo, and the use of compassionate treatment, i.e. the same has occurred with the Ebola pandemic [36]. Consequently, most studies were case series with repurposed medicines [31]. In addition, the FDA had approved ivermectin since in-vitro, and it inhibited SARS-COV 2 replication.[23]

The covid-19 scenario in Salvador in May 2020 was catastrophic since almost all hospitals had at least 90% of beds taken. Thus, health authorities recommended patients be isolated at home until respiratory symptoms occurred. Governments proclaimed partial lockdown and opened several new hospitals for COVID-19 [37]. The media showed a death scenario as May 2020 became the month with the highest number of deaths in Brazilian history [38]. So, we decided to initiate this protocol; however, several observational and interventional studies, even systematic reviews, most poorly designed, had shown debatable results.[30] After balancing the pros and cons, we decided to keep the protocol without a control group pending patients' safety instead of scientific rigour. After all, we were testing a protocol, and we believe all drugs of this protocol are essential, even ivermectin.

Although we cannot find well-designed RCTs, 11 of the 18 RCTs had positive effects; nevertheless, the last guidelines of the European

Table 2
Characteristics of patients with COVID-19 admitted to hospital units with viral pneumonia.

Patient	Sex	Age (years)	Comorbidities	Hospital Unit	Oxygen supplement	LOS
01-JRM	M	40	Obesity-1	ICU	Mask	06 days
02-RJBS	M	55	Obesity-II/ AH/DM	ICU	Mask	05 days
03-NDMF	M	61	Overweight	ICU	Mask	05 days
04-DCAA	M	33	Obesity-II	ICU	Mask	09 days
05-DNG	M	49	No comorbidity	ICU	Mask	09 days
06-PCM	M	56	Overweight	ICU	Mask	05 days
07-GM	M	55	Obesity-I/A.H./Asthma	CW	NHF O^2	02 days

Patients with O^2 saturation between 90% and 92% O^2 were admitted to C.W., whereas those below 90% to ICU. No patient required oro-tracheal intubation. M = male sex, Obesity1 = class I obesity (BMI = 30.0–34.9 Kg/m^2), Obesity-2 = class II obesity (BMI = 35.0–39.9 Kg/m^2), BMI = Body Mass Index, AH = Arterial hypertension, DM = Diabetes Mellitus, ICU = intensive care unit, CW = COVID ward, NHF O2 = nasal high-flow O2, LOS = length of stay.

Society of Clinical Microbiology and Infectious Disease (ESCMID) do not recommend ivermectin to treat COVID-19 [39].

Yet, due to the low rate of side effects, some authors intend to repurpose ivermectin to treat COVID-19 [40]. It is worth mentioning that drugs for treating the early stage of COVID-19 are debatable [41]. Therefore, the prescription of ivermectin is still a concern [39]. In addition, several studies included azithromycin [39]; however, none found evidence to treat COVID-19 [42, 43]. Nonetheless, one study shows that a treatment kit for COVID-19 might reduce hospitalizations and deaths [44]. Overweight and obesity were our population's most critical risk factors for COVID-19 severity, and they were responsible for 80% of hospital admission. Several reasons led to obesity increased disease severity in COVID-19, such as virus entry enhancement, the immune system being unable to provide an adequate response, increased risk for thrombus formation, and hemorrhages; the adipose tissue now considered a significant reservoir for SARS-CoV-2 and an essential source of inflammatory mediators [45, 46]. Other frequent comorbidities such as diabetes mellitus, arterial hypertension, and lung disease are well-known risk factors for bad outcomes in COVID-19 [47–49].

Moreover, we faced a patient with Rhabdomyolysis and another with elevated liver enzymes, which are not rare complications [50, 51]. Both recovered after resting and hydration. Therefore, the hospital admission rate was low for our patients. Although 8.6% of our patients developed moderate to severe viral pneumonia, none required orotracheal intubation.

We decided to share this report as we observed highly favorable clinical outcomes in patients submitted to CPET-COVID-198. We still believe our treatment has changed the natural history of COVID-19. Additionally, it seems clear to us the relationship between the chronology of pathophysiological events of COVID-19, the therapeutic rationale tied to them, and the clinical manifestations observed in these patients. Moreover, we had no clinical complications attributable to the drugs we prescribed.

Weakness of the study

The small sample size (n = 116) and the absence of a control group reduce the protocol's potential influence on the observed clinical outcomes.

