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Médecine et maladies infectieuses 50 (2020) 639–647

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Review

COVID-19 in clinical practice: A narrative synthesis☆

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ARTICLE INFO

Article history:
Received 4 August 2020
Received in revised form 27 August 2020
Accepted 24 September 2020
Available online 29 September 2020

Keyword:
COVID-19

ABSTRACT

The coronavirus disease 2019 (COVID-19) was first reported in the city of Wuhan, China. The disease rapidly spread to the rest of China, to Southern-East Asia, then to Europe, America, and on to the rest of the world. COVID-19 is associated with a betacoronavirus named SARS-CoV-2. The virus penetrates the organism through the respiratory tract, conveyed by contaminated droplets. The main cell receptor targeted is the surface-bound ACE-2. As of the 26th July 2020, 15,200,000 COVID-19 cases and 650,000 deaths were reported worldwide. The mortality rate is estimated between 1.3 and 18.3%. The reproductive rate without any public health intervention is estimated around 4-5.1 in France. Most hospitalized patients for COVID-19 present respiratory symptoms, which in some cases is associated with fever. Up to 86% of admissions to ICU are related to acute respiratory failure. To date, no anti-viral therapy has proven its efficacy considering randomized trials. Only immunomodulatory treatments such as corticosteroids have shown to cause significant improvement in patient outcome.

The first official information regarding a new disease originated from the Chinese health authorities after a cluster of atypical pneumonia was reported in the city of Wuhan, China in December 2019 [1]. At that point, an epidemiologic link with a wildlife trading market known as Huanan Seafood was suggested [2]. While it has been shown retrospectively that some of the early-infected patients did not show such link [3], this finding pointed out the likely zoonotic nature of the outbreak.

The disease rapidly spread to the rest of China, to Southern-East Asia (South Korea, Taiwan and India), then to the rest of world [4], and was declared a pandemic by the World Health Organization (WHO) on the 11th March 2020 [5]. As did many countries, France faced a first epidemic wave with a maximum of 27,077 weekly cases in the 13th week of 2020 [6].

Here we report a synthesis on COVID-19 literature. We focused on data that was needed daily in clinical practice to improve patients' care and the management of this epidemic.

1. Viral origin, genetic and phylogeny

This novel illness was rapidly associated with a previously unknown virus, temporarily named 2019-nCoV after genetic sequencing classified the virus as belonging to the *coronaviridae* family. Precise phylogenetic analysis has been performed in the past few months allowing a more accurate characterization of the virus. The International Committee on Taxonomy of Viruses (ICTV) officially named the virus severe acute respiratory syndrome associated coronavirus 2 (SARS-CoV-2) on the 2nd March [7] while the WHO referred to the new disease as COVID-19.

SARS-CoV-2 is an enveloped virus of the group IV of the Baltimore classification of viruses, owing to its single stranded non segmented RNA of positive polarity. It belongs to the order of *nidovirales*, the *coronaviridae* family and the *betacoronavirus* genera. It is related to SARS-CoV which sprung the first pandemic of the XXIst century in 2002-03 and which shares 79.6% sequence identity [8]. SARS-CoV-2 has a much lower identity with another recently emerged coronavirus, the middle-east respiratory syndrome associated coronavirus (MERS-CoV). With a genome of around 29.800 bp, SARS-CoV-2 possesses one of the longest viral RNA genomes, raising questions about the stability of the viral genetic material. The genome encodes 16 non-structural proteins (NSP), four structural proteins known as S for Spike, E for Envelope, M for Matrix and N for Nucleoprotein, and nine accessory proteins whose roles remains to be detailed [9]. NSP14 holds an exonuclease activity responsible for the proof-reading activity of the RNA-dependent RNA-polymerase (RdRp) complex, which accounts for the stability of the viral genome and its low mutation rate [10]. Different viral lineages have however been described [11]. The exact role of point mutations and viral lineages so far reported

☆ This work has yet to be presented in congress.

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https://doi.org/10.1016/j.medmal.2020.09.012
0399-077X/

remains to be described in detail [12,13]. As of today, no clinical implication of the viral variability has been unequivocally proved.

