Evolution of the management of COVID-19

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ABSTRACT

Since February 2020, in IHU Méditerranée Infection, Marseille, France, we managed more than 11,000 patients in our day-care hospital and more than 2,000 in our complete hospitalization wards. From day one, we have been offering early massive PCR screening for patients suspected of having COVID-19 and for their contacts. Here, we propose a brief review of the therapeutic management of COVID-19 including literature data as well as our personal experience based on the observation of our cohort and our previous reports.

We systematically proposed to evaluate patients in our day-care hospital (clinical examination, Sp02, standardized biological assessment including D-dimers +/- low dose CT-scan). We advised outpatients to buy pulse oximeters to detect “happy” hypoxemia, and proposed hospitalization if Sp02<95%. Treatment was proposed using hydroxychloroquine (200 mg, 3 times a day, 10 days), azithromycin (500 mg day one then 250 mg during 4 days) after eliminating the contraindications, and elemental zinc (15 mg, 3 times a day, 10 days). For patients with a NEWS-2 score> 5, broad-spectrum antibiotic therapy was prescribed (ceftriaxone or ertapenem). Anticoagulation treatment was considered depending on risk factors and D-dimer levels. After a couple of months, low dose of dexamethasone was prescribed (avoiding early stages of high viral load infection) for patients who had an increase in inflammatory parameters and a worsening of oxygen dependence. Finally, we used recently high-flow oxygen therapy devices for patients not eligible for intensive care unit transfer because of their age and / or comorbidities.

This step-by-step strategy allowed us to obtain one of the worldwide lower mortality rates of COVID-19. Long-term follow-up will be the next challenge of COVID-19 management.

INTRODUCTION:

The outbreak of COVID-19 has emerged as a world pandemic that has caused more than 1.8 million deaths for 86 million people infected worldwide [1]. This disease progresses through different phases ; first a viral phase, followed by an inflammatory phase in some patients with sometimes a life-threatening evolution, each of these phases requiring specific managements [2]. As early as February 2020, in our University Hospital Institute (*IHU Méditerranée Infection*, Marseille, France), we have been offering early massive PCR screening for patients suspected of having COVID-19 and for their contacts, although the capacities of early testing were low in the country. For positive cases, we proposed a standardized management including clinical, biological and radiological measurements as previously described [3-5]. Indeed, our laboratory has performed more than 375,000 PCR to detect SARS-CoV2 in more than 188,000 different individuals, and we managed more than 11,000 patients infected with COVID-19 in our day-care hospital and more than 2,000 in our complete hospitalization wards. Here, we propose a brief review of the management of COVID-19 infections including literature data as well as our personal experience.

ANTIVIRAL TREATMENTS:

Drug repurposing has been rapidly proposed during this outbreak, focusing mainly on two drugs, hydroxychloroquine with or without azithromycin, and remdesivir. From the first patients treated with hydroxychloroquine (HCQ) in our center, we observed that those who had azithromycin (AZ) for pneumonia had a faster viral clearance [6]. The synergistic antiviral effect of these drugs on SARS-Cov2 was confirmed in vitro [7]. The in vitro activity of AZ has also been documented in other work [8]. In our center, out of 3,737 patients, we observed that the dual therapy HCQ AZ allowed to divide by 2 the risk of mortality (ratio 0.5, difference -50%) and by 5 the risk of transfer to intensive care unit (ICU) (ratio 0.2, difference -80%) [3]. This effect was probably not only antiviral because the effect on viral

