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Review article

CURRENT SITUATION IN CHEMOPROPHYLAXIS AND THERAPEUTIC TREATMENT OF COVID-19

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Abstract

Two years have passed since the emergence of SARS-CoV-2 infection and even after all this time medical approach in prophylaxis and treatment of COVID-19 is still very relevant. The search for a magical drug which would be a game changer and which would significantly change the clinical course and the outcome of the disease continues with undiminished intensity but also with a great dose of reservation that this search can last for a long time. Until then, it is necessary to use the current knowledge based on conducted trials and gained experiences. Based on this premises, many relevant health organizations, institutions, universities and medical societies worldwide have developed appropriate guidelines for treatment of COVID-19, which are subjected to periodic updates based on the newest discoveries. Following these guidelines, the treatment of COVID-19 patients has been improved in many ways and very good results have been achieved at this time, which unfortunately is far from the best. This paper sublimates the current guidelines issued from respectable health authorities (organizations, institutions, universities and societies) based on the newest studies and meta-analyses which have been subjected to the most rigorous, strict, critical and competent review processes.

Keywords: SARS-CoV-2 infection, COVID-19, pandemic, World Health Organization, National Institute of Health, monoclonal antibodies

Introduction

Evidence-based treatment guidelines for SARS-CoV-2 infection have evolved rapidly since the novel virus was identified in January 2020[1]. We are talking about living guidelines based on emerging evidence from randomized controlled trials (RCTs) on drug treatments for COVID-19[2]. At the moment, many pharmacologic therapies are being used or considered for treatment of COVID-19[3] and more than 5000 trials on COVID-19 interventions have been registered or are ongoing[2]. The existing guidelines require for frequently updating based on critical evaluation of rapidly rising literature and therapeutic trials[3].

Although vaccines have showed a significant effect on the clinical course and outcome of COVID-19, it still remains unclear how long this protection acquired with vaccination or through natural infection will last, or how this might change with the emergence of new variants[2]. The emergence of new viral variants might affect the transmission rates, disease progression, efficacy of current vaccines and current therapeutics[4]. It is already confirmed that some SARS-CoV-2 variants have reduced susceptibility to certain monoclonal antibodies

(mAbs) that are being considered for prevention and treatment[4]. Current strategies for therapeutic treatment of COVID-19 depend on disease stage, illness severity, estimated risk for disease progression[5], supposed viral mutation as well as the general wellbeing of the patient (comorbidities, immunosuppression, age, vaccine status)[4]. Unfortunately, and in spite of all the extensive research, still no drug has been found that would be a game changer and that would allow sovereign control of the disease.

According to the current knowledge about the pathogenesis of COVID-19, it is composed of two main processes, namely replication of SARS-CoV-2 that happens during the first 7-10 days in the clinical course, and dysregulated inflammatory response to SARS-CoV-2 with tissue damage that happens later in the clinical course. Accordingly, antiviral therapies should be practiced early in the course of the disease. Immunosuppressive/anti-inflammatory therapies on the other side are considered to be beneficial later on in patients with severe COVID-19 and is expected these therapies to downstream suppression of cytokine production and modulate the inflammatory cascade that results in systemic inflammation[2-4].

Clinical spectrum and risk of disease progression

The clinical spectrum of SARS-CoV-2 infection includes asymptomatic infection, mild, moderate, severe, and critical illness[4]. Most of the symptomatic patients manifest mild (40%) or moderate (40%) disease, 15% develop severe disease, and 5% have critical disease[6]. However, a patient's clinical status may change over time in either direction[4].

Asymptomatic infection is considered in individuals who test positive for SARS-CoV-2 but who have no clinical symptoms that are consistent with COVID-19. Mild Illness is presented with various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell), but without pneumonia. Moderate Illness can be seen in individuals manifesting pneumonia by clinical assessment or imaging and oxygen saturation (SpO2) >94%. Severe Illness is presented with severe pneumonia plus one of the following: respiratory frequency ≥30 breaths/min, SpO2 ≤94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 mm Hg, or lung infiltrates >50% within 24 to 48 hours[4]. These patients require supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation[3]. Critical Illness is manifested in patients who have acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-end organ dysfunction including acute kidney and cardiac injury[4,6]. These patients require mechanical ventilation or ECMO or vasopressor therapy[2,4,6].