The zoonotic nature of the outbreak is now acknowledged by all authors but the exact path from the viral reservoir to human transmission still needs clarification. SARS-CoV-2 is closely related to a coronavirus infecting the bat *Rhinolophus affinis*, BatCoV RaTG13 [8], thus making this bat the most likely reservoir of the virus. As for SARS-CoV and for MERS-CoV, an intermediate host has been suggested (pangolin [14]), but this assertion awaits confirmation. The pathway of the introduction in the human host also needs clarification: whether animal-to-human transmission is the result of a single spillover event or repeated introductions has yet to be detailed.

2. Epidemiology

From the end of 2019, SARS-CoV-2 disseminated in an entirely susceptible population. The spread of COVID-19 matches the definition of a pandemic [15], and was declared as a global pandemic by the World Health Organization on the 11th March 2020 [16]. As of the 26th July, 15,200,000 COVID-19 cases were reported worldwide, and 650,000 deaths [4]. In France, up to that same day, 180,000 cases were reported, including 30,170 deaths [6].

2.1. Mortality rate

Estimation regarding the mortality rate of Covid-19 has varied during the first months of 2020, partly because a large, easily underestimated proportion of cases are asymptomatic. Reported mortality rates are still very heterogeneous depending on countries, and on the total amount of tests performed. Italy reported a case fatality rate between 1.6% and 18.3% (for Lombardy) [17]. In South Korea, as of 8th March 2020, the crude fatality rate was estimated around 0.4% for females, 1.1% for males, and 6% for people aged 80 and above [18]. The largest published cohort, from the Chinese Center for Disease Control and Prevention (72,314 cases), and issued early in the course of the pandemic (13th March), estimated a 2.3% case fatality rate, and a 14.8% fatality rate for patients aged 80 and above [19]; however, this series probably did not take asymptomatic cases into account sufficiently. Data from the Diamond Princess, a cruise ship quarantined at sea with 3711 passengers on board and 10 initial cases, is more relevant in the estimation of COVID-19 outcome. Indeed, PCR tests were performed in 3069 subjects, allowing 619 cases to be identified (17% of the ship passengers); 318 (51%) were asymptomatic, and 301 (49%) were symptomatic. The corrected infection fatality rate was estimated at 1.3% [0.38-3.6] for the whole population, and 6.4% [2.6-13] for passengers aged 70 or more [20].

The mortality rate in critically ill patients with SARS-CoV-2 infection was up to 62% at 28 days in a Chinese cohort [21].

2.2. Reproductive rate

A study estimated the R_t in the city of Wuhan, China, between the 1st January 2020 and the 8th March 2020 [22], during five successive time periods (corresponding to different public health interventions). R_t peaked at 3.82 on the 24th January 2020 (with no major public health intervention), and subsequently declined, to below 1.0 on the 6th February 2020 (after one week of city lockdown, traffic suspension, and home quarantine) and was below 0.3 on the 1st March 2020 (after 15 days of quarantine) [22]. In South Korea, reproduction number R_t was estimated at 1.5 (95% confidence interval (CI) 1.4-1.6) [18]. In France, Flaxman et al. estimated R_t before lockdown between 4-5.1 (95%CI), and around 0.5 during lockdown [23].

3. Virus replicative cycle

The virus penetrates the organism through the respiratory tract, conveyed by contaminated droplets. While the exact viral progression remains elusive, the virus seems to have a favorable tropism for epithelial cells within the airways, leading to viral replication both in the nasal cavities and in distal bronchioles [24]. The main cell receptor targeted by the viral surface glycoprotein (S) is the surface-bound angiotensin-converter enzyme 2 (ACE2) [8], yet it is still unclear if the virus can benefit from a second receptor to achieve gain cell entry. TMPRSS2 is a cellular serine proteinase whose role has been pointed out to prime SARS-CoV-2 cellular entry [25].

The viral S protein, also known as spike, is responsible for both cell attachment and membrane fusion. It is formed by three dimers of two non-covalently bound domains S1 and S2. Both subunits are synthetized as a protomer resulting from the expression of the S gene. S1 and S2 are efficiently cleaved by a cellular furin [26] thanks to a polybasic motif (PRRA) specific of SARS-CoV-2 [27]. Because of its specificity and key role in viral cycle, the S protein constitutes the main target for vaccine candidates [28].