carriage was of the order of -25% (ratio 0.75, [2]). This is consistent with the immunomodulatory and anti-inflammatory effect of the 2 molecules [9] and in particular the anti-interleukin 6 (IL-6) effect of hydroxychloroquine confirmed in COVID-19 patients [10]. Indeed, IL6 is one of the best predictors of ARDS in COVID-19 [11]. In the literature, when we look at studies that included 3 groups (1 HCQ AZ group, 1 HCQ group and 1 standard of care (SOC) group) and that reported the effect for each treated group (HCQ AZ vs SOC, HCQ alone vs SOC), dual therapy always did better than monotherapy in clinical studies [12-15], **Figure 1A**). In a meta-analysis, dual therapy was significantly more effective than monotherapy in reducing mortality by a factor of 3 (ratio 0.34, difference -66%), which was highly significant (p = .000011), whereas HCQ monotherapy showed a lower effect (ratio 0.77, difference -23%) and not significant (p=0.16). Overall, heterogeneity was substantial (I^2 = 60%) and significant (p = 0.012), whereas when dual and monotherapy were separated, heterogeneity was no longer significant (I^2 = 0% for HCQ alone and 44% (p = NS) for HCQ AZ). This further confirms the difference of effect between HCQ AZ and HCQ alone. The difference in the summary effect between dual and monotherapy was highly significant (OR(HCQ) = 0.77 versus OR (HCQ-AZ) = 0.34, Q-value = 11.0, p = 0.00088, **Figure 1A**). In contrast, the Big data studies concluded that HCQ was ineffective and that HCQ AZ had a significant deleterious effect (**Figure 1B**). As discussed earlier, clinical studies best represent management by specialist physicians who respect indications, contraindications, dosages and monitoring under treatment, whereas Big data studies represent studies associated with the absence of therapeutic details that are highly vulnerable to conflict of interest [16] and victim of Simpson's paradox [17]. In addition to our meta-analysis, all the studies published on the use of the hydroxychloroquine are summarized online (https://c19study.com/).

Remdesivir, is a precursor of a nucleotide analogue that inhibits viral RNA polymerases. As for Ebola, SARS-CoV and Middle East respiratory syndrome coronavirus,

remdesivir appears to be effective *in vitro* on SARS-Cov2 [18]. As for today, some clinical studies have been published as case reports [19-21], or RCTs. The first placebo-controlled study of remdesivir on hospitalized COVID-19 patients, found no statistically-significant benefit from the treatment—and the antiviral had no impact on levels of the coronavirus [22]. An interim analysis of a large-scale, placebo-controlled clinical trial carried out by the National Institutes of Health emphasized the fact that remdesivir had promise. A preliminary report of the announced study above showed that the survival benefits were significant in the overall-analyzed population [23]. This conclusion was however over-interpreted [24]. Results were given in intention to treat patients but only one third of the enrolled patients in both arms (33.8 / 35.7%) received the complete protocol. Of them, 27.4% were discharged because they were cured before the end of treatment and were loss of follow-up, the remaining still receiving the treatment or having missing treatment data at time of analyses. The final report of this study confirmed the over-enthusiastic efficacy of the drug which reduced time to recovery from 15 to 10 days without significant reduction on mortality [25]. Finally, the interim WHO Solidarity trial, concluded that remdesivir has little or no effect on hospitalized COVID-19 patients [26]. As for today no study convincingly supports the use of remdesivir in COVID-19 patients. It is however, interesting to notice that “a weak recommendation for the use of remdesivir” was previously made for severe cases [27] and was followed by the recommendation of the human medicine committee of the EMA to grant a conditional marketing authorization for patients with COVID-19 who required supplemental oxygen. As a consequence, both FDA and EMA ordered 2.2 billon dollars worth of the drug, this being severely criticized in Science magazine by John Cohen [28]. Because of all these biases, we decided that none of our patients would be treated with remdesivir, an exclusively IV drug with high renal toxicity.

