**Title:** Over 100 questions and answers on COVID-19 and allergy

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**Abbreviations:**  **ACE2,** angiotensin-converting enzyme 2**;** **AIT**, allergen immunotherapy; **ARDS,** acute respiratory distress syndrome; **BCG**, Bacillus Calmette‐Guerin; **BSL,** biosafety level; **COVID-19,** coronavirus disease 2019; **CP,** convalescent plasma; **CSS**, cytokine storm syndrome; **FDA**, Food and Drug Administration U.S.A; **HIV,** human immunodeficiency virus;  **ICU,** intensive care unit; **IFN,** Interferon; **IL,** interleukin; **LPV/r,** Lopinavir-boosted ritonavir**;** **MERS,** Middle East respiratory syndrome**; PPE**, personal protective equipment; **RSV,** respiratory syncytial virus; **RT-PCR**, reverse transcription polymerase chain reaction; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2; **TCZ,** tocilizumab; **Th,** T helper, **TMPRSS2,** transmembrane protease serine 2; **WHO,** World Health Organization;

**Abstract**

In December 2019, China reported the first cases of coronavirus disease 2019 (COVID-19). This disease, caused by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become pandemic. To date it has resulted in over 5 million confirmed cases and caused 320,000 related deaths worldwide. Unequivocally, the COVID-19 pandemic is the greatest crisis of our time. In this context, numerous doubts and questions have flourished in demand of basic scientific information and evidence-based medicine on SARS-CoV-2 and COVID-19. Although the majority of the patients show a very mild a one-week, self-limiting viral respiratory disease, many clinical appearances in severe patients are unique to COVID-19, such as severe lymphopenia and eosinopenia, extensive pneumonia, cytokine storm leading to acute respiratory distress syndrome, endotelitis, coagulopathy and multiorgan failure. The epidemiologic features of the disease are unique and showed changes throughout the pandemics. Vaccine and drug development studies and clinical trials have reached an immense speed which never occurred in the human history. However, clinical research on these topics should be based on more coordinated high-quality studies. Here, we answer pressing questions, formulated by young clinicians and scientists, on SARS-CoV-2, COVID-19 and allergy, which include the following topics: virology, immunology (antibody responses, B and T cells, eosinophils, cytokine storm, trained immunity), diagnosis, management of allergic patients, treatment, clinical trials, drug discovery, vaccine development and epidemiology. Over 100 questions were answered by experts in the field providing a comprehensive and practical overview of COVID-19 and allergic disease. Here, we answer pressing questions, formulated by young clinicians and scientists, on SARS-CoV-2, COVID-19 and allergy, which include the following topics: virology, immunology (antibody responses, B and T cells, eosinophils, cytokine storm, trained immunity), diagnosis, management of allergic patients, treatment, clinical trials, drug discovery and vaccine development and epidemiology. Over 100 questions were answered by experts in the field providing a comprehensive and practical overview of COVID-19 and allergic disease.

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**Main text**

***Introduction***

The first cases of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were reported in China in December 20191 and rapidly became pandemic. Currently, more than 5 million confirmed cases of COVID-19 and 320,000 COVID-19-related deaths have been reported globally (COVID-2019 situation reports). These counts, which are still rising, likely underestimate the cumulative incidence of the COVID-19 due to several factors; these include limitations of current diagnostic tests, the extent of population testing and reporting, and the type and timing of community mitigation strategies adopted by each country, among others.2 COVID-19 shows a complex clinical profile with many different presentations. Like many other viral infections, asymptomatic, mild, moderate or severe cases presented with or without pneumonia are observed. Asymptomatic cases are common but to date there is a lack of epidemiological surveys that provide a clear percentage of asymptomatic cases; 10-20% of patients require hospitalization and 2-4% intensive care.3,4

The COVID-19 pandemic is the world’s greatest public health crisis of the 21st century, and there is an urgent need for reliable and updated scientific information. COVID-19 is now a worldwide spread zoonosis and it will be practically impossible to fully eradicate the SARS-CoV-2 virus. The main question will be to learn how to live together with this virus, as COVID-19 is becoming the number one reason of morbidity and mortality in many countries. The aim of this paper is to provide short answers to pressing questions on epidemiology, virology, immunology, diagnostics, and treatment as well as optimal management of allergic diseases during the COVID-19 pandemic. These answers are provided by a group of expert scientists and physicians in the field and are grouped in 9 sections.

1. ***SARS-CoV-2 virology***

***What is known about the origin of SARS-CoV-2?***

The coronavirus family have caused zoonotic diseases that are called Rhinolophus bat coronavirus HKU2, Middle East respiratory syndrome (MERS) and SARS-CoV. While a direct ancestor of SARS-CoV-2 is not known, it is closely related to β-coronaviruses in bats and pangolins, which are likely its original reservoir. SARS-CoV-2 could have risen by selection in the animal host followed by zoonotic transfer and acquisition of further mutations in humans. It is possible that, during undetected human-to-human transmission, the virus mutated, optimizing spike protein binding to human angiotensin-converting enzyme 2 (ACE2). Importantly, available SARS-CoV-2 genetic data do not evince purposeful human manipulation of the virus.5

***What are the strains of SARS-CoV-2?***

Three SARS-CoV-2 variants have been identified (A, B, and C), which differ in their amino acid sequence. The ancestral type A and the mutated type C are found in significant proportions outside East Asia, mainly in Europe and in the United States. The type B, which has mutated and spread, is the most common strain in East Asia.6 Continuous genome sequencing of virus mutations is needed to monitor the pandemic.

***What are the receptors used by SARS-CoV-2 for cell entry?***

SARS-CoV-2 binds to ACE2 via its spike protein to enter human cells7. Cell entry is facilitated by the host serine protease TMPRSS2 that cleaves spike protein into S1 and S2 fragments, thus enabling cellular membrane fusion (**Figure 1**).8 ACE2 is highly expressed in the lungs, small intestine, kidney and heart, but not in innate and adaptive immune cells.9-12 SARS-CoV-2 also binds to CD147 (known as basigin or extracellular matrix metalloproteinase inducer), which is expressed in human airway and kidney epithelium, as well as in innate cells and lymphocytes13. Receptors reported for other coronavirus, such as CD26, aminopeptidase N and glutamyl aminopeptidase could be utilized by SARS-CoV-2 for cell invasion.12,14,15

***Are there ACE2 polymorphisms that affect COVID-19 severity?***

There is limited evidence about COVID-19-associated polymorphisms. ACE might be one of the candidate genes that influences pneumonia progression in SARS. It is conceivable that the D allele influences the renin–angiotensin system via elevation of serum or local ACE levels, which may damage the endothelium or epithelium of the lungs.16 The variance in COVID-19 prevalence and mortality cannot be only explained by an ACE insertion or deletion polymorphism alone, or one polymorphism of any single gene. However, polymorphisms in genes of toll-like receptors, inflammasome, intracellular molecular sensors, interferons (IFNs)17 and interleukins (ILs) may contribute.

***What are the main SARS-CoV-2 molecules eliciting the immune response?***

Structural proteins of SARS-CoV-2 virions, such as spike glycoprotein, envelope, membrane and nucleocapsid, are the main immunogenic molecules **(Figure 1)**.18,19 SARS-CoV-2 adaptive responses develop mainly to spike protein, and immunodominant T and B cell epitopes have been reported.20 Intracellularly, viral RNA replicase complex, non-structural protein and translated proteins activate innate immune pathways, leading to an IFN type I response, as well as NLRP3 and other inflammasomes pathways.19

***What are the main structural differences of SARS-CoV-1 and -2?***

The spike protein of SARS-CoV-2 has a receptor binding domain that binds ACE2 with higher affinity than SARS-CoV.7 In addition, the SARS-CoV-2 spike protein harbors a polybasic furin cleavage site (PRRAR) with an insertion of 4 amino acid residues, which is distinct from that found in SARS-CoV and other SARS-like viruses. This allows effective cleavage by furin and other proteases and determines viral infectivity and host range.5

***Are there any similarities in the immune response to human immunodeficiency virus (HIV) and SARS-CoV-2?***

The severe lymphopenia observed in COVID-1921 is similar to HIV infection and acquired immune deficiency syndrome. The latter shows a CD4+ T cell lymphopenia, whereas COVID-19 shows a general lymphopenia. However, severe lymphopenia development in COVID-19 happens in weeks, whereas HIV-induced lymphopenia takes years.22 HIV and SARS-CoV-2 are RNA viruses and follow similar replication pathways; hence some RNA replication drugs may work in both diseases.23

***Is it the generation of mutated and more pathogenic strains of SARS-CoV-2 expected?***

There are 2 strains of SARS-CoV-2 that are clinically relevant. Genome analysis of SARS-CoV-2 from human samples shows high rates of mutation and deletion in several viral genes, including the spike-glycoprotein gene.24 COVID-19 treatments, including future vaccination against SARS-CoV-2, may drive genetic evolution of the virus toward more pathogenic variants. For example, a report on a 382-nt deletion in ORF8 of SARS-CoV2 isolated from patients in Singapore implies mutations may arise as result of human adaptation and could be associated with attenuation.25 Nevertheless, the emergence of a SARS-CoV-3 is possible as long as there is contact between humans and living animals that harbor coronaviruses.