4. Laboratory confirmation test

Diagnosis of COVID-19 requires laboratory confirmation, usually performed by detection of viral RNA by a reverse-transcription polymerase chain reaction (RT-PCR). While the first laboratory confirmed cases in Wuhan early in January 2020 relied on deep sequencing techniques [29], highly scalable assays have since been developed after the viral sequence was published. The first RT-PCR protocol was published by Drosten and colleagues [30] from Charité University in Berlin, and since then adopted by the WHO. This approach relies on the amplification and detection of the following sequences among the SARS-CoV-2 genetic sequence: the E gene encoding the envelope protein is used as a screening assay targeting all members of the *betacoronavirus* genera, and both the RdRp gene or the N gene are used as confirmatory assays due to their specific sequence in the SARS-CoV-2 species. This protocol has been widely adopted in commercially available test kits and is now used in most facilities. The Paris *Institut Pasteur* has developed its own assay [31], based on the detection of two sequences in the RdRp gene spanning nucleotides 12621-12727 and 14010-14116. This protocol has been widely used in French laboratories to manage early COVID-19 suspicions and cases [32].

Such assays can be performed on several samples, and the choice of sampling site has been a debated issue considering the consequences of false negative results. Nasal swabs, oropharyngeal swabs, saliva, sputum and bronchoalveolar lavage fluid (BAL) were mostly reported. Nasal swabs have proven to be effective and provided adequate sensitivity (80%) [33,34], if performed properly. Oropharyngeal swabs tend to be less sensitive (32%) [35]. Saliva collection has been proposed as a viable alternative yielding higher sensitivity (91.7%) [36], also addressing the availability of swabs issue as worldwide demand surge and laboratories face shortages in stocks. Sputum samples, while being more sensitive than upper respiratory tract samples (95.7%) [37,38], raise security concerns for the safety of healthcare workers regarding the droplet dissemination nature of the COVID-19. BAL and other lower respiratory tract samples are widely used in intensive care units and yield very good results (93% sensitivity) [35]. The viral load seemed higher in early stages of the disease [39], with symptomatic patients exhibiting higher viral titers as assessed by the lower Ct numbers [40].

When analyzed by RT-PCR, stools are frequently positive (41%), and high viral loads have been pointed out in such samples in both asymptomatic and symptomatic patients [41]. No relation has been

established as of today between enteric viral excretion and clinical outcome and disease severity. In children, the average duration of viral RNA shedding in stools are 29 days (± 12 days). The duration of viral shredding seemed to decrease with age [42] and infectivity of stools is low to non-existent. Due to feces positivity, the sampling of wastewater has been proposed to assess viral circulation [43]. Plasmatic detection of SARS-CoV-2 has been reported but only with low viral titers, and mainly in clinically severe cases [44]; bloodstream infectivity has yet to be demonstrated. Urine has remained virus-free except in one study [45].

Most genomic testing in asymptomatic patients [46] returned negative after 2-3 weeks, with exceptional long shedding up to 45 days after symptom onset [47,48], raising the question of the infectivity of such viral shedding. Excretion of infectious virions is thought to span two days before onset of symptoms up to 8 days after onset [49], viral excretion peaking at day 4 post-infection [50], supporting the effectiveness of a 14-day quarantine period for case isolation. However, results do not fully correlate with infectivity: viral culture from clinical samples is usually infeasible after 8 days after onset of symptoms [51]. Nucleic acid testing (NAT) is key to patient management and surveillance of disease propagation.

5. Clinical presentation

5.1. Clinical timeline

According to several works, incubation period has been estimated between a mean of 4.8 and 6.4 days [52–55]. Lauer et al. estimated that symptom onset will occur within 11.5 days for 97.5% of patients, and that a 14 days quarantine would be sufficient [53]. A large work from Zhou et al. described clinical timeline for an 813 patient cohort [56]. The mean time from illness onset to intensive care unit (ICU) admission was 9-12 days [21,56]; it was 7 days (4-9) to dyspnea [56], 11-12.5 days to hospital admission [56,57], 9 days (7-13) to sepsis, 12 days (8-15) to respiratory failure, and 21-44 days to death, depending on studies [56,58]. Time between onset of symptoms and dyspnea is 5-7 days, to ARDS 8-12 days [56,59].

5.2. Clinical features

One initially described symptom was fever; however, up to 60% of patients were described as non-febrile, and up to 52% of patients admitted in ICU were non-febrile [52]. Coughing was reported in 60-82% of cases, asthenia in 38-70% of cases, myalgia in 11-44% of cases, dyspnea/shortness of breath in 19-55% of cases, and diarrhea in 2-10% of cases [55,59–61]. No symptoms are specific of COVID-19, but surprisingly, anosmia and ageusia appeared to be strongly linked with COVID-19 infection. Mechanism for these symptoms is still to be unveiled, as well as for digestive forms in elderly patients presenting with only diarrhea.