ANTICOAGULATION TREATMENT

COVID-19 leads to a hypercoagulable disorder with clinical consequences [29]. Elevation of D-dimer was one of the earliest manifestations of perturbed coagulation identified [29]. Moreover, enhanced D-dimer is correlated with disease severity [30]. Excessive inflammation, platelet activation, endothelial dysfunction, and stasis are the main causes of the hypercoagulable state and responsible for high incidence of thrombosis [31,32]. Indeed, both micro and macrovascular thromboses, and both arterial and venous thrombotic events are reported [31]. The autopsy series indicates multiorgan damage pattern consistent with microvascular injury, which is probably an under-appreciated complication of COVID-19 [33,34]. Although most patients received prophylactic anticoagulant treatment, a high prevalence of venous thromboembolism events (VTE) was reported compared to other viral infections [35]. The prevalence of VTE in ICU patients is evaluated to 22.7% with highly variable results between studies (5.8 to 61%) [36]. In non-ICU hospitalization, the VTE prevalence was estimated at 7.9 % [36]. Given the major risk of macrovascular and microvascular thromboses in patients with COVID-19, anticoagulation was rapidly proposed. The majority of patients received anticoagulant thromboprophylaxis [36-38]. Regarding the severity of embolism events and their high frequency, none of the studies allows any comparison between anticoagulant thromboprophylaxis and placebo. However, many reports have suggested that ICU patients with COVID-19 infection remain at a higher risk of VTE despite standard anticoagulation prophylaxis. The interest of curative anticoagulation remains discussed in ICU patients [38]. Recently, Nadkarni et al demonstrated in a large cohort of 4,389 hospitalized patients that anticoagulation was associated with lower mortality and intubation [39]. Today, recommendations on prevention and treatment are available [40-42]. In practice, all confirmed or presumed COVID-19 patients admitted to the hospital usually receive prophylactic anticoagulation to prevent VTE, unless contraindicated. LMWH is the drug of choice over unfractionated heparin or direct oral anticoagulants for prevention of

VTE. In hospitalized patients with COVID-19, DOACs and VKA should be replaced by LMWH due to potential interactions with antiviral or convalescence treatments. All confirmed or presumed COVID-19 patients admitted to the hospital undergo close monitoring for the risk of thrombosis. D-Dimer, PT, aPTT, fibrinogen and platelet counts need to be performed on admission and repeated during hospitalization. The duration of post-discharge thromboprophylaxis can be approximately 14 days at least (50% of respondents), and up to 30 days (20% of respondents). For COVID-19 patients with proximal DVT or PE, therapeutic anticoagulation with LMWH is proposed. DOACs in the post hospital discharge setting are recommended for a minimum duration of three months [40-42]. The inpatients with non-severe symptoms who usually have elevated D-dimer (2- to 3-fold above normal) should receive prophylactic LMW heparin in the absence of contraindications [43]. The benefits of heparin on COVID-19 patients are multiple. Indeed, heparin prevents infection by decreasing virus cell entry and hence viral load, modulates inflammatory response through reduction of IL-6 release, prevents activation of coagulation cascade and venous thromboembolism. In addition, heparin prevents and treats also thrombosis of small and middle size vessels leading to lung failure [44].

Both i*n vitro* data [45,46] and clinical studies [47,48] for thrombosis prevention in antiphospholipid syndrome have demonstrated that HCQ had several antithrombotic effects. Finally, one unresolved query is the potential role of aspirin on which controversial results have been published [49-50].

POTENTIAL OTHER EFFICIENT DRUGS:

Repurposing was also proposed for other anti-infectious agents such as doxycycline and ivermectin, whose safety has long been proven. These drugs have demonstrated efficiency for COVID-19 treatment with both in vitro and in clinical studies. The most promising drug is probably ivermectin, for which larger studies will be needed to confirm

these preliminary findings but that can be a good alternative for the early-onset mild COVID-19 in adult patients [51]. In addition, some studies have convincingly demonstrated that Cyclosporin A inhibited in vitro replication of SARS-CoV-2 [52-53]. Demir et al. in their cohort of 40 kidney transplant patients, have demonstrated in a multivariate analysis that Cyclosporin A was associated with a reduced mortality rate [54]. FDA approved some clinical studies proposing this drug to treat SARS-CoV2 infections in order to obtain strong results.