Patients older than 65 years, or with underlying comorbidities like cardiovascular disease or hypertension, chronic lung disease, chronic kidney disease, sickle cell disease, diabetes, cancer, transplant recipients, patients with immunosuppressive disease or immunosuppressive treatment, with neurodevelopmental disorders or other conditions that confer medical complexity, obese, pregnant, cigarette smokers, are at a higher risk of progressing to severe COVID-19[3,4,7].

This paper presents the newest standings of relevant and respectable world associations, organizations, institutes and universities (conclusive with 18th of March 2022) about prophylaxis of COVID-19 (in addition to vaccines) as well as the therapeutic treatment in patients with COVID-19 in regard to the stage of the disease. These opinions are upgrading and updating the discussed views previously published[5,8] and are based on the newest well-designed randomized studies and meta-analyses which have passed detailed and scrutinizing reviewing processes. Undoubtedly, with the acquiring of new facts the current opinions and recommendations are subjected to permanent updating.

COVID-19 prophylaxis

Even though several agents like hyperimmune gamma globulin, convalescent plasma, interferons, tenofovir with or without emtricitabine, hydroxychloroquine, ivermectin and supplements such as zinc, vitamin C, and vitamin D are included in clinical trials, current recommendation for SARS-CoV-2 prophylaxis is against the use of any of these drugs, except in a clinical trial[4].

Pre-Exposure Prophylaxis (PrEP)

The most effective way to prevent SARS-CoV-2 infection is vaccination. However, in individuals 12 years and older with body weight of at least 40 kg who do not have SARS-CoV-2 infection and who have not been recently exposed to an individual with SARS-CoV-2 infection and at the same time are moderately or severely immunocompromised which may result with an inadequate immune response to COVID-19 vaccine or individuals for whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction, recommendation for PrEP is administration of long-acting neutralizing monoclonal antibodies tixagevimab plus cilgavimab (EVUSHELD)[3,4,9]. This monoclonal Abs can provide temporary "passive immunity" against acquisition of the SARS-CoV2 virus. However, EVUSHELD is not in any case a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response[4]. The efficacy of tixagevimab-cilgavimab against the Omicron variant is uncertain; some *in vitro* studies suggest that tixagevimab-cilgavimab retains neutralizing activity against Omicron but at reduced levels[10]. Dosing for EVUSHELD is 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections once[10]. These doses are twice those originally authorized (150 mg for each component)[3,4,7], because of concern for reduced neutralizing activity against Omicron[10]. This kind of PrEP can be repeated every 6 months in persons who continue to meet the criteria for their use[7,10]. EVUSHELD should be administered for at least 2 weeks after COVID-19 vaccination[4,7,10]. So far, it is unclear whether there is an association between EVUSHELD and increased rate of adverse cardiac events in individuals with cardiovascular risk factors[10].

Post-Exposure Prophylaxis (PEP)

Anti–SARS-CoV-2 monoclonal antibodies (mAbs) are bound to the viral spike protein, preventing attachment and entry into cells[11]. Neutralizing monoclonal antibodies may prevent symptomatic infection in individuals at least 12 years old with body weight of at least 40 kg who are at high risk for progression to severe COVID-19 and had a recent close exposure to an individual with SARS-CoV-2 infection and are either not fully vaccinated or are fully vaccinated, but not expected to mount an adequate immune response. In these patients for PEP is recommended either bamlanivimab 700 mg plus etesevimab 1,400 mg administered as an IV infusion or casirivimab 600 mg plus imdevimab 600 mg administered as subcutaneous injections or an IV infusion once[4]. On the other hand, IDSA recommends solely administration of casirivimab 600 mg plus imdevimab 600 mg[3]. Although sotrovimab is active against Omicron, it has not been studied for post-exposure prophylaxis and should not be used for this purpose[10]. Medications like hydroxychloroquine or ivermectin should also not be used for post-exposure prophylaxis[10].