Conclusions

1. Whereas in May 2020, the case fatality rate of COVID-19 in Brazil reached 5.7%, there was no death among symptomatic patients submitted to CPET-COVID-19.
2. The study findings hypothesized that CPET-COVID-19 altered relevant clinical outcomes in patients with COVID-19; thus, randomized controlled trials should assess this hypothesis.

Consent for publication

All patients agreed to sign the informed consent form.

Availability of data and materials

Datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author's contribution

S.S. conceived the study idea, designed the methods, examined, and treated patients, collected data, and drafted the manuscript; F.P. collected data and cared for patients; G.M. performed the thorax imaging review end reviewed the manuscript. A.B. performed patient neurological reviews, drafted the manuscript, and executed English editing; All authors read, discussed, and approved the final manuscript.

Competitive interests

There is no conflict of interest.

Financing

Minimum budget, funded by authors themselves.

Acknowledgments

We thank Silas Santana, Rutielen Souza, and Ricardo Fortes for their participation in collecting data, revising data, and studying design, respectively.

References

1. Yang CL, et al. Coronavirus disease 2019: a clinical review. Eur Rev Med Pharmacol Sci. 2020;24(8):4585–96.
2. Vetter P, et al. Clinical features of covid-19. BMJ. 2020;369, m1470.
3. Wang C, et al. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470–3.
4. Liu L, et al. Epidemiological and clinical characteristics of patients with Coronavirus Disease-2019 in Shiyan City, China. Front Cell Infect Microbiol. 2020;10:284.
5. Chen T, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: a retrospective study. BMJ. 2020;368, m1091.
6. CONASS. Painel Nacional: COVID-19. https://www.conass.org.br/painelconasscovid19/ Maio; 2020.
7. Koffman J, et al. Uncertainty and COVID-19: how are we to respond? J R Soc Med. 2020;113(6):211–6.
8. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. Thromb Res. 2020;192:152–60.
9. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020;50(1):54–67.
10. Levi M, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7(6):e438–40.
11. Maier CL, et al. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? Lancet. 2020;395(10239):1758–9.
12. Demelo-Rodriguez P, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thromb Res. 2020;192:23–6.
13. Kutsuna S. Coronavirus disease 2019 (COVID-19): research progress and clinical practice. Glob Health Med. 2020;2(2):78–88.

14. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5), 405407.
15. Antinori S, et al. Bacterial and fungal infections among patients with SARS-CoV-2 pneumonia. Infez Med. 2020;28(suppl 1):29–36.
16. Lv Z, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. Microbes Infect. 2020;22 (45):195–9.
17. Feeney E, et al. The COVIRL-001 Trial: a multicentre, prospective, randomized trial comparing standard of care (SOC) alone, SOC plus hydroxychloroquine monotherapy or SOC plus a combination of hydroxychloroquine and azithromycin in the treatment of non- critical, SARS-CoV-2 PCR-positive population not requiring immediate resuscitation or ventilation but who have evidence of clinical decline: a structured summary of a study protocol for a randomized controlled trial. Trials. 2020;21(1):430.
18. Han J, Gatheral T, Williams C. Procalcitonin for patient stratification and identification of bacterial co-infection in COVID-19. Clin Med (Lond). 2020;20(3), e47.
19. Ramireddy A, et al. Experience with hydroxychloroquine and azithromycin in the Coronavirus disease 2019 pandemic: implications for Q.T. interval monitoring. J Am Heart Assoc. 2020;9(12), e017144.
20. Chaccour C, et al. Ivermectin and COVID-19: keeping rigor in times of urgency. Am J Trop Med Hyg. 2020;102(6):1156–7.
21. Rizzo E. Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. Naunyn Schmiedebergs Arch Pharmacol. 2020;393(7):1153–6.
22. Sharun K, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. Ann Clin Microbiol Antimicrob. 2020;19(1):23.
23. Caly L, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178, 104787.
24. Chaccour C, et al. The SARS-CoV-2 Ivermectin Navarra-ISGlobal Trial (SAINT) to evaluate the potential of ivermectin to reduce COVID-19 transmission in low risk, nonsevere COVID-19 patients in the first 48 hours after symptoms onset: a structured summary of a study protocol for a randomized control pilot trial. Trials. 2020;21(1):498.
25. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis. 2020;7(4):ofaa105.
26. Alijotas-Reig J, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the antiviral therapy: a comprehensive review. Autoimmun Rev. 2020;19(7), 102569.
27. Bimonte S, et al. Potential antiviral drugs for SARS-Cov-2 treatment: preclinical findings and ongoing clinical research. In Vivo. 2020;34(3 Suppl):1597–602.
28. Hill A, et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Open Forum Infect Dis. 2021;8(11):ofab358.
29. Hill A, et al. Retraction to: meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Open Forum Infect Dis. 2022;9(3):ofac056.
30. Popp M, et al. ivermectin for preventing and treating COVID-19. Cochrane Database Syst Rev. 2021;7:CD015017.