5.2.1. Asymptomatic presentation

A study described imaging data among 37 asymptomatic patients [48]. Chest CT evidenced in 11 of them (30%) focal ground glass opacities, and in 10/37 (27%) stripe shadows and/or diffuse consolidation; 16/37 (43%) had a normal CT scan. In a 63 asymptomatic Chinese cohort, 29/63 patients had abnormal CT scans; few patients (13%) had comorbidities [62].

5.2.2. Pneumonia

The most frequent presentation of hospitalized COVID-19 is pneumonia (91-100%) with dyspnea and a rarely productive cough [52,55,56,59,61]. In case of patients diagnosed with clinical pneumonia, chest X-ray and CT-scanner found bilateral ground-glass opacity in 25-100% of cases [56,59]. When considering all hospitalized COVID-19 patients, CT scans evidenced ground-glass opacities in 56-71% of patients and consolidation in 59% of patients [52,56]. Pulmonary injury was bilateral in 52-75% of patients [52,56].

5.2.3. Thromboembolic complications

Several works have described the high incidence in COVID-19 patients of both venous and arterial thromboembolic diseases. In Klok's study of 184 patients with proven COVID-19 pneumonia admitted to the ICU in the Netherlands, and who all received at least standard dose thromboprophylaxis, the incidence of thrombotic complication was 31% (95%CI 20-41%) [63]. In an Italian study of 362 cases (in ICU and on general wards), 28 presented a thromboembolic event (7.7%). The authors estimated that those events were highly underestimated due to the low number of specific imaging tests performed [64]. Known risk factors for thromboembolic events that are reported in COVID-19 are excessive inflammation and immobilization [65]. However, in a large multicenter international work published by Freund et al. among 3253 patients who underwent a computed tomography pulmonary angiogram for a suspected pulmonary embolism, a positive COVID-19 status was not associated with pulmonary embolism in multivariate analysis ($P = 0.40$) [66].

5.2.4. Cardiac injuries

Cardiac injuries have been described in COVID-19 patients. Viruses are a common cause of myocarditis [67]; myocardial injury can be related to direct cell injury caused by the virus, to T lymphocyte mediated cytotoxicity, to hemodynamic damage induced by hypoxia or shock, or related to cytokine storm [67]. Arrhythmia has been described as a cause of transfer in ICU in 44% of COVID-19 patients [59]; in an COVID-19 acute setting, it can result from direct cardiomyocyte injury, to an infection of the pericardium causing massive edema, or to an ischemia due to microcirculation lesions [68]. In a 416 cohort of patients in Wuhan, China, 82 patients with elevated levels of cardiac troponin had a higher risk of hospital death [69].

5.2.5. Neurological manifestations

Several neurological manifestations of COVID-19 have been reported. Manifestations are very diverse:

- olfactory dysfunction: Generally, post-viral olfactory loss account for 11% of acute olfactory dysfunction [70,71]. Several studies reported olfactory dysfunction among COVID-19 patients (5-86%) [72–74]. This may be related to a localized olfactory cleft edema (local inflammation), or a direct neuroinvasion of the olfactory nerve [70,73]. The loss of flavor perception is also frequently reported; it is considered to be mainly due to a loss of retronasal olfaction rather than a loss of sense of taste itself [70];
- central nervous system manifestations: confusion [72,75,76], acute cognitive disorder, acute myelitis, encephalopathy, encephalitis [77], intracranial hemorrhage, strokes [72,75,76], seizures;
- peripheral nervous system manifestations: Guillain-Barré syndrome [78–81], skeletal muscle damage (hyperCKemia, rhabdomyolysis, myopathy [72,76]), dysautonomia);
- neuropsychiatric symptoms [82]: anxiety, depression, insomnia, and psychosis.

Suggested mechanisms are the hypoxic brain injury on severe pneumonia with peripheral vasodilatation, hypoxia, hypercapnia, and anaerobic metabolism, immune mediated injury related to the cytokine storm, and SARS-CoV-2 direct neurovirulence, since it has already been described for other coronaviruses [76,83].

