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SARS-CoV-2 *vs.* SARS-CoV-1 management: antibiotics and inflammasome modulators potential

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Abstract. **The coronavirus SARS-CoV-2 at the origin of COVID-19 shares more than 70% genetic similarity with SARS-CoV-1 that was at the origin of 2003 SARS. Infection-associated symptoms are very similar between SARS and COVID-19 diseases and are the same as community-acquired pneumonia symptoms. Antibiotics were empirically given to SARS patients in the early stages of the pathology whereas a different strategy has been decided in the management of COVID-19 pandemic with a worldwide shutdown. The cytokine storm, both identified in SARS and COVID-19 severe cases, is generated through inflammasome activation, which opens therapeutic perspectives to counteract the pathogenic inflammation. As corticoids have numerous side effects that limit their use, focusing on anti-inflammasome agents could represent a safer alternative for patients with severe COVID-19.**

Key Words:
Coronavirus, Inflammation, Antibiotics, Inflammasome, P2X7 receptor, COVID-19.

Introduction

The World Health Organization (WHO) has declared Coronavirus Disease 2019 (COVID-19) as a pandemic on March 11, 2020[1]. This pandemic began in mainland China, like SARS pandemic in 2003. However, on June 18, 2020, the rate of increase in cases became greater in the rest of the world than inside China with a total of 8 242,999 confirmed cases[2]. The Coronavirus SARS-CoV-2 at the origin of COVID-19 shares more than 70% genetic similarity with SARS-CoV-1 that was at the origin of 2003 SARS[3]. The aim of this paper is to compare 2003 SARS and 2020 COVID-19 pandemics to open new perspectives in COVID-19 treatment. Table I summarizes the general characteristics of both SARS-CoV-1 and SARS-CoV-2.

Despite the similarities between SARS-CoV-1 and SARS-CoV-2, therapeutic care is quite different (Table II).

SARS-CoV-1: 2003 SARS Pandemic

Since the etiological agent of SARS was unknown during the initial phase of the epidemic, patients were given empirical antibiotics for the treatment of community-acquired pneumonia according to the American Thoracic Society guidelines, with coverage of both typical and atypical bacterial pathogens[37-39]. Macrolides, such as erythromycin, clarithromycin, and azithromycin, not only have anti-bacterial activity but also have immunomodulatory effects, including anti-inflammatory effects. Broad-spectrum antibiotics were also indicated in SARS-patients who developed nosocomial bacteremia, catheter-related sepsis, and nosocomial pneumonia[40,41]. In the meantime, a study[23] reported in 2004 a cohort of 132 hospitalized SARS patients who did not respond to antibiotics; antibiotics had therefore to be given in the early stage of the infection to be efficient. Later, three pathogenic stages of SARS were identified: viral replication, inflammatory pneumonitis and residual pulmonary fibrosis[22]. Antiviral therapy was first considered during the viral replication phase, but as there were no known effective antiviral agents for SARS, immunomodulation therapy was considered. Corticosteroids, including methylprednisolone to counteract the cytokine storm and the use of broad-spectrum antibiotics to cover secondary bacterial infection were the key treatment regimen[22]. In around 30% of the cases, patients developed an atypical form of pneumonia with acute respiratory distress, characterized by interferon-γ-related cytokine storm[42] and inflammasome activation[43]. Inflammasomes are multiprotein complexes that activate

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Table I. General characteristics of the two viruses.