***For how long is SARS-CoV-2 detected in oral and respiratory secretions from COVID-19 patients?***

Data from 96 COVID-19 patients in China show SARS-CoV-2 detection in respiratory samples for a median of 18 days (13-29 days). In this study, sputum and saliva were not analyzed separately. Viral shedding was significantly longer in patients with severe disease with a median of 21 days (14-30 days) compared to mild disease, 14 days (10-21 days). Furthermore, glucocorticoids treatment longer than 10 days significantly extended the duration of SARS-CoV-2.26 Viral load differed significantly by sample type, with respiratory samples showing the highest, followed by stool samples, and serum samples showing the lowest.26 Viral load range from 1.34 × 1011 copies per mL to 7.52 × 105 in sputum death and survived people, respectively.27

***What is the relevance of the fecal–oral route in SARS-CoV-2 transmission?***

SARS-CoV-2 infects gastrointestinal ACE2-expressing epithelial cells causing diarrhea in adults and children. It is frequently found in stool samples by reverse transcription polymerase chain reaction (RT-PCR), often 2-4 days earlier than in respiratory samples. Importantly, replicating SARS-CoV-2 has been isolated from stool. The median duration of virus in stool samples (22 days, interquartile range 17-31 days) was significantly longer than in respiratory (18 days, 13-29 days.26 Thus, fecal transmission of SARS-CoV-2 is possible and might contribute to spreading of COVID-19. 28,29

1. ***Immunology of COVID-19***

***2.1 B cell and antibody responses***

***What is the time of seroconversion and duration of IgM and IgG responses against SARS-CoV-2?***

From previous SARS studies, it is known that the median seroconversion time for detectable IgG was 17 days after infection.30 Detectable levels of SARS-specific IgG and neutralizing antibodies persisted for up to 720 days. This suggests that there is antibody-mediated protection from SARS-CoV recurrent infection for up to 2 years.31 There are inconsistent reports on the humoral response to SARS-CoV-2. One study with 285 COVID-19 patients reported that SARS-CoV-2 virus-specific IgG and IgM peaked 17–19 days and 20–22 days after symptom onset, respectively.32 On the other hand, another study of 26 hospitalized COVID-19 patients showed that seroconversion could take up to 50 days.33 These discrepancies may be related to the time of SARS-CoV-2 diagnosis or the clinical characteristics of each cohort and warrant additional studies.

***Are there differences in the SARS-CoV-2 antibody response between asymptomatic and symptomatic patients?***

Preliminary findings indicate that asymptomatic and mild cases of COVID-19 can generate detectable levels of SARS-CoV-2-specific antibodies in serum. However, seroconversion is observed less frequently in asymptomatic compared to mild or severe cases, and many asymptomatic cases yield undetectable SARS-CoV-2-specific antibody responses.32,34-36 So far, no robust data are available on the qualitative differences in humoral responses between asymptomatic and symptomatic COVID-19 patients.

***Children tend to have mild forms of COVID-19, what is known about the specificity and affinity of their SARS-CoV-2 antibody response?***

It is not clear which molecular mechanisms underlie the mild symptoms of COVID-19 in children. Children may mount a SARS-CoV-2 antibody response characterized by a more efficient production of so-called natural antibodies, which arise from activated IgM+ memory B cells.37 These cells, which are more prevalent in children than in adults, presumably produce broadly neutralizing antibodies early during the course of the infection. Young children also frequently carry other respiratory viruses, which probably limit SARS-CoV-2 infection, as reported for other viral infections.38 Differences between children and adults in the regulation of ACE2 expression may also play a role.37 For example, ACE2 mRNA expression was found to be high in type I and II alveolar epithelial cells, in nasal and oral mucosa and nasopharynx, in smooth muscle cells and endothelium of vessels from stomach, small intestine, colon, and additionally in the kidney of human adults (mean age 52±22).39 Furthermore, a recent study demonstrated age-dependent ACE2 gene expression in nasal epithelium, which was lowest in younger children and increased with age.40

***The generation of memory B cells is a key mechanism contributing to long-term immunity. Has the extent and quality of SARS-CoV-2 memory responses been evaluated?***

B cell receptor-sequencing has been conducted in blood of COVID-19 patients. Naive B cells exhibited little clonal expansion, whereas CD27+CD38+ memory B cells showed the highest expansion levels among diverse B cell subsets. COVID-19 patients had significantly expanded specific B-cell receptor clones compared to those in the healthy controls. These findings suggest that B cells had experienced unique clonal variable diversity joining gene rearrangements upon SARS-CoV-2 infection.41 The lifespan and functionality of these B cells remain to be elucidated.

***Is the immunity acquired during the first COVID-19 wave enough for “herd immunity”?***

The term “herd immunity” refers to the generation of population immunity that protects a region, or country, from infection. The number of confirmed COVID-19 cases has reached almost 5 million. The world population is estimated to be 7.8 billion. To determine the extent of herd immunity, it is pivotal to define the prevalence of SARS-CoV-2-exposed humans. It is thought that 60% is the minimum percentage of symptomatic or asymptomatic COVID-19 population required for herd immunity. That is to say that worldwide herd immunity may occur when ⁓5 billion humans have a protective immune response against SARS-CoV-2. To date, there are no reliable data, particularly on the number of asymptomatic individuals that show seroconversion, to determine the level of herd immunity.42

***Given the role of IL-4 in immunoglobulin class-switching and germinal center reactions, could IL-4 axis-targeting treatments cause defective B cells responses against SARS-CoV-2?***

IL-4 is pleiotropic and could theoretically cause negative effects on immune responses. However, based on phase II and III studies with dupilumab in the context of atopic dermatitis, chronic rhinosinusitis with nasal polyps and asthma, no increased risk of infections to viral or bacterial pathogens have been documented.43 Furthermore, dupilumab had no impact on responses to non-live vaccines.44

***2.2 Type 2 responses and eosinophils***

***Does type 2 airway inflammation protect against COVID-19?***

Allergic airway disease patients appear to be underrepresented among COVID-19 patients. Allergic patients, with or without concomitant asthma, have lower ACE2 expression.45 Moreover, allergen challenge, which induces T helper (Th)-2 inflammation, further reduced ACE2 expression in a murine model of asthma, and was inversely associated with type 2 biomarkers (IL-13, IgE, exhaled nitric oxide fraction).46 These results are in line with previous work showing that decreased ACE expression in the airway epithelium of asthmatic subjects was associated with eosinophilic inflammation.47 Altogether, these studies suggest that type 2 airway inflammation may reduce susceptibility of SARS-CoV-2 infection by reduction of ACE2 expression (**Fig. Type 2 immunity**).

***Some COVID-19 patients present with eosinophilic inflammation. Is it a Th2-driven response against the virus or an innate immune response?***

Eosinopenia has been reported in ⁓50-70% of severe COVID-19 patients. Only a minor population of COVID-19 patients present with eosinophilic inflammation.21,48 The Th1/Th2 cytokine balance may play a role, particularly as it pertains to IL-5, which promotes eosinophilopoiesis and eosinophil survival and activation. Eosinophilic inflammation suggests the dominance of type 2 inflammation, which may play a protective role against SARS-CoV-2. On the other hand, it may be the result of a hypersensitivity reaction to used drugs.49-51

***Do eosinophils exert antiviral activity in COVID-19 patients?***

Anti-IL-5 treatment, which induces eosinophil deficiency, results in a higher viral load in influenza and rhinovirus infection. This might be due to the ability of eosinophils to bind and inactivate influenza A virus and respiratory syncytial virus (RSV).52 A similar role seems possible in SARS-CoV-2 infection, where type-2 asthma patients potentially benefit from antiviral eosinophil responses. On the other hand, COVID-19 post-mortems did not show lung eosinophilia50, which argues against its local protective role in SARS-CoV-2 infection, although it is important to control for glucocorticoid-driven eosinophil reduction in these studies.49

***What is the mechanism underlying eosinopenia in COVID-19 patients?***

Eosinopenia is commonly reported in severe COVID-19.52 The underlying mechanisms are largely unknown and most likely multifactorial. A number of possible explanations have been proposed: decreased eosinophilopoiesis; defective eosinophil egression from bone marrow; and eosinophil apoptosis induced by type 1 INF released during the acute infection.49 Also, increased eosinophil migration and retention at inflamed tissues has been described,53 but disputed for the aforementioned reasons.50