Further reading

1. Guo, Y.R., et al. *The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status.* Mil Med Res. 2020;7 (1):p.11.
2. Karaahmet, F. and O.Z. Karaahmet. *Potential effect of natural and anabolizan steroids in elderly patient with COVID-19.* Med Hypotheses. 2020;140:p. 109772.
3. Shaffer, L.. *15 drugs being tested to treat COVID-19 and how they would work.* Nat Med. 2020.
4. Sharma, M. and S. Surani. *Searching an Effective Therapy for the Coronavirus Pandemic: Do We See Light at the End of the Tunnel?* Cureus. 2020;12 (3):p. 7415.
5. Wustner, S., et al. *Clinical Evidence Informing Treatment Guidelines on Repurposed Drugs for Hospitalized Patients During the Early COVID-19 Pandemic: Corticosteroids, Anticoagulants, (Hydroxy)chloroquine.* Front Public Health. 2022;10:p. 804404.
6. Hashem, H., et al. *Obstacles and Considerations Related to Clinical Trial Research During the COVID-19 Pandemic.* Front Med (Lausanne). 2020;7:p. 598038.
7. Martinho, K.. *Hospital exclusivo para Covid-19 será inaugurado nesta terça em Salvador.* https://www.metro1.com.br/noticias/cidade/91452,hospital-exclusivo-para-covid-19-sera-inaugurado-nesta-terca-em-salvador.
8. Uol. *Maio de 2020 torna-se o mês com maior número de mortes na história do Brasil.* https://noticias.uol.com.br/saude/ultimas-noticias/redacao/2020/06/25/com-covid-19-maio-se-torna-o-mes-com-mais-mortes-na-historia-do-brasil.htm.
9. *ESCMID COVID-19 living guidelines: drug treatment and clinical management.* Clin Microbiol Infect. 2022;28(2):p. 222238.
10. Shirazi, F.M., et al. *Repurposing the drug, Ivermectin, in COVID-19: toxicological points of view.* Eur J Med Res. 2022;27 (1):p. 21.
11. Zhang, C., et al. *Efficacy of COVID-19 Treatments: A Bayesian Network Meta-Analysis of Randomized Controlled Trials.* Front Public Health. 2021;9:p. 729559.
12. *COVID-19: A systematic review and update on prevention, diagnosis, and treatment.* MedComm. 2020,2022;3 (1):p. 115.
13. Gyselinck, I., et al. *Azithromycin for treatment of hospitalized COVID-19 patients: a randomized, multicentre, open-label clinical trial (DAWn-AZITHRO).* ERJ Open Res. 2022;8 (1).
14. Ascencio-Montiel, I.J., et al. *A Multimodal Strategy to Reduce the Risk of Hospitalization/death in Ambulatory Patients with COVID-19.* Arch Med Res. 2022.
15. Demeulemeester, F., et al. *Obesity as a Risk Factor for Severe COVID-19 and Complications: A Review.* Cells. 2021;10 (4).
16. Basolo, A., et al. *Adipose tissue in COVID-19: detection of SARS-CoV-2 in adipocytes and activation of the interferon-alpha response.* J Endocrinol Invest. 2022:p. 19.
17. Rajpal, A., L. Rahimi, and F. Ismail-Beigi. *Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes.* J Diabetes. 2020;12 (12):p. 895908.
18. Mirjalili, M., et al. *Does Losartan reduce the severity of COVID-19 in hypertensive patients?* BMC Cardiovasc Disord. 2022;22 (1):p. 116.
19. Bloom, C.I., et al. *Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC WHO Clinical Characterisation Protocol UK.* Lancet Respir Med. 2021;9 (7):p. 699711.
20. Toro, L., et al. *[Rhabdomyolysis as the presentation form of COVID-19 infection. Report of one case].* Rev Med Chil. 2021;149 (5):p. 796802.
21. Esteban, J.P., L. Sobotka, and D.C. Rockey. *Coronavirus disease 2019 and the liver.* Curr Opin Gastroenterol. 2022.