CORTICOSTEROID TREATMENT

Corticosteroids have long been used as an adjunctive treatment for pneumonia with acute respiratory distress syndrome [55]. They are not antiviral drugs but have immunomodulatory effects against the inflammatory response and possibly against some SARS-Cov2-induced coagulopathy. The two first large randomized controlled trials on the use of corticosteroids in COVID-19 patients yielded conflicting results and potential biases. One randomized trial on 6,425 hospitalized patients with COVID-19 found that dexamethasone reduced mortality [56], although the other one did not show any benefit on 28-day mortality and on several secondary outcomes of treatment with methylprednisolone [57]. Then, a multicenter observational study in Italy, failed to find a lower mortality rate among hospitalized COVID-19 patients treated with corticosteroids, although the authors suggested by analyzing subgroups that the effect of corticosteroid treatment on mortality might be limited to patients with severe respiratory failure [58]. More recently [59], a meta-analysis with a total of 5,270 patients from 15 studies highlighted that corticosteroid treatment was associated with higher mortality, longer length of stay, and a higher rate of bacterial infection. However, patients with severe conditions are more likely to require corticosteroids. Then, a multicenter retrospective study in China [60], suggested that early (starting in 7 days after admission), low-dose and short-term methylprednisolone therapy could significantly decrease the 60-day fatality. However, admission usually occurs after several days of disease evolution, except in places where early

test and ambulatory therapy have been proposed, such as in our center. Also, using corticosteroids too early may cause immunosuppression and thus weaken the viral clearance, especially when high dosages are administered [61]. In the end, the use of corticosteroids remains controversial and empirical. It is associated with the experience of the clinicians in charge of the patients, being able to analyze and identify the possible markers for the therapeutic window, but the timing to start still remains uncertain [62]. Our strategy of early home/outpatient COVID-19 treatment excludes the early use of corticosteroids. However, when we admit patients with several days of evolution, without having had the opportunity to get early HCQ-AZ treatment, with excessive inflammation (CRP >100), acute respiratory distress syndrome and/or increased need of oxygen, marked radiologic progression, antiphospholipid syndrome, low to moderate doses of corticosteroids with antibiotic coverage (azithromycin plus ceftriaxone or ertapenem) and combined or not with hydroxychloroquine, are included in our therapeutic options on a case-by-case basis. Observational studies of large cohorts might help to identify better criteria for the use of corticosteroids in COVID-19 patients.

Other immunomodulatory drugs were proposed without convincing efficiency and were detailed elsewhere [2].

MICRONUTRIENTS

Before SARS-CoV-2 pandemics, zinc supplementation has been used as both prophylaxis and treatment of respiratory infections with positive outcomes [63-65]. Being involved in both innate and adaptative immunities [66], zinc possesses a natural antiviral activity against various viruses and is notably capable to inhibit SARS-CoV-1 replication in vitro through the inhibition of RNA polymerase [67]. There is currently no evidence of in vitro activity against SARS-CoV-2. Chloroquine and derivatives are interestingly zinc ionophores that thereby increase the zinc concentration in cells [68]. Zinc was thereby

associated with hydrochloroquine and azithromycin in a retrospective study, in which a reduction of hospitalization frequency and mortality was observed when compared to untreated patients [69]. If the impact of zinc supplementation could not be assessed in the present work, a retrospective study shows that when compared to chloroquine + azithromycin alone, the addition of zinc to chloroquine + azithromycin is associated with a reduced mortality in patients that did not require ICU and an increased frequency of patients discharged home [70]. Zinc deficiency could be a predictive factor of severity [71] as affected patients have higher rates of complications, prolonged hospital stay, and an increased mortality [72]. As zinc supplementation is not harmful for humans, it may be an adjuvant treatment for SARS-CoV-2 infections in particular when associated with a zinc ionophore. We included this supplementation in our therapeutic protocol.

Various studies have suggested before the SARS-COV-2 pandemics that Vitamin D could be used to prevent respiratory infections [73,74]. The mechanism of action involved is so far not fully explained but includes the production of antimicrobial peptides [75], the modulation of ACE2 expression [76] which is implied in the advent of ARDS, or the reduction of the production of pro-inflammatory cytokines [77]. During the pandemics it has been demonstrated that testing positive for SARS-CoV-2 was associated with likely deficient vitamin D status [78]. In addition, a large observational study in the U.S. shows that the incidence rate can vary from 6.5% for 25(OH)D=40-50 ng/mL to 11.3% for 25(OH)D = 20 ng/mL [79]. The severity of the disease was also associated with lower vitamin D levels [79, 80]. These findings should be however interpreted according to geographic location and season as they influence UVB exposure [81]. Few therapeutic interventions were reported so far, but regular bolus vitamin D supplementation in the elderly diagnosed with SARS-COV-2 infection was associated with less severe outcome and a decrease of mortality [82]. Vitamin D was also administered with other nutrients in some trials, rendering difficult to assess its

impact on the positive outcomes observed [83]. Taken together these data raise the question of interventions among people at increased risk of vitamin D deficiency.