5.2.6. Severe presentation

Prevalence of reported comorbidities among patients with COVID-19 has largely varied according to countries. The largest published cohorts are among Chinese and American patients, and main comorbidities are hypertension (17-57%) [19,84,85], obesity (42%) [84], diabetes (8-34%) [84], and cardiovascular disease (4%) [19,85]. Being a man was described as the main risk factor for COVID-19 [61,85].

Most ICU admissions were related with a respiratory failure (54-86%) [56,86,87], that is also the leading cause of mortality (93-100%) [56,87]. Patients with respiratory failure are described to present an acute respiratory distress syndrome (ARDS), defined as a respiratory failure not fully explained by cardiac failure or fluid overload, bilateral opacities in chest imaging, and oxygenation $PaO_2/FiO_2 < 300$ mmHg [88].

Report from critically-ill-patients series suggested that those patients presented a "cytokine storm". Biological data showed a higher level of IL-6 in critically-ill and non-surviving patients, a higher level of CRP and a higher level of ferritin [56,59,86,89]. Among severe patients, the lymphocytes count was lower than mid patients or healthy controls (respectively 1132 μmol/L, 1256 μmol/L, and 2215 μmol/L). CD4+ and CD8+ lymphocytes were also lower in the severe-patients group [89].

Necropsy of patients who died from COVID-19 allowed histological analysis of lung tissue samples. Reported patients spent between 1 and 23 days in ICU before death. Macroscopic examination found lungs which were heavy, congested and edematous with patchy involvement. Histological examination found features corresponding to the exudative and early or intermediate proliferative phases of diffuse alveolar damage (capillary congestion, interstitial and intra-alveolar edema, dilated alveolar ducts, collapsed alveoli and loss of pneumocytes). Authors also reported interstitial pneumonia (inflammatory lymphomonocytic infiltrate along the slightly thickened interalveolar septa), organizing pneumonia, and acute fibrinous organizing pneumonia [90].

5.2.7. COVID-19 in children

A review article on children presenting COVID-19 was published by Cui et al. reporting clinical, biological and imaging features on 2.597 children [91]. Among all cases 7.6% were asymptomatic, 45.5% were mild, 41.5% were moderate, 4.4% were severe, 0.9% were critical, and 0.1% (3) led to death. Regarding clinical characteristics, authors collected data from 23 articles (452 children): 43% presented with fever, 43% with cough, 20% with sore throat, 17% with tachycardia, 16% with rhinorrhea, 15% with nasal congestion, and 13% with shortness of breath. Among 23 critical cases, six had an underlying disease. Pulmonary imaging in 294 cases reported 30% of ground glass opacities, 20% of local patchy shadow, 15% of bilateral patchy shadow, and 1% of interstitial lesions. In an international study among 582 children presenting COVID-19 infection, reported risk factors for admission to ICU or requiring mechanical ventilation were being less than 1-month-old ($P < 0.001$) and having an underlying disease ($P < 0.001$) [92].

Observations described a higher risk of Kawasaki-like inflammatory syndrome in children infected by SARS-CoV-2, also called by WHO the COVID-19 associated pediatric multisystem inflammatory syndrome [93]; e.g., a 497% increase of children admitted for a Kawasaki-like syndrome during COVID-19 epidemic was described in a small French cohort [94]; IgG antibodies against SARS-CoV-2 infection were detected among 19/21 of children presenting with a Kawasaki-like syndrome during the epidemic in another French cohort [95]. Kawasaki disease is described as an acute febrile systemic vasculitis that affects medium and small-sized blood vessels. One suspected mechanism is a post-viral immunological reaction to several viruses (influenza [96], enterovirus [97], adenovirus [98], parvovirus [99], VZV [100], EBV [100], measles [101], or Dengue [102]).

6. Serology

Upon infection, humoral antiviral immunity is triggered, owing to the development of specific antibodies. A vast majority of infected patients will generate anti-SARS-CoV-2 antibodies [103]. Antibody titers peak around day 30 post-infection [104], but from this point forward only decrease. IgM and IgG kinetics do not differ significantly [105], thus making differential isolation of these markers void. Seroconversion is witnessed at a median of 14 days after symptom onset [106]. High antibody titers are associated with severe respiratory symptoms, asymptomatic patients having lower titers [105]. This raises the so far unresolved question of COVID-19 immune mechanisms and protection. It is not clear whether high antibody titers could promote severe clinical presentations by a mechanism similar to antibody dependent enhancement [107,108]. On the other hand, pauci-symptomatic forms of COVID-19 could trigger a reduced humoral response only that could correlate with a shortened duration of protection [109].