	SARS-CoV-1	SARS-CoV-2
Country where the virus emerged	China Transmission from animal to human	China Transmission from animal to human
Number of countries affected with more than 100 persons	3 (China, Canada, Singapore)[4]	>160[5]
Infection-associated symptoms	• Not very specific, mainly influenza-like: fever, fatigue/tiredness, malaise, myalgia, headache, diarrhea and shivering, and after about a week cough, shortness of breath[6] • Evolution for severe conditions: adult respiratory distress syndrome[6] • Asymptomatic patients: conflicting reports[7-12]	• Not very specific: headache, muscle pain, fatigue/tiredness then fever and respiratory signs 2 or 3 days later • Other symptoms: sudden loss of taste and/or smell, disorientation in elderly people • Evolution for severe conditions: chest pains and respiratory discomfort, pneumonia affecting both lungs and adult respiratory distress syndrome • Asymptomatic patients (current estimates as of now): 12 to 45 %[13-17]
Host cell receptor for virus entry	ACE2[18]	ACE2[19]
Case Fatality Rate	15 % (800 deaths)[20]	7 % (to date > 220 000 deaths)*
Genome	29 kilobases in length	29 kilobases in length
Tissue manifestations after infection	Cytokine storm	Cytokine storm

*The case fatality rate is extremely hard to estimate since between 18 to 23% of patients infected with SARS-CoV-2 are asymptomatic[21].

caspase-1, which generates the key inflammatory cytokine IL-1β from pro-IL-1β through proteolytic cleavage. It was demonstrated that SARS-CoV-1 itself was able to activate inflammasome[43]. It is also well known that bacteria can activate inflammasomes mainly upon TLR4 binding[44], aggravating SARS-CoV-1-induced cytokine storm in case of secondary bacterial infection. In patients infected by SARS-CoV-1, the presence of diabetes or other comorbid conditions including chronic heart failure, kidney disorders, breast cancer, Parkinson, osteoporosis and HIV-1 infection increased the risk of medical conditions with further morbidity and mortality[45].

SARS-CoV-2: 2020 COVID-19 Pandemic

At present, no drug has been proven to be safe and effective for treating COVID-19. Back in 2003, the WHO expert panel on SARS treatment requested a systematic review and comprehensive summa-

Table II. Therapeutic cares in 2003 and 2020 pandemics.

2003 SARS PANDEMIC	2020 COVID-19 PANDEMIC
First stages of infection: - Antibiotherapy prescribed by general practitioners (mainly before SARS diagnosis): macrolides, 3rd generation cephalosporins, and antipneumococcal quinolone[22,23] - Mask use - Antiviral drugs: ribavirin, lopinavir[24]	**First stages of infection**: - Stay at home/quarantine - Antipyretic medication: paracetamol[27,28]
Second stage: intensive care unit - Supplemental oxygen to provide respiratory support - Mechanical ventilation - Corticoids in China and Hong Kong (mainly methylprednisolone and prednisolone)[23,25,26] - Convalescent plasma[24]	**Second stage**: intensive care unit - Supplemental oxygen to provide respiratory support - Mechanical ventilation **Main international recruiting clinical trials:** - Antimalarial agents: hydroxychloroquine[29,30] - Macrolide antibacterial drug: azithromycin[31] - Antiviral drugs: remdesivir[32,33], lopinavir/ritonavir[34,35] - Convalescent plasma[36]

ry of treatments used for SARS-infected patients. The aim of this review was to guide future treatment and identify priorities for research. Unfortunately, none of the research on SARS was likely to be useful in helping to decide on the best treatments to use in such an outbreak[24]. Recommended clinical management of patients with COVID-19 includes prevention of health care workers infection and control measures and supportive care, like supplemental oxygen and mechanical ventilatory support[46]. Interestingly, it seems that antibiotics have been left aside by general practitioners in suspected COVID-19 patients, despite the well-established fact that respiratory viral infections predispose patients to co-infections. Co-infections increase disease severity and mortality; that's why worldwide therapeutic guidelines recommend the use of antibiotics to treat community-acquired pneumonia when the origin of the pneumonia is not clear[39,47-49]. A retrospective, multicenter cohort study[23] including a total of 191 patients reported in March 2020 that 50% of patients with COVID-19 who have died had secondary bacterial infections. Overuse and misuse of antibiotics since decades may explain the tendency of general practitioners to avoid antibiotics prescription in case of viral infections.