OUR EXPERIENCE

Management

Our strategy was based since the beginning of the COVID-19 outbreak on the "earliness" doctrine : early massive testing, early home treatments, early LDCT, early hospitalization if necessary (**Figure 2**). Firstly, we decided to early test all patients presenting with or without symptoms using RT-PCR [84]. We systematically suggested that positive patients be evaluated in our day-care hospital (clinical examination including anosmia status, Sp02, standardized biological assessment including D-dimers) [3, 85]. Initially all the patients benefited from a LDCT to detect infra-clinical damage [4], then we adapted the criteria according to our first results (patient over 55 years old or with clinical history) [3,5]. As previously described [86], having detected cases of happy hypoxia in our first patients [87], we purchased pulse oximeters for each healthcare worker and advised our outpatients to purchase one. In case of saturation <95% we asked them to come back to be hospitalized. In order to be able to take care of the maximum number of patients in conditions of optimal safety concerning the management of the contagion, we controlled the RT-PCR in a nasopharyngeal sample every morning. In the event of a CT> = 34, having demonstrated the absence of risk of contagion (negative culture) [88], we transferred the patients to another department.

Regarding therapeutic strategy (**Table 1**), following our preliminary study having demonstrated the effectiveness of the hydroxychloroquine and azithromycin combination in decreasing the duration of viral load [6], we decided to propose this treatment from March 22nd, 2020 after eliminating the contraindications, performing an EKG and a kaliemia measuring [3, 84], off label. From April 15th, following preliminary results we have added the prescription of elemental zinc [89]. In addition, for patients with a NEWS-2 score> 5,

broad-spectrum antibiotic therapy was prescribed (ceftriaxone or ertapenem). Anticoagulation was appropriate for age, risk factors (obesity) and D-dimer levels (**Table 1**). Besides inpatients, all of these elements described above led us to propose preventive anticoagulation with LMWHs on an outpatient basis for at-risk patients (**Table 1**). Corticosteroid therapy with dexamethasone was prescribed after collegial discussion in patients who had preferably negated their viral load but had an increase in inflammatory parameters and a worsening of oxygen dependence. In addition, we have paid great attention to anemia especially in elderly people with hypoxia and on a case-by-case basis used blood transfusions or erythropoietin. Also, we compassionately used ivermectin in few cases. Finally, since September 15th, 2020, we have purchased high-flow oxygen therapy devices that we use in patients who are not eligible for resuscitation because of their age and / or their comorbidities, and for whom transfer in ICU was not possible. Thanks to this oxygen supportive care, we managed to save 1/3 of these patients (unpublished data).

Future challenges of the long-term follow-up:

The evaluation of long-term sequelae in COVID-19 patients is a major issue. Firstly, because of the interstitial abnormalities within the lung in severely-infected patients, a potential post-infectious chronic fibrotic interstitial lung disease, as observed in the follow-up of patients after MERS and SARS-CoV-1 infections could be suggested [90]. We are organizing a close follow-up of patients with chest CT scan for early detection of these abnormalities and understanding of their determinants [91].

Secondly, persistent anosmia is increasingly reported and evaluated approximately in 10 to 25% of the patients [92, 93]. We recently reported the case of a patient with a 4-week persisting anosmia after COVID-19, who presented a hypometabolism of the olfactory/rectal gyrus in brain 18 F-FDG PET CT-scan confirming the neurotropism of SARS-CoV-2 [94,95]. Olfactory training (https://www.mediterranee-infection.com/jai-perdu-le-gout-et-lodorat-

concretement-que-faire/) should be systematically proposed for these patients and the interest of precocious intranasal corticosteroid is still under investigation [96].