***Do eosinophil-targeting biologics affect COVID-19 patients?***

There is no evidence for an enhanced susceptibility of patients on anti-IL-5/IL-5R treatment to develop viral infections. Observational studies in COVID-19 patients reported elevated eosinophil counts with a favorable outcome, whereas eosinopenia was observed in more severe cases.21,54 Neither was there proof of causation nor evidence for enhanced tissue presence in lungs of COVID-19 patients.55

***Do IL-5-targeting therapies for asthma have a protective effect in COVID-19 patients with severe asthma who are already receiving these therapies?***

There is neither evidence for a protective effect of these biologicals nor for a negative effect regarding SARS-CoV-2 infection. Importantly, maintaining good asthma control is imperative and so is to follow up on severe asthmatics during times of COVID-19, for example via telemedicine.43

***2.3 T cells and lymphopenia***

***Is T cell function impaired on SARS-CoV-2 infection?***

SARS-CoV-2 infects human T cells via CD147-binding.56 T cells are severely affected by SARS-CoV-2, which reduces T cell counts nearly 2 times below the reference limit. This effect is even more pronounced in critically ill COVID-19 patients.48,57,58

***What is the specificity of the T-cell response generated in COVID-19 patients?***

Circulating SARS-CoV-2−specific CD8+ and CD4+ T cells have been reported in ∼70% and 100% of COVID-19 convalescent patients, respectively.59 CD4+ T cell responses to spike were robust and correlated with SARS-CoV-2-specific-IgG and -IgA titers. The M, spike and N proteins each accounted for 11-27% of the total CD4+ response, with additional responses commonly targeting nsp3, nsp4, ORF3a and ORF8, among others. For CD8+ T cells, spike and M were recognized, with at least 8 SARS-CoV-2 ORFs targeted. Interestingly, SARS-CoV-2−reactive CD4+ T cells were detected in ∼40-60% of unexposed individuals, which indicate cross-reactive T cell recognition between circulating ‘common cold’ coronaviruses and SARS-CoV-2.59

***Is a long-term T cell memory established during SARS-CoV-2 infection?***

Three SARS-recovered individuals, 9- and 11-years post-infection, were analyzed for T cell responses against 550 SARS-CoV peptides that may also share homology with MERS-CoV. SARS-specific memory T cells persisted at 9 and 11 years post-SARS in the absence of antigen.60 These data suggest that specific T and B cell epitopes may be applied for eliciting a robust T cell or antibody response in SARS-CoV-2 or in response to its mutual vaccine. However, conclusive data on SARS-CoV-2 are pending.

***What are the hypothetical mechanisms of lymphopenia?***

Different mechanisms have been proposed for lymphopenia: 1) T cell exhaustion. The expression of the exhausted marker PD-1(programmed cell death-1) was higher in T cells from COVID-19 patients than in healthy controls; the expression of PD-1 and another exhaustion marker Tim-3 increased when the COVID-19 progressed.61 2) Activation of apoptosis and P53 signaling pathway in lymphocytes suggesting a role of apoptosis for lymphopenia. 3) Pyroptosis of lymphocytes, which not only induces lymphopenia but may be proinflammatory.62 4) Evidence is accumulating on direct infection of T cells with SARS-CoV-2, which may also cause cytopathic effect on infected T cells. 5) Other mechanisms of lymphopenia that remain to be studied are bone marrow suppression during cytokine storm, and sequestration in the lungs during extensive bilateral pneumonia.48

***Can lymphopenia be an early predictor of COVID-19 severity?***

Lymphopenia could be not only an early predictor of severity but also a predictor for clinical outcome. Significant reduction in lymphocyte counts was associated with severe and critically ill COVID-19 patients; continuing or gradual decrease of lymphocyte counts was an indicator of clinical progression and requiring ICU admission (**Table X**)48. In addition, many studies suggested lymphopenia as an independent risk factor for mortality of COVID-19.21,63

***Which cells are particularly decreased in lymphopenia?***

In COVID-19 patients, decreases in total lymphocytes, CD4+ T cells, CD8+ cytotoxic T cells, B cells and natural killer cells were observed. T and natural killer cell counts were below normal levels, while B cell counts were at the low end of the normal range. Other lymphocytes subsets such as CD16+CD56+ natural killer cells and regulatory T cells were also decreased in severe COVID-19 patients.48

***2.4 Immunopathology, immunosuppression and immune regulation***

***What is it meant by cytokine storm syndrome (CSS)?***

CSS is associated with a wide variety of infectious and noninfectious diseases. It is a complex cascade of multicellular activation events that leads to excessive or uncontrolled release of proinflammatory cytokines. Inflammation associated with CSS begins at a local site and spreads throughout the body via the systemic circulation and can cause multi-organ failure and hyper-ferritinemia.48,64

***Which cells are critically contributing to CSS in severe COVID-19?***

CSS encompasses the activation of large numbers of blood cells, including B cells, natural killer cells, macrophages, dendritic cells, neutrophils, monocytes, resident tissue cells, epithelial and endothelial cells causing a massive release of pro-inflammatory cytokines, which cause pathology.65 The cells involved in COVID-19 cytokine storm are not clearly determined. In SARS-CoV and MERS-CoV infection, airway epithelial cells, dendritic cells and macrophages were most important cell types that release large amount of proinflammatory cytokines.48,66

***Which cytokines are most affected during CSS?***

Multiple proinflammatory cytokines and inflammasome activation may contribute to the pathogenesis of CSS.48 Elevated serum ferritin, IL-6, IL-1β, IFN-γ, CXCL10 (known as IP-10) and CCL2 (known as MCP-1) levels have been observed in the pathogenesis of severe COVID-19.49,67 A recent study compared 48 cytokines in 53 COVID-19 patients and 8 healthy individuals and found 14 of them were increased in COVID-19: IFN-γ, IL-1Rα, IL-2Rα, IL-6, IL-10, IL-18, hepatocyte growth factor, monocyte chemotactic protein-3, monokine induced γ-IFN, macrophage colony stimulating factor, granulocyte colony-stimulating factor, macrophage inflammatory protein 1α, cutaneous T-cell-attracting chemokine and IP-10. A consistently high high level of IP-10, monocyte chemotactic protein-3 and IL-1Rα was associated with deterioration and fatal outcome.68

***Which other diseases can also develop CSS?***

CCS can also develop in other infectious diseases such as bacterial sepsis, Leptospirosis, Ebola and other hemorrhagic fever influenza, other pathogenic coronavirus infection including SARS-CoV and MERS-CoV, severe respiratory syncytial virus infection, and non-infectious diseases such as blunt trauma, and as a side effect of immune stimulatory drugs.48,64

***Does systemic immunosuppression influence the course of COVID-19?***

Immunosuppression is a double edged sword in viral infections.69 Patients receiving systemic immune suppression (*e.g.*, chemotherapy) at the time of infection tend to develop a severe form of the disease. There are conflicting results regarding systemic corticosteroid treatment but their usage is not generally recommended in viral infections.48,70,71 However, CSS treatment requires systemic immune suppression. Therefore, immune suppression may facilitate viral infection but, at advanced stages of infection, it may be beneficial to counteract immunopathology due to excessive inflammation or CSS.

***Are primary immunodeficiency patients at increased risk to develop severe COVID-19?***

Primary immunodeficient patients are a high-risk group in the current pandemic, but to date it is unknown if a particular immunodeficiency poses a higher risk of severe disease. International primary immunodeficiency monitoring is being carried out and few cases have been documented. Patients at higher risk are those with complications resulting from their primary immunodeficiency and strict follow-up must be done in those cases. A consensus has been established that baseline chronic treatment should be continued in those patients if they are asymptomatic or mildly symptomatic. Furthermore, recommendations regarding primary immunodeficient patients adhere to individual national guidelines emphasizing social distancing and strict hygiene measures. Systematic testing of primary immunodeficient patients is not advised, however recommendations may change as the pandemic evolves.72

***What is the role of T regulatory cells in COVID-19 pathogenesis?***

There are no longitudinal studies analyzing T regulatory cells in COVID-19. A limited number of studies have reported decreased numbers of circulating T regulatory cells (CD3+CD4+CD25+CD127low+) as a part of lymphopenia. Further studies are needed to explore their roles in COVID-19 pathogenesis as well as in controlling severe tissue injury or CSS.48,73

***Does metabolic fitness at the cellular and individual level affect COVID-19?***

Systemic dysregulation of metabolism in a form of obesity and diabetes is a risk factor of SARS-CoV-1 and SARS-CoV-2 infection and of COVID-19 severity55. These diseases lead to chronic systemic inflammation, upregulation of SARS-CoV-2 receptors in the lungs and in the periphery, and they disturb the glucose and lipid metabolism of tissues and immune function.13,74,75