Anti-SARS-CoV-2 antibodies are directed towards both the spike (S) protein and the nucleocapsid (NP) [110]. Neutralising antibodies are observed in most patients and recognise specifically the spike (S) protein [111]. Neutralising activity appears to be correlated with the presence of antibodies binding the receptor-binding domain (RBD) in its closed conformation within the spike protein [112], and the detection of such antibodies could be a surrogate marker of protection. No cross-reactivity with other human coronavirus (HCoV-OC43, HCoV-NL63, HCoV-229E and HCoV-HKU1) has been evidenced to date (ref). However, cross-reactivity with SARS-CoV-1 has been shown at least *in vitro* [26].

While serological assays allow large epidemiological studies and enable better evaluations of epidemic parameters (R_t, for instance), individual benefit is scarce, if existent. Accordingly, we believe patient management should focus on molecular based assays.

7. Therapeutics

To date, no anti-viral therapy has proven its efficacy and the current management of COVID-19 remains supportive care and ventilatory support when needed.

7.1. Anti-viral drugs

7.1.1. Remdesivir

Remdesivir (GS-5734) is a nucleotide analog that targets viral RNA polymerases. It has an established *in vitro* (culture cells) and *in vivo* (mouse and primate models) efficiency on multiple genetically distinct coronaviruses, and on Ebola virus [113,114]. Its *in vitro* effect on SARS-CoV-2 has been reported in Wang et al.'s work, with a high 90% effective concentration value against infection of Vero E6 cells [115]. Williamson explored remdesivir's efficiency in 12 rhesus macaques infected with SARS-CoV-2 infection [116]. One over six macaques in the remdesivir group developed a respiratory disease vs. 6/6 in the control group. After euthanasia and lung analysis, no virus was detected in lung tissue samples in the remdesivir group; remdesivir was detected in all six lungs of the treated animals. Only 3/36 lobe lungs in the control group were virus-free. There was no difference in viral load in BAL between both groups.

Gilead restricted access to remdesivir since the beginning of COVID-19 pandemic to compassionate use and to clinical trials [117]. The first clinical study on remdesivir was published by Grein et al. on 53 patients, without any control group. Treatment was started 12 days after symptom onset; 68% of treated patients

showed an improvement regarding oxygen support, and 13% of patients who completed treatment died [118]. A large international clinical trial compared 541 patients receiving remdesivir with 522 patients treated with placebo. A shorter time to recovery (11 days vs. 15 days) was reported in the remdesivir group ($P < 0.001$). Adverse events were reported (21% in the remdesivir group and 27% in the placebo group [119]). Goldman et al. compared 5 vs. 10 days of remdesivir treatment in a multicentric, international clinical trial among 397 patients and did not observe any difference between the 2 groups at 14 days after treatment onset on primary outcome (clinical efficacy on a 7-points scale) [120].

7.1.2. Lopinavir/Ritonavir (LPV/RTV)

Lopinavir is an antiviral agent developed to target HIV protease; it is generally used in association with ritonavir, a pharmacokinetic "booster" increasing lopinavir plasma concentration. It is widely used in adults living with HIV/AIDS [121]. LPV/RTV is regarded as a potential anti-SARS-Cov-2 agent since several trials on SARS-CoV-1 showed a favorable effect. Indeed, in a 2003 study of 1,521 patients with SARS, Chan et al. reported a 2% death rate in the LPV/RTV group vs. 16% in the SoC group ($P < 0.05$) if LPV/RTV was used as initial treatment, but with no difference as a rescue treatment [122]. In a 2004 study exploring the efficacy of LPV/RTV in patients with SARS regarding a composite primary outcome (severe hypoxemia or death at day 21), Chu et al. observed that 2% in the LPV/RTV group met the primary outcome, vs. 29% in a historic control group ($P < 0.001$) [123]. The first large clinical trial published on LPV/RTV on SARS-CoV-2 compared 99 patients receiving the antiviral vs. 100 receiving SoC alone [124]; there was no difference between the 2 groups regarding the primary end point (time to improvement) (15 vs. 16 days, $P = 0.09$). Noteworthily, the median time between symptom onset and treatment was 13 days. 48% of patients in the LPV/RTV group vs. 50% in the SoC group who underwent an adverse event.

