



Research Paper

## Vue générale de de la gestion ambulatoire du COVID-19

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### Abstrait

*Le virus SRAS-COV-2 est au centre de l'attention du monde depuis un an et demi. Les personnes avec et sans formation scientifique suivent les actualités du COVID-19 et les études les plus récentes. Cependant, il n'y a pas de données factuelles claires pour les médecins et la population générale à suivre concernant le traitement de la maladie Corona. Plus précisément, les données manquent de manière significative en ce qui concerne le traitement, l'approche, le suivi et le pronostic des patients externes. Par conséquent, dans cette revue, nous essayons de résumer les principaux sujets qui intéressent la communauté et les médecins de premier recours, sur la base des lignes directrices et des études les plus à jour. La revue aborde les informations sur l'histoire naturelle du COVID-19, la présentation clinique, les médicaments les plus populaires et les plus fréquemment utilisés tels que les stéroïdes, les antiviraux, les anticoagulants et les vitamines. Nous avons également mentionné certaines complications qui doivent être traitées et étroitement surveillées pour le patient ambulatoire, après la sortie à domicile.*

### ABSTRACT

*SARS-COV-2 virus has been the center of attention worldwide for the past year and a half. People with and without scientific background follow COVID-19 news and recent studies. However, there is no clear evidence based data for scientists, physician and the general population to follow regarding the treatment of Corona Disease. More specifically, data lacks significantly when talking about out-patients' treatment, approach, follow up and prognosis. Therefore, in this review, we try to summarize the main topics that interest the community and the primary care physicians, based on the most updated guidelines and studies. The review tackles information about natural COVID-19 history, the clinical presentation, the most popularly and frequently used drugs such as steroids, antivirals, anticoagulants and vitamins. We also mentioned some complications that need to be addressed and closely monitored for the out-patient, after discharge.*

**KEYWORDS:** COVID-19, SARS-COV-2, corticosteroid, antivirals, vitamins, azithromycin, outpatient management.

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### The natural history of the disease

SARS-COV-2 also known as Novel Corona Virus 19, has taken over the world for over a year now. Most of the crucial information about the virus pathophysiology, mutagenicity, treatment, and post infectious complications are still undergoing studies. However, reports continuously conducted to acquire better understanding of the disease and the spectrum. Nevertheless, some valuable information has already been established. It is now known that the incubation period varies between 2 to 14 days, with most cases ranging between 5 and 7 days. Viral replication happens in the early phase of the disease, where patients can be asymptomatic, or suffer from mild to moderate flu-like symptoms. The late phase of the disease is a hyperinflammation, exaggerated immune response, leading to tissue damage [3]. Data suggested that 80% of affected people have mild to moderate diseases, 15% have severe disease and 5% have critical disease with associated complications. The overall mortality rate has been estimated to be between 0.66 and 0.9% [5].

### Clinical Presentation

Most patients experience fever (83 to 99%), cough (59 to 82%), fatigue (44 to 70%), anorexia (40 to 84%), shortness of breath (31 to 40%), and myalgias (11 to 35%).

Other non-specific symptoms include conjunctivitis, nasal congestion, sore throat, headache, diarrhea, nausea, vomiting, anosmia, ageusia are present as well.

Older people and immunosuppressed patients have atypical symptoms such as decrease level of consciousness, delirium, loss of appetite and decrease of mobility. Absence of fever in this category is noted. Moreover, some specific symptoms or signs should be considered as red flags to warn about disease severity, such as blue lips or blue face, cold, clammy, pale, mottled skin, hemoptysis, confusion, syncope, non-blanching rash, chest pain, severe dyspnea and decrease urine output. A heart rate >110 BPM, oxygen saturation < 94%, respiratory rate > 22 breath per minute and a systolic blood pressure <100 mmHg are alarming signs. [3,5]. Some conditions predispose patients to worse prognosis and more severe clinical outcome. Of these conditions we count coronary vascular diseases, chronic kidney diseases, liver diseases, asthma, chronic obstructive lung disease, obstructive sleep apnea, diabetes, dyslipidemia, hypertension, malignancy, obesity (BMI  $\geq 30$ ), male gender, pregnancy and age above 65 years-old. To note that severe clinical outcomes and fatalities were reported in young healthy patients [3,5].

### **Isolation in COVID-19**

Isolation is necessary to contain viral transmission. Viral shedding can continue up to 9 days for mild patients and 20 days for hospitalized cases. Studies and guidelines recommend for discontinuing isolation for asymptomatic patients after a minimum of 10 days for detected test results and for patients who has remained asymptomatic for an entire 10-day period. Recommendations for symptomatic patients is to remove isolation when at least 10 days have passed since symptom onset and patient has been at least 3 days without new symptoms, with improvement of other symptoms [12].