***What is the pathogenesis of acute respiratory distress syndrome (ARDS) in COVID-19*?**

ARDS is an acute life-threatening inflammatory lung injury due to infection, trauma, or inﬂammatory conditions. Excess inflammation response leads to alveolar damage and increased permeability of endothelial and epithelial, resulting in protein-rich fluid accumulation in interstitium and the air space, which causes impaired gas exchange and hypoxemia. Reactive oxygen species, leukocyte proteases, chemokines, and cytokines also contribute to lung injury. Lung microvascular barrier impairment due to increased endothelial and epithelial permeabilities is central to the pathogenesis of ARDS.76 In fact, COVID-19 patients with ARDS had a histological pattern of diffuse alveolar damage with perivascular T cell infiltration. Pulmonary vascular endothelial injury associated with the presence of intracellular virus and disrupted cell membranes contribute to the increase of permeability of endothelial. Alveolar capillary microthrombi, secondary to endothelial injury, in patients died of COVID-19 may be an important cause of refractory hypoxia in ARDS.48,71,77,78

***What are the clinical phenotypes of ARDS in COVID-19 patients?***

In COVID-19 patients, ARDS is more common in older people, those with multiple comorbidities, and those with continuing or gradually progressed neutrophilia, lymphopenia, higher level of C-reactive protein, LDH, D-dimer and PCT.48,71 There are at least 2 clinical phenotypes of ARDS: 1) near normal pulmonary compliance with isolated viral pneumonia; 2) decreased pulmonary compliance.78,79

***What specific therapies can be suggested for ARDS?***

Different treatments were suggested for ARDS. Corticosteroids treatment is generally not recommended, although widely used in critically ill patients. Convalescent plasma (CP) was administered to a small number of patients and was associated with virus clearance and clinical improvement. Low tidal mechanical ventilation, positive end expiratory pressure (PEEP), prone positioning ventilation and fluid management guidelines were associated with improved outcome. Extracorporeal membrane oxygenation (ECMO) could be used according to the inclusion and exclusion criteria of EOLIA trial. Other potential therapies such as mesenchymal stem cell therapy and cytokine inhibitors are still in trial and without definite results.48,80

***Is Bacille Calmette-Guerin (BCG) vaccination protective against SARS-CoV-2?***

BCG vaccination induces metabolic and epigenetic modifications by enhancing trained immunity (innate immunity to subsequent infections). It was hypothesized that general BCG vaccination policies adopted by different countries might have impacted the transmission patterns and/or COVID-19 associated morbidity and mortality.81 BCG vaccination in childhood was not protective against SARS-CoV-2 infection in an Israeli cohort.82 In contrast, randomized controlled trials of BCG-Danish indicated immunomodulation against pre-COVID-19 respiratory infections with fewer deaths from sepsis and pneumonia. Two clinical trials of BCG-Danish (BRACE and BCG-CORONA) are evaluating its impact in healthcare workers against COVID-19 infection and its severity.83,84

***What is the mechanism underlying Kawasaki syndrome in the context of COVID-19?***

The mechanisms underlying Kawasaki disease -a generalized vasculitis, in young children, of unknown, potentially post-viral etiology- are poorly understood. The rare COVID-19-associated inflammatory syndrome also features vasculitic changes, affects older children too and is often only associated with positive SARS-CoV-2 serology, but not viral shedding. Its mechanisms need to be elucidated and may include post-infectious, antibody and immune-complex mediated pathology. In adults, there are occasional cases of COVID-19-associated cutaneous vasculitis, possibly a localized manifestation of the disease that leads to severe generalized vasculitis in some children.85-87 Interestingly Kawasaki-like disease was not reported in Chinese cases and the first months of European cases. The season of the disease and environmental factors should be considered. The Chinese epidemic was mainly from January to March whereas the US epidemic started in mid-March and is still ongoing.

***Which acute phase reactants are the most decisive ones for follow-up of COVID-19 patients?***

Although initial results of acute phase reactants such as C-reactive protein, alanine transaminase, lactate dehydrogenase, D-dimer, procalcitonin, serum ferritin and IL-6 on admission were used to evaluate the severity and predict the mortality, dynamic changes of these data will be more precisely to predict the recovery or progression of COVID-19. Continuing or progressive increase of C-reactive protein, procalcitonin, D-dimer and lactate dehydrogenase were proved to be associated with high risk of death in severe COVID-19 patients.21,48,88

1. ***Diagnosis of COVID-19***

***What are the principal signs of SARS-CoV-2 infection?***

Patients with acute respiratory illness (*i.e*., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) and a history of contact with a confirmed or probable COVID-19 case, history of travel to, or residence in, a location reporting community transmission of COVID-19 during the 14 days prior to symptom onset. Patients with any acute respiratory illness in the context of a pandemic should have SARS-CoV-2 infection in their differential diagnosis. Special attention should be given to patients with sudden onset of anosmia, loss of taste gastrointestinal symptoms or skin lesions without respiratory symptoms who also have epidemiological links.4,21,89

***What is the importance of smell loss in the diagnosis of COVID-19?***

Smell loss is now a well-established diagnostic symptom of COVID-19 and can be present in otherwise asymptomatic patients, making it a useful tool in initial diagnosis.90 This has resulted in anosmia to be included in the list of symptoms used in early screening tools for possible COVID-19 infection in many international bodies.90

***What are the prognostic parameters of severe COVID-19?***

Rapidly progressive respiratory failure and sepsis, elevated serum proinflammatory cytokine levels, elevated acute phase reactants (*e.g.* C-reactive protein), cell-free-hemoglobin-leukopenia and markers of disseminated intravascular coagulation.91

***What is the most reliable method to determine positive COVID-19 cases?***

RT-PCR to generate cDNA of SARS-CoV-2 specific RNA extracted from respiratory samples, followed by quantitative PCR (**Figure on diagnosis**).92 Common RNA gene targets for SARS-CoV-2 include the envelope, nucleocapsid, spike, RNA-dependent RNA polymerase, and ORF1 genes. It is recommended to include in the analysis, at least, 2 target genes.93

***What is the most suitable location to perform a swab for SARS-CoV-2 detection via RT-PCR?***Nasopharyngeal and oropharyngeal (throat) swabs are the primary specimens for SARS-CoV-2 RT-PCR testing. Lower respiratory tract specimens (*i.e.* sputum, endotracheal aspirate or bronchoalveolar lavage) may have higher viral loads and be more likely to yield positive tests. However, these locations carry a high risk of aerosolization and therefore should be reserved for severe patients with a negative test on an upper respiratory tract specimen and high suspicion for lower respiratory tract SARS-CoV-2 infection.94,95

***Is serology a feasible way to screen for SARS-CoV-2 infection at a population level?***

Serology is useful to determine prior exposure to SARS-CoV-2 within a given period of time (the length of time following infection that one remains positive is unknown). Detection of antibodies specific to the receptor binding domain of the spike protein indicates neutralization capacity, hence informing better about protective immunity development.32,92

***What is the relationship between clinical manifestations and SARS-CoV-2 seroconversion?***

The antibody response occurs later than initiation of symptoms as well as of the detection of viral RNA by RT-PCR in respiratory tract specimens, which usually peaks within the first week of symptom onset. Although antibodies to SARS-CoV-2 have been detected as early as the first week after symptom onset, IgM and IgG seroconversion commonly occurs between the 2nd and 3rd week of clinical illness onset. Thereafter, IgM starts to decline, reaching low levels by week 5 and almost disappears by week 7, while IgG persists beyond this period.32,92

***What are the main approaches for the development of a rapid and specific point-of-care diagnostic test for COVID-19?***

The main approaches include nucleic acid amplification on respiratory samples using mobile devices (RT-PCR or isothermal nucleic acid amplification) and viral antigens or host antibodies (viral protein fragments) detection using immunoassays.96 However, individual tests need validation in large populations before use and their sensibility, specificity, positive and negative predictive values have to be accurately studied. Otherwise, they may lead to COVID-19 under or over diagnosis, threatening the public health efforts to limit the disease.97

***There is a high rate of false negatives with rapid serology tests for SARS-CoV-2, is there an alternative method to determine positive cases?***

A high rate of false negatives with antigen point-of-care assays may be due the fact that the majority of patients produces antibody versus SARS-CoV 2, only in the second week after onset of COVID-19 clinical manifestations.98 Furthermore, an effective antibody response is connected with several determinants, comprising severity of the disease, age and nutritional status of the patient, medications administered and concomitant infections.97 Nucleic acid amplification using PT-PCR directly targeting the virus, does not suffer from the above-mentioned limitations.99 However, with the latter techniques, false negative results are possible as well.