7.2. Hydroxychloroquine

Hydroxychloroquine (HCQ) is a widely used molecule in limited forms of lupus, with a low price, and it has an established clinical safety profile [125] In vitro studies showed the effect of chloroquine [115] and HCQ in inhibiting SARS-CoV2 infection [126]. *In vitro* activity of HCQ and chloroquine against SARS-Cov-2 were not different in Liu et al.'s work [126], and HCQ was found, in vitro, to reach three times the potent antiviral activity of chloroquine in Yao et al.'s work [127]. Noteworthily, HCQ was four times less toxic than chloroquine in animal study [128]. However, a recent *in vitro* study showed that chloroquine did not block SARS-CoV-2 infection of the TMPRSS2-positive lung cell [129]. Another *in vitro* study also found that HCQ did not show any antiviral activity in a model of reconstituted human airway epithelium [130]. Due to such *in vitro* results, several trials assessed the efficiency of HCQ on viral load in respiratory samples (without clinical considerations [131–133]). Tang et al. did not observed any difference in 150 patients treated with HCQ or with only standard of care (SoC) (negativity of PCR at 28 days of 85% vs. 81%) [131]. However, two other studies reported a significant difference between patients receiving HCQ and the others: Gautret et al. reported 70% of negative PCR at day 6 of HCQ treatment vs. 12.5% ($P = 0.001$) (42 patients) [132], but the design of this study have been widely criticized after its publication, and it is generally regarded as inconclusive; and Huang et al. reported that viral extraction was negative 5.4 days earlier ($P < 0.001$) in the HCQ group (197 patients) [133]. To date, only one HCQ published trial used a clinical outcome on 1446 patients [134]. The authors used a composite outcome (intubation or death); there was no difference between the HCQ group and the control group (HR 1.04 95%CI [0.82-1.32]).

Several trials have assessed toxicity of HCQ in Covid-19 patients or in association with azithromycin (which some experts had recommended applying). Tang et al. (150 patients) observed 30% of adverse events in the HCQ vs. 9% in the SoC group [131]. Nguyen et al. studied cardiac toxicity in patients receiving HCQ and/or azithromycin in all patients in their database since 1967 [135]. Association of HCQ and azithromycin was associated with a higher risk of ventricular tachycardia and prolonged QT. HCQ alone was responsible for more conduction disorder. However, in patients receiving azithromycin alone compared with HCQ alone, there was more prolonged QT and ventricular tachycardia.

A French group studied HCQ plasma peak in Covid-19 patients in ICU after a 400 mg administration; HCQ concentration was around 0.5 mg/L (0.28-0.62) (efficient drug concentration > 0.1 mg/L [136]). In this study, patients with an acute kidney injury received only 200 mg of HCQ daily, and their plasma peak was 0.22 mg/L (0.2-0.24). Median time to obtain concentration of 1 mg/L was 4 days (3-7). Toxic levels (> 1 mg/L [136]) were reached after 5 days of treatment. The concentration of HCQ remained unchanged before and after hemodialysis [137].

Moreover, several observations reported the onset of severe COVID-19 in patients who were already receiving HCQ as a long-term treatment for an inflammatory disease [138].

One randomized trial evaluated the outcome of HCQ whether or not in association with azithromycine on mild to moderate COVID-19 [139]. No difference was found on clinical status at 15 days among 504 patients between the standard of care group, the HCQ group (effect estimate [95%CI] 1.21 [0.69-2.11]), and the HCQ and azithromycin group (0.99 [0.57-1.73]).

7.3. Corticosteroids

Due to the cytokine storm phase, discussion around the use of corticosteroid emerged early during the pandemic. On the one hand, corticosteroids could reduce tissue edema and decrease exudate at the site of inflammation, but on the other, they may favor secondary infections, long-term complications and slow down the virus clearance. A letter from Liu et al. reported the use of methylprednisolone in 15 severe or critical patients. They observed an improved oxygenation and no death in the group of patients treated with methylprednisolone. However, no difference was found with the no-corticosteroid group during the early convalescence phase [140]. Fadel et al. reported the results of early use of corticosteroid among 132 patients (vs. 82 patients in the control group). The composite primary endpoint (escalation in ICU, mechanical ventilation or death) was reached by 35% of patients in the early corticosteroid group vs. 54% in the control group ($P = 0.005$) [141]. RECOVERY was a randomized, controlled trial of the use of 6 mg of dexamethasone vs. SoC in hospitalized patients with COVID-19. At 28 days, 454/2104 (21.6%) patients had died in the dexamethasone group vs. 1065/4321 (24.6%) in the SoC group ($P < 0.001$) [142].