Treatment

There is an existing recommendation against use of hydroxychloroquine with or without azithromycin and lopinavir/ritonavir in treatment of patients with COVID-19[2,3].

Also, it is suggested not to use interferons, ivermectin, famotidine, nitazoxanide or colchicine in treatment of hospitalized and in ambulatory patients with COVID-19, regardless of illness severity[2-4]. Despite the beneficial efficacy of antidepressant fluvoxamine and inhaled corticosteroids (budesonide) in prevention of progression in non-hospitalized patients with mild-moderate COVID-19, additional randomized controlled trials are necessary, so they should not be recommended as routine therapy, but may be considered on a case-by-case basis[9,12,13].

Convalescent plasma is generally not longer recommended for treatment of COVID-19, except in clinical trials, in inpatients or outpatients with mild, moderate, severe and critical COVID-19 and without impaired humoral immunity[1-4,14,15]. However, early administration of high-titres COVID-19 convalescent plasma within 8 days of symptom onset might be considered beneficial in ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options[3,12] and in severely immunocompromised individuals who are not expected to mount an antibody response[7,16]. Specific intravenous immunoglobulin (IVIG) should not be used for the treatment of acute COVID-19, except in a clinical trial; however, IVIG should be used for the treatment of complications that arise during the course of COVID-19[4]. mAbs against COVID-19 are a possible option in seronegative patients that have no seroconversion during infection or after vaccination regardless of the disease severity and whether the patients are hospitalized or not[16]. Patients with no need for supplementary oxygen and those requiring mechanical ventilation or ECMO are not advised to be treated with remdesivir routinely[3,4,13].

All hospitalized patients with COVID-19 should receive standard anticoagulation with heparin or low molecular weight heparin (LMWH) in the absence of contraindications[6,7,14]. LMWH is recommended rather than heparin or a novel oral anticoagulant. Dosing should be adjusted according to the illness severity (described in detail in every subtitle), body weight/BMI and renal function[6,8]. The suggested duration of standard thromboprophylaxis is until hospital discharge, but extended anticoagulation prophylaxis should be considered in patients at high risk for thromboembolism and at low risk of bleeding[4,6]. Hospitalized patients with COVID-19 who are receiving anticoagulant or antiplatelet therapy for underlying medical conditions should continue this treatment[4]. In hospitalized patients with COVID-19 regardless of the illness severity and additional risk factors for venous thromboembolism (obesity, previous VTE, thrombophilia, intensive care treatment and highly increased D-dimers), or with high suspicion for thrombotic complications, therapeutic anticoagulation may be considered[6,8,15,17]. In patients at high risk for thromboembolism, post-discharge prophylaxis has been shown to be beneficial and should be based on rivaroxaban 10 mg daily for 31 to 39 days[4].

Most guidelines do not address aspirin[3,4,6] or advice against its use, except in a clinical trial[7]. There is one recommendation against the routine use of aspirin among non-hospitalized patients with COVID-19 who do not have another indication for aspirin[14]. Patients with COVID-19 who are on aspirin for a separate indication, e.g., coronary artery disease, should continue taking aspirin[9].

In patients admitted to a hospital with non-severe COVID-19, antibiotics should not be prescribed in the absence of proven bacterial infections, or absence of highly suspected bacterial co-infection or superinfection[5,6,8,15]. Empiric antibiotic therapy may be indicated in patients with leucocytosis and/or hemodynamic instability[13]. In the case of empirical antibiotic treatment, selection of agents to be administered should follow standard practice for the treatment of bacterial pneumonia[5,8,15]. For critically ill patients with COVID-19, the use of empiric antimicrobials based on clinical diagnosis, local epidemiology and patient host factors is recommended as soon as possible. Empiric antibiotic therapy should be de-

escalated on the basis of microbiology results and clinical judgment and duration should be as short as possible[6,9].