***When can a suspected/confirmed case of COVID-19 discontinue home isolation/quarantine?***

The decision to discontinue home isolation/quarantine should be adapted to specific groups of patients based on factors such as symptom severity, healthcare systems´ capacity, laboratory diagnostic resources and local epidemic status. Patients with suspected or confirmed symptomatic COVID-19 can discontinue self-isolation/quarantine if all the following 4 conditions are met: a) resolution of fever (without the use of fever-reducing medications) for at least 3 days; b) clinical improvement in respiratory symptoms (*e.g.*, cough, shortness of breath) for at least 3 days; c) at least 8 days have passed since the onset of symptoms for mild cases or at least 14 days for severe cases and immunocompromised patients; d) 2 negative RT-PCR tests from respiratory specimens at 24 hours interval. If there is limited or no testing capacity, the combined symptom/test-based strategy should be reserved to hospitalized COVID-19 cases and healthcare workers, whereas for mild or asymptomatic COVID-19 cases (suspected or confirmed) the symptom-based strategy (condition a) AND b) AND c)) without lab testing is considered acceptable to end the self-isolation.100

1. ***Organization of allergy outpatient clinics and laboratories during COVID-19 pandemics***

***What are the emergency measures in an ongoing allergy clinic during COVID-19 pandemics?***Strategies for risk minimization should be elaborated, harmonized and followed as such in allergy clinics, centers and practices.101 In the EAACI/ARIA Position Paper byPfaar *et al.102* experts in the field have developed practical recommendations for optimizing allergic patients ‘care whilst ensuring a high grade of safety for all health care professionals involved. General guidance from national health authorities should be strictly followed (i.e., WHO, European Centre for Disease Prevention). In-person consultations should be minimized to the lowest necessary level and triaged by telemedicine whenever possible.103 Special attention should be paid to data-protection in adherence with national data-security and –protection laws. Non-delayable diagnostic and therapeutic measures should strictly follow reasonable preventive measures. Several individual considerations regarding diagnostic and therapeutic measures are important in different allergic diseases (**see below**). Moreover, socio-psychological aspects play a fundamental role in the care of allergic patients during the current pandemic and should be especially recognized and followed. Stress caused by isolation and stigmatization due to allergic symptoms may amplify the development of allergic symptoms.104

***Is pre-visit specific telephonic triage useful to identify patients possibly infected with SARS-CoV-2?***

Virtual doctor consultations have been regarded as an alternative to on-site clinical encounters and are increasing during the COVID-19 pandemic.102 Firstly, pre-visit specific telephonic communication is helpful to screen for patients with potential SARS-CoV-2 infection **(Fig on prevention)**.105 The epidemiological history should be investigated to determine if patients have fever or respiratory symptoms. In addition, pre-visit specific triage improves the efficiency of the patient's visit, thus reducing the stay time in the hospital. Lastly, doctors can guide at home treatment in some patients based on the information obtained through telephone to reduce face-to-face meetings.

***Should every allergic patient be tested for SARS-CoV-2 prior coming to the clinic?***

A strict screening protocol is needed to identify SARS-CoV-2 infected patients. Ideally, only SARS-CoV-2 negative patients (diagnosed via RT-PCR and/or rapid test) should come to the clinic. In places where systematic testing is unavailable, at least, normal temperature and negative epidemiological history should be mandatory to proceed to the outpatient departments. Patients with a body temperature higher than 37.3ºC should have additional screening examinations, including routine blood tests, chest computed tomography scanning and even throat swabs for SARS-CoV-2 RT-PCR testing.106

***What should be considered when performing diagnostic procedures during the COVID-19 pandemic?***

The indication and the urgency of the tests for diagnosis should be considered. Contraindications for skin, provocation and lung function tests can be explained beforehand to the patient, which helps to avoid unnecessary in-person consultations.102 Any test generating aerosol particles should be avoided because it is considered high risk **(Fig on Procedures).**

***What kind of procedures should be performed in biosafety level (BSL)-2 and -3 laboratories during the COVID-19 pandemic?***

Personal protective equipment (PPE) must be used when collecting biological samples. Biological samples collected on-site from suspected or confirmed COVID-19 patients (*e.g.* antibody assays, RNA isolation, flow cytometry) should be processed following BSL-2 practices. During and after the COVID-19 pandemic, the usage of BSL-2 facilities is mandatory for all newly arriving patient samples due to infection risk. Research procedures involving SARS-CoV-2 isolation or culture should be conducted in a BSL-3 facility.102,107

1. ***COVID-19 and allergic disease***

***Do patients with allergic disease have a higher risk of developing severe COVID-19?***

Patients with common allergic diseases do not develop additional distinct symptoms or severe outcomes, and allergic children show a mild course similar to non-allergic children4. For example, in a recent study of 182 hospitalized children, 43 of them were reported allergic; allergic rhinitis was the most prevalent allergic disease (83.7%), followed by drug allergy, atopic dermatitis, food allergy and asthma. In this study, the allergic children showed less increase in acute phase reactants, procalcitonin, D-dimer and aspartate aminotransferase levels compared to all patients. There were no deaths in allergic children in that study (Du H, 2020).

***5.1 Allergic Rhinoconjunctivitis***

***What is the strategy to distinguish between hay fever/pollen allergy and COVID-19 infection?***

Clinical history is very helpful to identify seasonality- and exposure-related symptoms driving the diagnosis of pollen-induced allergic rhinitis. An atopy test (*in vivo* or *in vitro)* reinforces the diagnosis. However, COVID-19 can be superimposed on AR symptoms.102 Symptoms such as fever, fatigue and sudden loss of smell, are suggestive of COVID-19 infection and should be monitored closely.

***What is the recommended mask to prevent allergic rhinitis symptoms during the COVID-19 pandemic?***

N95 facial masks have been proven useful in reducing allergen exposure via blocking pollen access to nose and mouth. On the other hand, surgical masks do not protect against inhalation of small airborne contaminants and are not designed to seal tightly against the user´s face, thus the contaminated air can pass through the gaps.108

***Does AR impact the susceptibility of SARS-CoV-2 infection?***

There are no conclusive data on the impact of allergic rhinitis on COVID-19 susceptibility109. However, a recent study with 24 AR patients demonstrated a reduction of ACE2 expression in nasal brush samples following an allergen challenge.45 Also, this study reported lower ACE2-expression in the epithelium of asthmatic patients. Altogether, these data seem to suggest that allergic rhinitis patients may even be at lower risk of SARS-CoV-2 infection, but further studies are needed.

***Are AR patients´ at higher risk of severe COVID-19?***

Although limited, available evidence suggests that allergic rhinitis patients are not at higher risk of developing severe COVID-19. In a Chinese cohort of 140 hospitalized COVID‐19 adult patients, allergic rhinitis and asthma were not risk factors for SARS‐CoV‐2 infection.*21* A similar finding was also reported in children. In a recent study addressing the clinical characteristics of 182 children with COVID‐19, 43 of them had an allergic condition, which was mainly allergic rhinitis (83.7%). In this study the allergic children showed a disease progression comparable to that of non-allergic ones (Du H, 2020).

***What are the recommendations for patients suffering from severe conjunctivitis and keratoconjunctivitis during COVID-19 pandemic?***

Patients should continue baseline treatment as established by their physician and current guidelines. According to a panel of experts, low-dose corticosteroids or antiallergic eye drops continue to be the first line of treatment for allergic conjunctivitis during the current pandemic. Although there is no evidence on the possible effect of SARS-CoV-2 on patients using ocular immunomodulating drugs, in patients with vernal keratoconjunctivitis and allergic keratoconjunctivitis the use of local immunomodulatory treatment is considered safe in non-infected patients and should be monitored closely in those with active infection. The use of systemic immunosuppressants for severe cases should be considered on an individual basis110.

**5.2 Chronic rhinosinusitis and other upper respiratory tract diseases**

***Is there a difference in the mechanism driving anosmia in*** ***chronic rhinosinusitis and SARS-CoV-2 infection?***

The loss of smell in chronic rhinosinusitis is caused by type-2 inflammation of the olfactory epithelium.111 In COVID-19, the exact mechanism of potential olfactory neuropathy is still unclear.112 However, an interesting recent study shows that sustentacular cells of the olfactory epithelium express ACE2 and TMPRSS2, which enable SARS-CoV-2 entry and subsequent impairment of the sense of smell.113

***Is intranasal corticosteroid treatment recommended for patients with COVID-19 that present with loss of smell?***

A significant percentage of COVID-19 patients experience loss of smell.90 However, in many patients smell recovers in 1-2 weeks and there is no indication that intranasal corticosteroid treatment has a positive impact on the recovery.114 On the other hand, there is no evidence suggesting that this treatment has a negative impact on symptomatology and/or development of COVID-19. It is recommended to continue regular intranasal corticosteroid treatment for chronic rhinosinusitis.102,109