### **Outpatient Management Medical Therapy**

#### **Corticosteroids**

Safety and Efficacy of corticosteroids in out-patients have not been well studied. Steroids suppress the immune system allowing viruses to spread; however, they are potent anti-inflammatory and anti-fibrotic drugs. They also are responsible for many side effects such as hyperglycemia, neuropsychiatric symptoms, secondary infections, and adrenal insufficiency after stopping the drug [14]. Not enough studies or randomized clinical trials were conducted to assess the use of steroids in out-patients; but literature showed that Methylprednisone at 1-2 mg/kg/day given intravenously for 5 to 7 days, or Dexamethasone at 6 mg intravenously administered daily for 10 days, have beneficial outcomes on severe cases. In fact, they were shown to decrease mortality mainly in patients on oxygen therapy or requiring mechanical ventilation. The Recovery trial, a multicenter randomized controlled open label trial, evaluated hospitalized patients in UK. Patients were given 6 mg per day for up to 10 days which resulted in decrease in length of the oxygen therapy, decrease in mortality, and better likelihood of hospital discharge. Patients on oxygen showed maximum benefit, but patients not requiring oxygen showed no benefit. [2,6,9].

IDSA guidelines regarding systemic corticosteroid use in patients with COVID-19, updated on the 11<sup>th</sup> of March 2021, recommends against the use of corticosteroids in mild COVID cases, recommends the use of corticosteroids in cases of acute respiratory distress disease (weak level of evidence), recommends for the use of dexamethasone in hospitalized patients with severe, but noncritical, COVID-19 (6 mg orally or IV daily for 10 days or until hospital discharge, whichever comes first) [1]. The NIH are against the use of corticosteroids in outpatients (no clinical trial data) or in hospitalized patients who are not on supplemented oxygen. They are for the use of dexamethasone (6 mg daily for up to 10 days or until hospital discharge, whichever comes first) in patients with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen [4,21] The WHO also is against the use of systemic corticosteroids for non-severe cases, against the use of systemic corticosteroids in the treatment of non-severe patients, regardless of hospitalization status [4].

As for inhaled corticosteroids, the NIH recommends inhaled corticosteroids already used daily for the management of asthma and COPD to control airway inflammation should not be discontinued in patients with COVID-19 [4].

#### **Azithromycin**

These Macrolide has some activity against Zika, Ebola and influenza A; it decreases Rhinovirus viral load in bronchial epithelial cells [4]. It has an anti-inflammatory activity, but data from various RCT showed no evidence of clinical benefit when the drug was used alone or in conjunction with Hydroxychloroquine. There is insufficient data to evaluate possible clinical benefit (on-going clinical trial) of Azithromycin, but if antibacterial coverage for CAP is indicated in COVID-19 patients, the recommended regimen for empiric treatment of CAP should be used [4].

Following the guidelines updated on the 11<sup>th</sup> of March 2021, the NIH recommends against the use of a combined regimen of chloroquine and Azithromycin for hospitalized pts and against use of a combined regimen for non-hospitalized patients. However, experts also stated that the use of doxycycline (instead of Azithromycin)

should be considered for empiric therapy of atypical pneumonia in COVID-19 patients receiving Hydroxychloroquine. The benefits and risks of a combined regimen of Azithromycin and Hydroxychloroquine should be carefully assessed [21]; if the therapeutic regimen is used, some testing and monitoring are recommended in order to minimize adverse effects, mainly drug-induced cardio-toxic effects [4]

IDSA guidelines do not encourage the use of a combined regimen of Hydroxychloroquine and Azithromycin for the treatment of in hospital COVID-19 diseases [1].

### **Chloroquine**

An antimalarial drug, used in Rheumatoid Arthritis and Lupus for many years, with a well-established safety profile. It has antiviral activity (effect reinforced by Azithromycin, synergistic effect), in-vitro inhibition of other corona viruses, has anti-inflammatory effect via decreasing cytokine storm. This family of drugs has many side effects: cardiomyopathy, QT prolongation, arrhythmias, gastrointestinal and retinal toxicity [20,22].

Guidelines were updated on the 25<sup>th</sup> of February 2021, in which NIH and IDSA recommend that use of Hydroxychloroquine (with or without Azithromycin) in hospitalized and non-hospitalized patients is not recommended, except in a clinical trial [1,21]. NIH also recommends against the use of any drugs, including Hydroxychloroquine, for pre-exposure prophylaxis (PrEP) to prevent SARS-CoV-2 infections, except in a clinical trial [21]. The FDA recommend against the use of Chloroquine or Hydroxychloroquine for treatment or prevention of COVID-19 outside of a clinical trial or hospital setting [4]

### **Ivermectin**

This antiparasitic agent is known to have antiviral activity against HIV, dengue, influenza. Some studies done in vitro showed its capability of inhibiting the replication of SARS-COV2, it remains noteworthy to know its effect in vivo [4].