Asymptomatic outpatients

In this category of patients only follow-up and supportive care is recommended, and there is a strong recommendation against the use of steroids and antibiotics[4,7].

Outpatients with mild to moderate COVID-19 (oxygen saturation >94%)

Management of outpatients with mild to moderate COVID-19 is consisted of supportive and symptomatic treatment such as antipyretics, adequate nutrition and appropriate rehydration[6].

Patients with mild disease that do not need hospitalization are believed to be able to recover without the need of immunotherapy[16]. Corticosteroids should not be used[2,4,6,7]; still patients with COVID-19 who are receiving steroids for an underlying condition should continue this therapy[3,4,15]. Antibiotic therapy, supplemental oxygen and routine treatment with remdesivir are not recommended[2,4,6-8]. In these (non-hospitalized) patients, the use of anticoagulants and antiplatelet therapy for prevention of venous thromboembolism or arterial thrombosis is not recommended[4]. Outpatients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications after diagnosing COVID-19[4].

However, in ambulatory patients with mild to moderate COVID-19 and patients admitted to a hospital for reasons other than COVID-19, who are at high risk for progression to severe COVID-19 (unvaccinated, older, patients with immunodeficiencies or with co-morbidities), one of the following therapeutics is recommended (in order of preference) [1-4,7,13]:

a) A combination of oral protease inhibitors, paxlovid (nirmatrelvir 300 mg plus ritonavir 100 mg) orally twice daily for 5 days administered within 5 days of symptom onset. Paxlovid has the potential for numerous significant and complex drug-drug interactions with concomitant medications and potential life-threatening adverse effects; so, before prescribing paxlovid, clinicians should carefully review the patients' concomitant medication list including over-the-counter medicines, herbal supplements, and recreational drugs and evaluate potential drug-drug interactions[11]. Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance because elevated concentrations are associated with serious life-threatening reactions. It is also contraindicated with drugs that are potent CYP3A inducers because significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance[3,13]. The most common adverse effects of paxlovid are dysgeusia, diarrhoea, hypertension, and myalgia. Paxlovid is not recommended in patients with an eGFR of <30 mL/min and in patients with severe hepatic impairment, and it should be used with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis[11].

b) Anti-SARS-CoV-2 mAb sotrovimab is administered 500 mg as a single intravenous infusion. It is recommended in areas with a high prevalence of the Omicron variant. If the Delta variant is still significantly present in the region, patients can be offered bamlanivimab plus etesevimab or casirivimab plus imdevimab (doses are mentioned above), with the understanding that this treatment would be ineffective if the patients are infected with the Omicron variant. Hypersensitivity, including anaphylaxis and infusion-related reactions, has been reported in patients who received anti-SARS-CoV-2 mAbs as well as rash, diarrhoea, nausea, dizziness, and pruritus, due to which patients should be monitored during the infusion and observed for at least 1 hour after infusion[2-4]. Anti-SARS-CoV-2 mAbs treatment should be started as soon as possible and within 10 days of symptom onset. The CDC no longer

recommends deferring vaccination after treatment with a monoclonal antibody for COVID-19[1,7]. For people who develop COVID-19 after vaccination, prior vaccination should not affect decisions regarding the use and timing of anti-SARS-CoV-2 mAb treatment[4]. The European Medicines Agency had approved the use of the mAb regdanvimab, administered at a dose of 40 mg/kg as a single IV dose, maximum 8000 mg, for outpatients with COVID-19 that fulfil criteria for mAbs therapy; still data suggest that regdanvimab is likely ineffective against the Omicron variant[12].

c) Immunocompromised patients who are unable to control viral replication may still benefit from a nucleotide analogue remdesivir despite SpO2 that exceeds 94% on room air. Remdesivir should be initiated as soon as possible and within 7 days of symptom onset. Dosing for remdesivir is 200 mg on day one followed by 100 mg on days two and three[3,4].