***What are the recommendations for performing nasal endoscopy surgery in COVID-19 patients?***

Diagnostic procedures involving upper airway manipulation, such as nasal endoscopy, should be considered high risk for viral transmission. Before clinical examination, it is recommended to question all patients about contact with confirmed COVID-19 patients, fever, respiratory symptoms and recent sudden loss of smell and/or taste. During nasal endoscopy, distance between the endoscopist and patient can be maximized by using a tower with camera, screen and light source instead of using an eyepiece to avoid too close physical contact. Also, manipulations should be limited if possible, *i.e.* nasal inspection versus debridement with suction and/or forceps. The use of local anesthetic spray can be replaced by alternatives such as soaked pledgets because atomized anesthesia can aerosolize the virus.115 Given that the COVID-19 status of patients consulting the outpatient rhinology clinic is often unknown and the risk of transmission through clinical procedures is high, wearing adequate PPE is mandatory.102,116 For all surgical cases, pre-operative screening of the COVID-19 status of the patient is recommended to adapt the PPE accordingly. In case of an emergency where COVID-19 screening would imply an unacceptable time-delay, the patient should be considered as COVID-19 positive and PPE used.115

***Is corticosteroid treatment prior to surgery for chronic rhinosinusitis with nasal polyps recommended during the pandemic? And if so, intranasal or oral?***

There does not seem to be a negative impact on symptoms and/or development of COVID-19 with the use of intranasal corticosteroids.109 Therefore, intranasal corticosteroids treatment should be continued perioperatively if possible. The use of f corticosteroids either during an exacerbation or perioperatively should be carefully considered on a ‘per-patient’ basis. Recent guidance from the WHO has advised against the use of systemic corticosteroids if COVID-19 is suspected due to concerns that these agents may impair protective innate antiviral immune responses.117

***What are the treatment recommendations for COVID-19 children with chronic otitis media with effusion?***

Chronic otitis media with effusion is a common childhood disease usually with the absence of signs or symptoms of acute ear infection. It is therefore preferable to treat COVID-19 first and delay elective surgery. The indication and choice of surgery (*e.g.*, tympanostomy tubes and/or adenoidectomy) should comply with the professional Clinical Practice Guidelines.118,119

***5.3 Asthma***

***How can an acute asthma attack be differentiated from a SAR-CoV-2 infection?***

An asthma exacerbation is difficult to differentiate from COVID-19 ARDS or pneumonia by the patient, especially if it is triggered by rhinovirus, or other common respiratory viruses, because both conditions have dry cough and dyspnea. The British Thoracic Society advises patients experiencing fever, fatigue and loss of taste or smell to alert their physician as these are suggestive of COVID-19.120 The distinction can be made by the physician based on the presence of wheeze which is generally (but not always), absent in COVID-19 pneumonia as well as high resolution chest tomography and viral diagnostic tests.102

***Are COVID-19 patients with asthma at a higher risk of severe COVID-19 than the general population?***

Patients with controlled asthma are not at higher risk of severe infection. In fact, ACE2 expression was decreased in patients with allergic asthma45 and in those receiving inhaled corticosteroids.121 However, ACE2 expression in asthmatic patients was increased in African-Americans, in males and in association with diabetes.45 On the other hand, uncontrolled asthma is a risk factor, thus all efforts should be focused in keeping asthma control by regular use of controller medication, including inhaled corticosteroids and biologicals.122

***Are patients on chronic inhaled corticosteroids maintenance at higher risk of infection or more severe COVID-19?***

There is no evidence available that patients on inhaled corticosteroids are at higher risk of COVID-19 infection or of more severe symptoms. It is strongly advised by international scientific societies that patients continue with their routine control medication including inhaled corticosteroids during the pandemic.109,123

***Corticosteroids inhibit rhinovirus and RSV-induced cytokine release in vitro. May inhaled corticosteroids have a protective effect against SARS-CoV-2?***

Recent evidence indicates that inhaled corticosteroids treatment reduces, in a dose-dependent manner, the expression of viral membrane receptors used to infect the human airways.121 However, there are no clinical studies investigating the effect of inhaled corticosteroid on SARS-CoV-2 infection rates.

***Given the current restrictions should spirometry and other lung function tests for initial diagnosis in patients suspected of asthma be performed?***

Spirometry is essential for the diagnosis of new asthma cases as stated by the Global Initiative for Asthma (GINA) guidelines. Therefore, it should be conducted, but under special conditions (negative pressure chamber, *etc*.) and only in areas with low SARS-CoV-2 infection incidence. Healthcare providers performing lung function testing need to wear maximum PPE (filtering face-piece particles 2 or 3 face mask, goggles or disposable face shield covering the front and sides of the face, clean gloves, and clean isolation gowns), and the spirometer devices should be properly disinfected between patients.124 An alternative, less precise, is monitoring morning and evening peak expiratory flow variability over a week.125,126

***Should routine spirometry and lung function control be performed in asthmatic patients during the COVID-19 pandemic?***

Current GINA guides for COVID-19 state that routine spirometry should be avoided, especially in areas of high risk of COVID-19 transmission. In case spirometry needs to be performed, maximum PPE should be used.123 The treatment of asthmatic patients can be monitored using personal devices measuring forced expiratory volume and peak expiratory flow. Many of these devices are equipped with remote transmission functions and thus are amenable for the telemedicine management of patients.127

***Should asthma exacerbations be treated with*** ***oral corticosteroids during COVID-19 pandemic?***

There is no evidence suggesting that the current approach to treat asthmatic patients during an exacerbation should change. Also, there is no proof that a short course of systemic corticosteroids impacts the evolution of COVID-19. Thus, oral corticosteroids should be given as usual for the treatment of an asthma exacerbation.120,123In the few cases in which patients are treated with long term oral corticosteroids in addition to their high dose inhaled corticosteroids this should be continued in the lowest dose possible to prevent exacerbations.123 The cause of the asthma exacerbation should be studied thoroughly to rule out potential exacerbations due to viral infections.72

***During an asthma exacerbation, what is the safest way to administer medication that creates airborne particles during COVID-19 pandemic****?*

The preferred treatment is a pressurized metered dose inhaler with a spacer. Each patient should have their individual spacer, and this should not be shared at home. The use of nebulizers should be avoided when possible as they increase the risk of disseminating viral particles which could affect other patients and healthcare personnel.123

***What is the correct way to manage anti-IgE treatment during the COVID-19 pandemic?***

Anti-IgE treatment with omalizumab should be continued in non-infected patients. Self-administration devices at home, whenever this option is available, is preferred, to minimise face-to-face contact in clinic. In infected patients, omalizumab administration should be delayed until complete clinical recovery and viral clearance is achieved.43,128

***CSS in COVID-19 patients is characterized by increased IL-6 levels. Given that an IL-6/Th17 endotype is associated with severe asthma in obese patients, are obese asthmatic patients more likely to develop severe COVID-19?***

Obesity, as part of the metabolic syndrome, increases the risk of severe COVID-19. This is due to the pre-existent systemic low-grade inflammation and increased expression of SARS-CoV-2 entry receptors (ACE2, TMPRSS2 and CD147).129,130 Obese patients tend to have worse asthma control, increased hospitalizations and suboptimal response to standard controller therapy. Thus, both difficult-to-control asthma and an underlying metabolic syndrome are risk factors for severe COVID-19. The IL-6/TH17 endotype encountered in late-onset obese asthma might be an additional risk factor.131,132

***5.4 Atopic dermatitis and other skin lesions***

***What are the dermatological manifestations of COVID-19?***

The dermatological manifestations of COVID-19 range from an un-specific macular erythematous rash, urticarial lesions, chickenpox-like vesicles and acro-ischemic lesions.133,134 They can result from local inflammation due to circulating immune complexes or from systemic manifestations leading to vasculitis and thrombosis.135 These patients are also at increased risk of drug hypersensitivity lesions (**Fig. Skin**).136

***Are patients with epithelial barrier disorders at higher risk of skin complications?***

There is no evidence that patients with barrier defects such as atopic eczema have a higher risk for SARS-CoV-2 infection or skin complications during COVID-19. However, patients with atopic dermatitis are often on systemic immunosuppressants and should be monitored closely. Optimal topical treatment regime should also be encouraged in all patients.137

***Does frequent hand washing for COVID-19 prevention increase the risk of atopic dermatitis?***

Hand hygiene procedures are pivotal to prevent self-infection and virus spreading. However, extensive water contact enhances dry skin, disturbs the commensal microbiota and leads to barrier disruption in healthy individuals. Moreover, it exacerbates diseases with an intrinsic barrier defect such as atopic dermatitis.138,139 Effective skin care after hand hygiene is therefore essential to prevent barrier disruption and sensitization events. Here, emollients containing hyaluronic acid, Vitamin E, ceramide or urea are recommended.140

***Does dupilumab treatment increase SARS-CoV-2 infection susceptibility?***

Dupilumab inhibits the function of IL-4 and IL-13 and is approved for the treatment of moderate-to-severe atopic dermatitis. First data from Italy on dupilumab-treated non-infected in high epidemic areas, and current evidence from dupilumab trials, suggest no negative effect of dupilumab regarding viral infections141 with reports on a reduced number of herpes simplex superinfections and less bacterial superinfections.142-144

***Should dupilumab treatment for atopic dermatitis patients be suspended or modified during the COVID-19 pandemic?***

The current EAACI statement on the usage of biologicals in the context of COVID-19 advices no change of therapy in non-infected individuals and to withhold/delay the application of biologicals for a minimum of two weeks or the resolution of the disease in case of SARS-CoV-2 infection.43 This is based on expert opinion in the light of missing data and may be adapted if more information becomes available.