However, one study showed that Ivermectin, with the approved dose of 200mcg/kg, does not reach the lungs, but a combination therapy with other agents might be beneficial.

NIH states that the data are insufficient, to date, to recommend for or against the use of Ivermectin for the treatment of COVID-19 [22].

IDSA also recommends against use of Ivermectin for treatment of severe COVID-19 in hospitalized patients and in out-patients outside of the context of a clinical trial.

Finally, the FDA warns of concerning possible inappropriate use of Ivermectin products intended for animals as an attempt to self-medicate for the treatment of COVID-19 [4]

### **Colchicine**

Known to have an anti-inflammatory and anti-fibrotic activities with beneficial effect on endothelial function. Also has inhibitory effect on neutrophils and lymphocytes.

Safety and efficacy for treatment of COVID-19 is not established. In fact, the toxic potential to alveolar type II pneumocytes (which may inhibit surfactant release and contribute to ARDS) and the risk of multiple-organ failure and disseminated intravascular coagulation (DIC) has been raised as a possible concern with the use of colchicine in infected patients [20, 22].

### **Remdesivir**

FDA guidelines about this anti-viral updated on February 2021 sets Remdesivir as the only approved drug for treatment of COVID-19 in adults who are hospitalized and requiring supplemental oxygen. They recommend its use for a 10-days regimen, intravenously, 200 mg on day 1, then 100 mg daily, for hospitalized patients on supplemental oxygen, noninvasive ventilation or invasive mechanical ventilation [4]

However, for non-hospitalized, mild to moderate disease the panel states that data are insufficient to recommend either for or against any specific antiviral or antibody therapy.

The IDSA recommends that patients with severe COVID-19 (i.e., saturation  $\leq$ 94% on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO) should use Remdesivir [1]

Similarly, those on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA suggests a 5-day Remdesivir regimen rather than a 10-days regimen; and it recommends against its use in non-hospitalized patients [1].

### **Statins**

The NIH states that patients who are receiving a statin for the treatment or prevention of cardiovascular diseases should continue the treatment, but it recommends against the use of statins for the treatment of COVID-19 except in the context of a clinical trial.

In addition, in patients with active COVID-19 who may develop severe rhabdomyolysis, recommendations are to withhold statin therapy for a short period of time [4]

### **ACE inhibitors / ARB**

Many controversial studies and theories emerged in the beginning of the disease pandemic, some recommending stopping the therapy and others no. Updates in February 2021 stated that the AHA, ACC, ESC and NIH recommends continuing this therapy if patient was already on it.

In fact, abrupt withdrawal of RAAS inhibitors in high-risk patients (e.g., heart failure patients, patients with prior myocardial infarction) may lead to clinical worsening clinical outcome and adverse health consequences [4]

### **Anticoagulants**

The NIH recommends giving prophylactic doses of anticoagulation for VTE prevention in all hospitalized adults with COVID-19, unless contraindicated.

Data is insufficient to recommend for or against the use of doses higher than the prophylactic dose. Low molecular weight heparin is preferred, however, specific drug characteristics, patient-specific factors (e.g., renal function), and practical concerns may influence choice of anticoagulant [21].

The WHO recommends administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients with COVID-19, especially if they do not have an established indication for higher dose anticoagulation. Long term VTE prophylaxis after hospital discharge is not routinely recommended but may be considered based on risk-benefit analysis [4].

### **Supplements and Vitamins**

#### **Vitamin C**

Vitamin C is an antioxidant which boosts immune system. It has an immunomodulatory effect, decreases interleukins, decreases level of proinflammatory cytokines (IL-6-IL-10), has antiviral activities mainly for influenza viruses, antihistamine properties, prevent viral infection, reduces duration and severity. This drug is safe, doesn't have major side effects.

Some studies showed a decrease in vitamin C plasma concentration in patients with acute respiratory infection [15]. As per COVID-19 infection, guidelines updated on the 11<sup>th</sup> of March 2021, different regimens studies encouraged the use of 1 gram orally 3 times daily or 8 grams daily divided in 2-3 doses for 7-14 days [4] The NIH states that data is insufficient to recommend for or against the use of Vitamin C in critically and non-critically ill patients [21].

The role of ascorbic acid in non-critically ill patients is unknown since these patients are less likely to experience oxidative stress or severe inflammation[4].

#### **Vitamin D**

This vitamin maintains the integrity of epithelial tight junctions damaged by the virus. Some meta-analysis reports showed that some protection against acute respiratory infections is offered when vitamin D deficiency is treated with daily doses rather than bolus doses. A study done in the United Kingdom showed that there is no link between vitamin D concentration and COVID infection, nevertheless Vitamin D deficiency was linked with more coagulopathy and ICU admissions [15].