d) Anti-SARS-CoV-2 mAb bebtelovimab 175 mg, as a single IV infusion, administered as soon as possible and within 7 days of symptom onset is the newest anti-SARS-CoV-2 monoclonal antibody for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. It is expected bebtelovimab to have activity against a broad range of SARS-CoV-2 variants, including the Omicron variant and its subvariants. Nevertheless, bebtelovimab is recommended only in cases where none of the preferred therapies (a-c) are available, feasible to deliver, or clinically appropriate[4].

e) A nucleoside analogue molnupiravir at a dose of 800 mg orally is to be given twice daily for 5 days, initiated within 5 days of symptom onset in cases without other treatment options, i.e., only when paxlovid, sotrovimab, or remdesivir cannot be used[2,4]. Molnupiravir is not recommended in pregnant and breastfeeding patients[3,4,7,11]. Patients with childbearing potential should use effective contraception during and for 4 days after the last dose and individuals with partners of childbearing potential should use contraception during treatment and for 3 months after the last dose[7]. Breastfeeding mothers are advised to avoid feeding during molnupiravir treatment and for 4 days after the final dose.

Paxlovid, sotrovimab, bebtelovimab and remdesivir are administered in patients aged ≥12 years and weighing ≥40 kg, and molnupiravir in those aged ≥18 years[3,4,11]. In pregnant women, monoclonal antibodies and remdesivir are generally considered safe, and no data on nirmatrelvir exist. No data exist for the combined treatment[3]. Paxlovid, remdesivir, and molnupiravir, which target more conserved viral regions, are expected to remain active against Omicron, whereas anti–SARS-CoV-2 monoclonal antibodies except sotrovimab and bebtelovimab have reduced activity[11].

Hospitalized with mild to moderate COVID-19 (do not require supplemental oxygen)

In inpatients without risk for disease progression, treatment should be symptomatic[4]. For hospitalized patients with mild to moderate COVID-19, the use of corticosteroids is not recommended, except in patients who are already receiving corticosteroids for an underlying condition, and they should continue this therapy[4]. Routine treatment with remdesivir is not recommended[2-4,6], although it might be appropriate in patients at high risk of disease progression[3,4]. SARS-CoV-2-specific mAbs are recommended for use in hospitalized patients with mild COVID-19 and an elevated risk of progression who either have not developed an antibody response or are not expected to mount an effective immune response to SARS-CoV-2 infection. These mAbs should be also given to patients with mild to moderate COVID-19 hospitalized for a reason other than COVID-19 if they otherwise meet criteria for outpatient treatment[4,6]. If the patient does not need oxygen therapy but biomarkers indicate worsening inflammation, for e.g., CRP more than 50 mg/l and ferritin higher than 700 mg /l, then administration of the IL-1 receptor blocker anakinra might be considered[16]. In hospitalized patients that do not require supplemental oxygen prophylactic dose of LMWH is advised[4,7].

Hospitalized patients with severe illness that require low-flow supplemental oxygen

Hospitalized patients who require low-flow supplemental oxygen should be treated with dexamethasone (or alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone at a dose that is equivalent to dexamethasone) with[3-5] or without remdesivir[2]. The administration of remdesivir is 200 mg IV once, then 100 mg IV once daily for 4 days; for dexamethasone 6 mg IV or PO once daily for up to 10 days[3,4,13].

Patients with severe or critical covid-19 that have seronegative status and where viral genotyping can confirm a susceptible SARS-CoV-2 variant might be treated with casirivimab-imdevimab, at doses lower than 8000 mg[2].

Results from some new RCSs suggest that therapeutic-dose heparin is beneficial in patients with non-critical COVID who require low-flow oxygen (less than 20 L/min), have D-dimer above the upper limit of normal, and have no increased bleeding risk (dual antiplatelet therapy, platelet count <50 x 109/L, haemoglobin <8 g/dL, known acquired or inherited bleeding disorder, history of heparin-induced thrombocytopenia, recent ischemic stroke)[4,7,16]. Other patients in this category that require supplemental oxygen but with patient's or provider's preference for prophylactic rather than therapeutic dosing should be treated with prophylactic doses of LMWH[4,7].