***Should patients presenting acro-vasculitis be studied for coagulation defects and considered for preventive therapy even if they are asymptomatic?***

Acro-ischemic lesions on toes and fingers have been identified in a subgroup of COVID-19 patients.21,145 Data available are scarce and it is unclear if preventive or active anticoagulation should be initiated. However, acro-ischemic lesions could precede other SARS-CoV-2 symptoms in children and young adults.

***5.5 Drug hypersensitivity***

***How to differentiate skin lesions caused by COVID-19 itself from those secondary to drug hypersensitivity during the treatment of the disease?***

Skin lesions caused by COVID-19 can be related to thrombovascular events (*i.e.* petechiae, acro-ischemia, dry gangrene) or to typical viral infections (*i.e.* erythematous rash, urticaria, maculopapular exanthema).136 Drug hypersensitivity has to be considered as a differential diagnosis, mainly in the second group, being distinction difficult during the acute phase. Diagnosis relies mostly on clinical observations, besides the chronology of the reaction development, in comparison with the drug exposure timeline give important clues51. Laboratory and histopathological findings may also help.

***Of the drugs being assessed for COVID-19 treatment, which ones are more immunogenic or associated with hypersensitivity reactions?***

Immunomodulatory drugs (including azithromycin), hydroxychloroquine/chloroquine and IFNs, are the ones most frequently involved in hypersensitivity reactions. Most reactions are non-immediate and further studies are required to clarify whether this increased frequency is caused by the drug immunogenicity or simply derives from a greater consumption as compared to other treatments.136

***Should drug provocation testing be performed during the COVID-19 the pandemic?***

Drug provocation tests are not recommended because reactions can occur during the tests, including the generation and spreading of virus-containing aerosols. However, they may be considered after careful risk-benefit assessment in cases of urgent need, such as chemotherapy in cancer patients, perioperative drugs and radiocontrast media in subjects needing urgent procedures, and antibiotics if no effective alternative drug is available.102

* 1. ***Handling of allergen immunotherapy (AIT) during the COVID-19 pandemic***

***Should AIT in allergic rhinitis and/or asthma patients be interrupted to reduce visits to health care centers during the COVID-19 pandemic?***

Most AIT products authorized for use in Europe establish that AIT should be discontinued in case of an infection; the same principle will apply to the COVID-19 pandemic. Patients on subcutaneous or sublingual AIT, who are infected with SARS-CoV-2 should discontinue therapy. In patients who have recovered from the infection, AIT could be continued as planned. Subcutaneous AIT replacement with sublingual AIT would entail AIT re-initiation, which would not be indicated.146

***Should venom AIT be stopped during the COVID-19 pandemic?***

AIT should continue in non-infected patients or in those recovered from COVID-19. This is especially important in patients with life-threatening conditions such as venom allergy. It is possible to extend the intervals between vaccines during subcutaneous AIT to minimize visits to the allergy clinic. If venom AIT was stopped due to SARS-CoV-2 infection, it is unclear when it should be re-initiated as more data from convalescent patients are scarce.146 See **Table on AIT** recommendations for more information.

***What is the correct way to manage oral immunotherapy for food allergy during the COVID-19 pandemic?***

Food oral immunotherapy should be interrupted in COVID-19 patients regardless of the infection severity. The treatment can be continued in non-infected patients including those who have recovered from COVID-19. The oral immunotherapy dose should not be increased in patients at high risk of infection until they can safely resume visits to the allergy clinic.146

1. ***Treatment of COVID-19***

***Is it more important to treat the viral infection or the CSS in COVID-19 patients?***

COVID-19 treatment entails three main approaches: i) anti-viral; ii) systemic anti-inflammatory and immunologic; iii) and symptomatic and supportive treatment. The patient's viral load detected at the onset of COVID-19 is typically associated with mortality. Consequently, SARS-CoV-2-specific anti-viral treatments, once licensed, are expected to be central to COVID-19 treatment. Systemic anti-inflammatory treatments are essential in severe COVID-19 cases with CSS as the latter is a decisive risk factor for mortality, multiorgan failure, ARDS and disseminated intravascular coagulation. For these reasons, COVID-19 treatments must induce quick viral clearance while precluding systemic inflammatory syndromes.48

***In home-treated mild COVID-19 patients, what are the alarm symptoms to seek hospital assistance?***

These patients are generally on symptomatic treatment. They need to look out for symptoms suggesting hypoxia or pneumonia, such as shortness of breath, deep shallow breathing, chest pains or persistent tachycardia. Special attention needs to be given to those with risk factors for disease progression, such as patients older than 65 years, cardiac or pulmonary comorbidities and immunosuppression.147,148

***Whom of the COVID-19 patients would benefit from anticoagulant treatment?***

Prophylactic low molecular weight heparin, or heparin, has been recommended by the WHO in severe to critically ill COVID-19 patients.117 However, the International Society on Thrombosis and Haemostasis recommended that all hospitalized COVID-19 patients, not just those in intensive care unit (ICU), should receive prophylactic low molecular weight heparin in the absence of contraindications.149

***Does systemic corticosteroid treatment at the initial phases of COVID-19 prevent the immunopathology seen in severe cases?***

During the SARS outbreak in 2003, corticosteroids did not change the course of the viral infection and delayed viral clearance.150 On the other hand, a retrospective study on SARS patients in Hong Kong evidenced a better survival rate in patients treated with prednisolone for milder pneumonia or methylprednisolone in more severe cases.151 Recently, Chinese experts stated that, in COVID-19 patients, systemic corticosteroids should be considered on individual indications in a low-to-moderate dose and for no longer than a week.152 The National Institutes of Health in their COVID-19 Treatment Guidelines advises against the use of systemic corticosteroids in non-critically ill patients.153

***Is there enough evidence to support that current COVID-19 treatments are better than placebo in terms of symptoms’ severity and aftermath?***

There are over 170 clinical trials on COVID-19 treatment registered now in the international databases and very few have completed. Currently promoted pharmacological treatments are, at the most, based on anecdotic data collected in small numbers of COVID-19 patients. These studies did not satisfy evidence-based medicine criteria, but caught general attention through news media, for example hydroxychloroquine.

***Tocilizumab (TCZ) has been used for ICU patients with severe COVID-19, what is the rationale?***

TCZ is a humanized monoclonal antibody specific for the IL-6 receptor, and it is approved for rheumatoid arthritis. A positive response to TCZ points towards an imbalanced innate immune response in severe COVID-19. Luo *et al*.154 reported on 15 patients treated with TCZ, seven of them critically ill; eleven patients recovered within a week. Prompt resolution of symptoms and encouraging results have also been reported in uncontrolled or retrospective trials.155-166

***What lessons learned from the previous SARS-CoV and MERS-CoV viruses have proven useful to identify therapeutic targets for COVID-19****?*

These animal-born human beta-coronaviruses share structural and genomic similarities that are useful to understand COVID-19. SARS-CoV and MERS-CoV have lower transmission rate, shorter incubation time and higher fatality rates than SARS-CoV-2. In all of them, the S-protein plays a key role in infection via ACE2-binding, hence is a clear therapeutic target. Potential treatments already used for SARS-CoV and MERS-CoV included remdesivir, chloroquine, TCZ and CP, among others. However, none of them have been tested in robust clinical trials **(see below section 8**). Lessons in epidemiological surveillance and isolation measures have also proven useful.167

***What is the impact of nonsteroidal anti-inflammatory drugs use in symptomatic COVID-19 patients?***

Fang *et al*.168 suggested that there is ACE2 overexpression upon treatment with ACE inhibitors, thiazolidinediones and ibuprofen. This caused concerns about the use of nonsteroidal anti-inflammatory drugs in COVID-19 patients. Since then, the European Medicines Agency clarified in their Drug and Therapeutics Bulletin that no scientific evidence established a link between ibuprofen or other nonsteroidal anti-inflammatory drugs and a risk to worsen COVID-19.169