7.4. Anti-interleukin (IL) drugs

Tocilizumab is a monoclonal antibody against IL-6 receptor. It is mainly prescribed in rheumatoid arthritis. An Italian team reported the use of tocilizumab to the first 100 patients presenting to the Brescia University hospital with a COVID-19 ARDS requiring ventilatory support. At 72 h, 58% of patients showed an improvement, and at 10 days after treatment inset, 77% of patients had improved and/or stabilized [143].

Anakinra is an antagonist of IL-1 receptor. An Italian team reported the use of anakinra in 29 patients with moderate to severe COVID-19 ARDS before mechanical ventilation,

compared with 16 patients not receiving anakinra. Survival rate at 21 days was 90% in the anakinra group vs. 56% in the control group ($P = 0.009$). However, there was no difference regarding the mechanical ventilation-free survival (72% in the anakinra group vs. 50% in the control group, $P = 0.150$) [144].

7.5. Convalescent plasma therapy

A Chinese team reported the use in 51 COVID-19 patients of convalescent plasma compared with a control group of 50 patients. Their primary endpoint was clinical improvement within a 28 day-period (reduction of 2 points on a 6-points disease severity scale). There was no difference between both groups ($P = 0.260$). In subgroup analysis among patients presenting a severe disease, 91% of patients met the primary endpoint in the plasma therapy group vs. 68% in the control group ($P = 0.003$) [145]. In another study, the outcomes of 1430 severe or critical patients treated with SoC and 138 patients treated with convalescent plasma therapy were compared; 2.2% of patients died in the plasma group vs. 4.1% in the SoC group (no comparison). 2.4% of patients were admitted to ICU in the plasma group vs. 5.1% in the SoC group ($P = 0.2$) [146].

7.6. ACE inhibitor and angiotensin 2 receptor blocker (ARB)

The effect of ACE inhibitor and ARB treatment on COVID-19 severity and/or mortality has been reported in several studies but seems variable. In Zhang et al.'s work, on 1128 patients with hypertension and COVID-19, multivariate analysis found a lower all-cause mortality in the ACE inhibitor/ARB group, than in the other group ($P = 0.03$) [147]. However, Li et al. did not found any difference in COVID-19 severity ($P = 0.645$) or mortality ($P = 0.340$) among 362 patients admitted for hypertension and COVID-19 [148].

7.7. Non-pharmaceutical interventions

In Chu et al.'s meta-analysis, social distancing was considered as efficient with a −10.2% risk difference (95%CI [−11.5 to −7.5%] of infection in short distance vs. further distance [149]. Wearing respirators or face masks was associated with a large reduction in risk of infection (risk difference −14.3%, 95%CI [−15.9 to −10.7%]) [149]. Eye protection also seemed efficient in infection reduction with a risk difference of −10.6% 95%CI [−12.5 to 7.7%] [149]. However, lockdown had the larger impact on transmission with an 81% [75%-87%] reduction [23].

8. Conclusion

In France, the number of daily cases of COVID-19 was growing by the end of summer 2020, suggesting the debut of a second epidemic wave, as many other countries are facing. The first wave allowed us to develop and strengthen our laboratory tests. Since then, French health authorities have implemented a systematic contact tracing (CONTACT-COVID) around each patient presenting a positive SARS-CoV-2 RT-PCR. This highlighted the high number of asymptomatic and mild cases, and made French people massively adapt their daily habits with a systematic face mask protection in all public areas, and restrictions in social events. However, none of the evaluated pharmacological treatments have showna clear efficacy on SARS-CoV-2. One of the main limitations seem to be the long period between symptom onset and initiation of treatment. An effective vaccine against SARS-CoV-2 appears to be the only way to end this pandemic. At the end of August 2020, 203 trials were registered on Clinicaltrial for a vaccine against COVID-19, thus raising hope to end this pandemic in a reasonable amount of time.

Funding

This work was carried out as part of our routine work.

Authors' contributions

MLM and BN drafted the manuscript. All authors read and approved the final manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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