Thirdly, viral neurotropism of SARS-CoV-2 through the olfactory bulb may also spread to other limbic structure, such as the amygdala, the hippocampus and the cingulate cortex which are involved in cognition and emotion. We previously reported the case of a patient with persisting lower leg crushing sensation alternating in the toes with no clinical deficit at examination, who had bilateral marked hypometabolism involving limbic structures in brain 18F-FDG CT Scan [94,95]. A one-case series (personal data) highlighting some abnormalities, we think that brain 18F-FDG CT-scan is an interesting tool to explore patients with neurocognitive disorder after COVID-19.

Finally, vasculitis in patients with post-infectious manifestations after SARS-COV-2 infection has been suggested by a recent study [97]. The authors reported ten patients who underwent full body 18 F-FDG PET CT-scan finding significantly higher target-to-blood pool ratio in three vascular regions (thoracic aorta, right iliac artery and femoral artery) than controls [96]. Further studies are needed to better know the post-infectious vascular consequences of COVID-19.

CONCLUSION

The early diagnosis of COVID-19 infections [98], associated with standardized management allowed us to obtain a significantly-reduced mortality rate [3]. The same strategy has obtained similar results of reduced mortality in fragile elderly patients living in retirement homes [99]. In conclusion a pragmatic approach perpetually updated (including progressively elemental zinc, optimized anticoagulation treatment, corticosteroids, HFNO), has allowed us during the emerging outbreak caused by SARS-CoV2 to have one of the worldwide lowest mortality rates. Standardized long-term follow-up will be the next challenge of COVID-19 management.

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Figure 1. Meta-analysis of studies with treatment by HCQ AZ or HCQ vs standard of care for COVID-19 mortality

CI: confidence interval, HCQ: hydroxychloroquine, CQ: chloroquine, AZ: Azithromycin, RCT: Randomized controlled trial. This meta-analysis was performed with a random-effect model using Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA).

Figure 2: flowchart of the management of COVID-19, IHU Méditerranée Infection, Marseille, France

336 **Table 1 :** therapeutic proposal, IHU Méditerranée Infection

Clinical involvement	Treatments	Precautions
Antiviral treatment		
COVID-19 infection diagnosed by positive RT-PCR	Hydroxychloroquine 200 mg, 3 times a day, 10 days + Azithromycin 500 mg day 1, then, 250 mg during 4 days + Elemental zinc 15 mg, 3 times a day, 10 days	Contraindication checking (including drug interactions) Electrocardiogram Kaliemia measurement
Potassium		
Hypokaliemia < 3.6 mmol/L*	Potassium chlorure 600mg 2 x 3/d until potassium > 3,6 mmol/L then 600 mg 1 x 3/d for ten days in total	Kaliemia monitoring every 48h
Antibiotics		
NEWS-score 2 >5	Ceftriaxone : 2g a day, 5 days (<65 years) Ertapenem 1g a day, 5 days (> 65 years)	After checking allergies
Anticoagulation		
INPATIENT D-dimers > 0.5 and/or body mass index > 30 and/or fibrinogen > 8g/L and/or lupus anticoagulant	Low molecular weight heparin, twice a day	+/- after pulmonary CT angiography depending of the clinical involvement
OUTPATIENT** Obesity, cancer, history of thromboembolic disease (phlebitis, pulmonary embolism), coronary disease (infarction, stent, bypass), autoimmune disease (thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis...), hemoglobinopathy (thalassemia, sickle cell	LMWH Enoxaparin 0,4 mL SC/day 10d (normal weight) Enoxaparin 0,6 mL SC/day 10d (obesity)	pulmonary CT angiography in patients with D-dimer > 2000 µg/L

disease), Crohn's disease, ulcerative colitis, D-dimer > 500 µg/L, Fibrinogen > 8 g/L, lupus anticoagulant or antiphospholipid antibodies.		
	Anti-inflammatory treatment	
Severe clinical involvement or increase of inflammatory syndrome coupled with oxygen requirement from day 8-day 12	Dexamethasone 6 mg a day, 10 days	In our experience corticosteroids should be contraindicated in acute phase of the disease Ideally corticosteroids should be used if CT value > 30

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