Hospitalized patients with severe illness that require oxygen through a high-flow device or non-invasive ventilation

Hospitalized patients who require high oxygen support (through a high-flow device or non-invasive ventilation) should receive 6 mg dexamethasone a day (or alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg) with or without remdesivir[3,4]. Guidelines and available evidence do not support the use of doses higher than 20 mg of dexamethasone (or equivalent) per day or recurrent courses of systemic steroids for progressive or resistant critical COVID-19[9].

In recently hospitalized patients (within 96 hours of hospitalization) who have progressive, rapid clinical worsening that is not improving despite the use of steroids, with rapidly increasing oxygen requirements as well as with significantly increased markers of systemic inflammation (CRP ≥75 mg/L), a second immunomodulator (e.g., tocilizumab or baricitinib) should be added to dexamethasone or to dexamethasone plus remdesivir[1-4,7]. Furthermore, baricitinib with remdesivir may be given in persons for whom corticosteroids are indicated but who cannot receive them due to a contraindication[3,7,8]. So far, there is no data about which of the two drugs (tocilizumab and baricitinib) is superior and at the same time there are no recommendations about their concomitant use. As baricitinib and IL-6 receptor blockers have similar effects, the choice should be based on their availability, clinician's experience, local institutional policies, patient comorbidities, route of administration and cost[2]. Prior use of baricinitib is not a contraindication to using tocilizumab[13]. Baricitinib is administered orally 4 mg per day up to 14 days and tocilizumab dosing is 8 mg/kg (maximum dose is 800 mg) administered as a single IV dose[2,4,7]. These agents should be avoided in pregnancy given lack of safety data[2,17], but may be used during lactation[7]. If baricitinib is administered, breast milk should be discarded until 3 days after last dose[7]. When tocilizumab and baricitinib are not available, the suggestion is for sarilumab (single dose, 400 mg in 100 cc 0.9% NaCl and administered as an IV infusion over 1 hour), or tofacitinib (10 mg PO twice daily for up to 14 days)[3,4].

The use of empiric antimicrobials based on clinical judgment, patient host factors and local epidemiology cannot be ruled out and if antimicrobials are initiated their use should be reassessed daily for de-escalation[4,6]. In the absence of proved or suspected venous thromboembolism, prophylactic doses of LWMH unless contraindicated are advised[4].

Hospitalized patients with critical illness (require mechanical ventilation or extracorporeal membrane oxygenation)

In patients with COVID-19 admitted within 24 to 48 hours to the ICU with rapidly increasing O2 needs that require mechanical ventilation or ECMO, dexamethasone or dexamethasone plus tocilizumab is the recommended treatment[1-4,7]. In patients who are on mechanical ventilation or ECMO, baricitinib is not routinely recommended[3,4], but could be a reasonable alternative to tocilizumab if it is not available[2,18]. Routine initiation of remdesivir among patients on invasive ventilation and/or ECMO is not recommended[1,3,4,18].

In patients with critical COVID-19 and in absence of known DVT/PE, prophylactic anticoagulation should have priority over therapeutic, having in mind that therapeutic doses do not prevent progression of disease or death, and may be associated with increased rates of significant bleeding[4,6,7,14,16]. In patients who start on therapeutic-dose heparin while on low-flow oxygen due to COVID-19 and then transfer to the intensive care unit, it is recommended to switch from therapeutic to prophylactic-dose LMWH unless a VTE is confirmed[4].

Conclusion

The current recommendations for prophylaxis in COVID-19 are directed towards vaccination and in rare instances in patients who should not be vaccinated or would not have a benefit from the vaccination the use of some mAbs. In patients with clinically manifested COVID-19, the principles for the treatment depend on the stage of the disease. In the early replicative phase, in patients with high risk factors and risk of disease progression the recommendation is antiviral drugs or mAbs, while in the late inflammatory mediated phase the treatment is based on potential administration of an immunosuppressive/anti-inflammatory therapy.

Conflict of interest statement. None declared.

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