Accumulating evidence revealed that a part of severe COVID-19 patients have an elevated cytokine profile resembling cytokine storm in SARS outbreak in 2003[51]. Tay et al[52] reviewed the chronology of events during SARS-CoV-2 infection. When SARS-CoV-2 infects cells expressing the surface receptors ACE2, the active replication and release of the virus cause the host cell to undergo pyroptosis and release damage associated molecular patterns, including ATP. These are recognized by neighboring cells, triggering the generation of proinflammatory mediators that attract immune cells to the site of infection, promoting further inflammation and establishing a proinflammatory feedback loop. In a defective immune response, this may lead to further accumulation of immune cells in the lungs, causing overproduction of proinflammatory cytokines, which eventually damages the lung infrastructure. The resulting cytokine storm circulates to other organs, leading to multiorgan damage. Anti-inflammatory strategies have been considered in COVID-19 treatment. These strategies include rheumatoid arthritis medications like Janus Kinase Inhibitors (JAK inhibitors), IL-6, IL-1 and TNF-α inhibitors, but also medications used to treat infectious diseases like Intravenous immunoglobulin (IVIG), immunomodulatory agents like colchicine and antimalarial agents, mainly chloroquine and hydroxychloroquine[53]. Those treatments present some disadvantages as they may impair anti-viral immunity and be hepatotoxic[54,55]. Plus, on 17 June 2020, WHO announced that the hydroxychloroquine arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped due to the absence of significant effect on hospitalized COVID-19 patients[56].

Diseases such as hypertension, diabetes mellitus, respiratory system disease, cardiovascular disease, and their susceptibility conditions, may be linked to the pathogenesis of COVID-19[57]. Underlying mechanisms remain to be elucidated but several hypotheses are raised. Diseases with increased ACE2 expression like diabetes or ACE2-stimulating drugs prescribed to treat hypertension could facilitate infection with SARS-CoV-2 and increase the risk of developing severe and fatal COVID-19[58]. P2X7 receptor mediates inflammasome activation in diabetes[59], pulmonary hypertension[60] and cardiovascular diseases[61]. P2X7 receptor may consequently be involved in the pro-inflammatory cytokine generation and secretion in COVID-19[62]. As in SARS, secondary bacterial infection would aggravate SARS-CoV-2-induced cytokine storm.

Inflammasome activation has both proviral and antiviral roles; it may generally contribute to innate antiviral response, but defective immune response or comorbidities can lead to inflammasome dysregulation and subsequent cytokine storm and pathogenic inflammation. Rosli et al[63] recently observed that P2X7 receptor inhibitors dampen mouse pulmonary hyperinflammation following severe influenza virus infection. They concluded that targeting NLPR3-mediated inflammation may reduce pulmonary inflammation associated with severe influenza A virus infection. Similar laboratory studies could be conducted in the actual COVID-19 context to identify new anti-inflammatory strategies since corticosteroids have been associated with increase in adverse outcomes in patients infected with SARS-CoV-1, MERS-CoV and SARS-CoV-2[64,65].

Conclusions

The management of the SARS and COVID-19 pandemics has been different so far, regardless similarities between the two viruses. Shutdowns are easing all over the world, and the question regarding COVID-19 therapeutic care still remains.

Several vaccines are under investigation to provide long-term protection. To date, WHO has listed 8 candidate vaccines that are in clinical evaluation and 100 candidate vaccines in preclinical evaluation[66] but it will take months to years to develop a vaccine accessible to the world population – if any is ultimately identified as efficient and safe. Deslandes et al[67] reported an observation of a SARS-CoV-2-infected patient 1 month before the first reported cases in France, that is late December 2019. Back then, European countries were struggling with seasonal influenza and alleged French patient zero was diagnosed with influenza-like illness, with a medical background of type II diabetes mellitus and asthma. He received antibiotic therapy and his clinical evolution was favorable until discharge two days later. Could macrolides be an international first-step strategy to fight COVID-19[68]? Should anti-inflammasome drugs be considered as late stage care option?

Conflict of Interests

The Authors declare that they have no conflict of interests.

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