Data was updated in January 2021 and the NIH states that insufficient data to establish evidence about the benefit of the use of vitamin D [21] and NICE states that no evidence is there to support taking vitamin D supplements to specifically prevent or treat COVID-19.[12]

#### **Zinc**

This supplement has antiviral properties; it blocks viral replication in vitro and inhibits its activity. Studies showed that it also has anti-inflammatory properties in animal models and it enhances Chloroquine intracellular uptake [15]

In March 2021, NIH stated again that data is insufficient to recommend either for or against use of zinc, in the treatment of COVID-19 and it moreover recommends against using zinc supplementation above the RDA for the prevention of COVID-19, except in a clinical trial setting [4]

### **General Management**

The symptomatic treatment for mild to moderate cases consists of antipyretic and analgesics (NSAID, paracetamol, ibuprofen), adequate nutrition, appropriate hydration and vitamin supplementation Managing the cough by avoid lying on bed (decrease ability to cough, increase risk of pneumonia), honey and antitussive is also part of the treatment.

Managing breathlessness by identifying the underlying cause, providing supportive care (keep the room cool, relaxation, breathing technique exercises, good body positioning, open windows) can help as well. Moreover,

managing anxiety, delirium, agitation, identify reversible causes, explore patient concerns and assess sleep problems is an essential part of the management.

Other important tips are to refrain from using antibiotics (higher bacterial involvement rate) unless suspicion of superimposed bacterial infection.

To note that for elderly patients, reviewing medications can reduce polypharmacy and prevent D-D interactions.

### **Post-Covid Complications**

Several long term or persistent complications can be noted from the literature. For example, anosmia and ageusia were reported post infection in several patients and anosmia tend to take more time to resolve than ageusia [13].

40% of asymptomatic individuals and 13% of symptomatic ones become seronegative 8 weeks after infection. Re infection can occur if patients are exposed to higher dose of virus or if they are re-infected with a strain of greater virulence [8,15]. Some pulmonary complications are also noted such as secondary bacterial pneumonia, pneumothorax, impaired PFTs. More than 50% of patients in early convalescent phase (30 days after discharge) present with such complication and up to 10%, 90 days after discharge [7,11,16].

Post infection pulmonary fibrosis, happens due to up regulation of pro fibrotic molecules ( TGF-B) and dysregulated release of matrix metallo-proteinase during the inflammatory phase epithelial and endothelial injury with fibroproliferation. Patients should be followed up with PFTs 3 months after discharge [10]. Pulmonary Rehab (respiratory muscle training, UE, LE muscle strengthening, aerobics, neuromuscular electrical stimulation) is highly recommended [10,16,18]. Some indirect evidence showed that virus can spread through the olfactory canals to the blood brain barrier, causing some neurological damages, but further studies needed to identify what kind of diseases will emerge [8,19].

Furthermore, other studies identified cardiovascular sequelae such as myocarditis, pericarditis (for which patients should avoid intense exercise for 3 months), infarcts, arrhythmias, heart failure, ventricular dysfunction, left ventricular systole dysfunction, and thromboembolism [17].

### **Conclusion**

Management of covid-19 in the out-patient setting is focused on supportive care and reducing transmission via home isolation. Currently the treatments are mainly repurposing the available drugs. For patients with mild to moderate COVID-19 who are not hospitalized there is insufficient data to recommend for or against any specific antiviral or antibiotic therapy. Systemic Corticosteroids is not recommended but patients receiving Corticosteroids for any other underlying condition should continue their therapy. There is no clear benefit for Hydroxychloroquine treatment or post exposure prophylaxis. There is Insufficient evidence to recommend Ivermectin or Colchicine and there is no evidence to recommend vitamin or zinc use. Recommendations are to continue statins, ACE-I and ARBs if indicated outside the COVID-19 infection and to start anticoagulants for in-hospital patients at a prophylactic dose.

### **Abbreviations**

IDSA: Infectious Diseases Society of America  
NIH: National Institutes of Health  
HIV: Human Immunodeficiency Virus  
NSAID: Non-Steroidal Anti-inflammatory Drug  
NICE: National Institute for Health and Care Excellence  
RDA: Recommended Dietary Allowance  
RCT: Randomized Control Trial  
IL : Interleukin

VTE : Venous Thromboembolism  
AHA: American Heart Association  
ACC: American College of Cardiology  
ESC: European Society of Cardiology  
RAAS: Renin-Angiotensin-Aldosterone System  
ECMO: Extracorporeal Membrane Oxygenation  
ARDS: Acute Respiratory Distress  
WHO: World Health Organization  
CAP: Community Acquired Pneumonia

### **Declaration and conflict of Interest**

Ethics approval and consent to participate: study is based on readily available online data and does not include participants

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