1. ***Clinical trials and drug discovery in COVID-19***

***What are the main recommendations for organizing clinical trials during the COVID-19 pandemic?***

Adaptations for clinical trials during the pandemic must include all concerned parties such as patients, clinical research organizations, clinical trial units, ethical committees, regulatory authorities and sponsors. For major deviations, changes must be approved by the responsible ethical committee and covered by the Informed Consent Form. Additional risks to participants should be addressed in the benefit-risk assessment section of the protocol, together with risk reduction measures. For patients who continue study participation, site visits should be postponed or, whenever possible, replaced by remote data assessment via telemedicine under strict observation of data protection regulations. In case needed, the duration of staying in the clinic should be limited and travel arranged to include alternatives to local public transport. Initiation of new clinical trials should be critically evaluated (**Table X**). The International Committee of Medical Journal Editors has clarified that, in the event of public health emergencies such as COVID-19, information with a direct impact on public health should be disseminated without fear that this would preclude subsequent review for publication in a scientific journal.146

***What are the main recommendations for clinical trial design during the COVID-19 pandemic?***

Hundreds of registered clinical trials regarding potential therapies for COVID-19 are currently open in international registries. The study designs and outcomes are often divergent and based on single center’s experiences or on compassionate use of the candidate treatments. In order to improve the quality of the evidence and their secondary analysis, the scientific community should lead multi-center, multi-arm and highly powered clinical trials and foster the global sharing of knowledge on the topic. In this way, hopefully, high quality data on efficacy and safety of potential therapies will be soon available.170

***What are the main drugs under investigation that block SARS-CoV-2 cell entry?***

There are drugs that interfere with ACE2 and TMPRSS2, which are molecules used by the virus to enter the cell.8,171 For example, camostat mesylate is a clinically proven serine protease inhibitor with affinity for TMPRSS2. It has shown activity against SARS-CoV-2 in human lung Calu-3 cells.8 Several drugs that target virus internalization are being investigated, including chloroquine phosphate and hydroxychloroquine, which have shown limited efficacy in humans and raised concerns because of side effects. Also, a combination of cepharanthine (an anti-inflammatory alkaloid), selamectin (an avermectin used as an anti-helminthic and parasiticide drug in veterinary medicine) and mefloquine hydrochloride (used for the prophylaxis and treatment of malaria)172 and meplazumab173 (**see below**), among others. Although still at the experimental level, a clinical-grade human recombinant ACE2 has shown efficacy to block SARS-CoV-2 growth in kidney epithelial cells (Vero cells) (**Fig. 1**).174

***What are the main drugs under investigation that block SARS-CoV-2 replication?***

Drugs designed to inhibit the viral replication machinery may be effective against SARS-CoV-2. For example, remdesivir inhibits viral RNA polymerases, which prevents SARS-CoV-2 replication. In a cohort of severe COVID-19 patients, compassionate-use of remdesivir showed clinical improvement in 68% of patients (36 out of 53).175 Of note, a double-blind, randomized, placebo-controlled trial of intravenous remdesivir was conducted in 1,063 adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement; remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection.176 Furthermore, in a study of 5 HIV-positive hospitalized patients with severe COVID-19, 3 of them were given lopinavir-boosted ritonavir (LPV/r) and 2 darunavir-boosted cobicistat for 14 days. Four patients recovered and 1 remained hospitalized as of April 2020.177 In another study with 99 hospitalized adult patients with severe COVID-19, no benefit beyond standard care was observed with LPV/r treatment twice daily for 14 days.178 It is uncertain whether LPV/r and other antiretrovirals improve clinical outcomes or prophylaxis among patients at high risk of SARS-CoV-2 infection.179 Additional potential candidates include other broad-spectrum antiviral drugs such as arbidol and favipiravir and phytochemicals with anti-viral activity such as resveratrol (**Fig. 1**).172

***Is meplazumab a potential therapy for COVID-19 patients?***

Meplazumab is a CD147-specific humanized monoclonal antibody that has shown efficacy by preventing SARS-CoV-2 infection of fibroblasts (VeroE6 cells).56 Currently, there is insufficient evidence to draw a conclusion on benefits of meplazumab for the therapy of COVID-19 patients. In a *preprint* observational Chinese study, hospitalized adults with COVID-19 pneumonia (n=17) who were treated with intravenous infusion of meplazumab, as an add-on therapy, showed a better recovery rate than patients not receiving such treatment (n=11).173 However, this study has a high risk of bias with very low certainty of evidence, being a non-randomized, non-stratified study, with a small sample size and suboptimal reporting of methods and outcomes. Large-scale investigations are needed to assess the effectiveness and safety profile of meplazumab as a potential therapy for COVID-19.

***Is CP therapy a therapeutic option for severe COVID-19 infection?***

CP therapy represents a fruitful approach for COVID-19 treatment. For example, in a trial of 10 severe COVID-19 patients,180 CP therapy was well tolerated and improved the clinical outcomes. The viral load was undetectable after CP transfusion in 7 patients who had viremia. No severe adverse effects were observed. Other clinical trials have shown the beneficial effect of CP therapy in COVID-19 patients, and ongoing clinical trials will inform comprehensively about its efficacy and safety (**Table CP studies**). In that regard, it is unclear whether in patients with a high viral load, such as severely ill patients, CP therapy may drive tissue pathology due to immune complexes or complement activation.

***Do Janus kinase inhibitors represent a therapeutic option for severe COVID-19?***

Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK-STAT signaling inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. These drugs are powerful anti-inflammatory medications that likely reduce the systemic levels of cytokines associated with COVID-19.181 Indeed, in a pilot study of 12 COVID-19 patients, baricitinib limited the CSS and was beneficial for the patients.182

***What is the therapeutic value of ivermectin for treating SARS-CoV-2 infection?***

Ivermectin (avermectin B1a and avermectin B1b) is an FDA-approved anti-parasitic drug that has shown broad-spectrum anti-viral activity *in vitro*. In SARS-CoV-2-infected fibroblasts (Vero-hSLAM cells), a single addition of Ivermectin at 2 h post infection reduced viral RNA ~5000-fold at 48 hours.183 However, plasma concentrations of total and unbound Ivermectin did not reach the IC50 determined *in vitro*, even at a 10-times higher dose than the approved by the FDA.184 Consequently, the likelihood of a successful clinical trial using approved Ivermectin is low.

***What is the evidence that hydroxychloroquine is effective for the treatment, or prophylaxis, of SARS-CoV-2 infection?***

In an observational study of 1,446 COVID-19 patients, 811 received hydroxychloroquine treatment. This study found that hydroxychloroquine treatment did not change the risk of intubation or death.185 Furthemore, in a Brazilian randomized control study evaluating 2 different doses of chloroquine in COVID-19 patients with severe respiratory symptoms, mortality was 2.5 times higher in the high chloroquine arm.186 Pre-published results from US Veterans Health Administration Hospitals did not support any advantages of hydroxychloroquine administered alone or with azithromycin.187 Importantly, the side effects may outweigh benefits as the FDA reports (April 24, 2020) that hydroxychloroquine can produce QT interval prolongation and other heart rhythm problems in some patients.

***What is the evidence for mesenchymal stem cell therapy in COVID-19 patients?***

Mesenchymal stem cells may exert antiviral mechanisms in the context of SARS-CoV-2 infection. The basal IFN-stimulated gene expression of mesenchymal stem cells is high. This enhances MSC responsiveness to IFN signaling, potentially inducing broad viral resistance. Mesenchymal stem cell therapy is being used in some centers but its efficacy in COVID-19 has not been proven. Data available are mainly experimental with few records in humans and no reports on its efficacy in randomized clinical trials.188

***Are common anti-hypertensive drugs useful in the prevention and treatment of COVID-19?***Common anti-hypertensive drugs inhibit ACE, but not ACE2. Importantly, ACE2 opposes ACE actions and lowers blood pressure by converting angiotensin-II (a vasoconstrictor peptide) into its metabolites- angiotensin (1–7) (vasodilators). It was shown in animal models that ACE inhibitors might increase ACE2 expression, thus increasing susceptibility to infection, but it has not been proven in humans.189 Other common related antihypertensive drugs are angiotensin-2 receptors blockers such as angiotensin II receptor, which block AT-1. However, AT-1 is not known to be used by SARS-CoV-2 to infect cells.

***What are the preclinical models available to investigate SARS-CoV-2 infection? Which ones resemble human COVID-19 the most?***

At the moment, the animal model that resembles more closely human COVID-19 is the Rhesus macaque, whose ACE2 receptor is identical to that in humans. This model recently showed that SARS-CoV-2 reinfection was hampered due to infection-acquired immunity and demonstrated the therapeutic effect of remdesivir in COVID-19 prior use in human clinical trials (Bao L 2020; Williamson 2020). The murine ACE2 receptor is different from humans, hence humanized murine models with recombinant human ACE2 are necessary.190

1. ***Vaccine development for COVID-19***

***What are the most advanced vaccine candidates for COVID-19?***

Previous vaccine research for SARS/MERS facilitates rapid translation.191 In the WHO vaccine platform, 110 candidate vaccines are in preclinical evaluation and 8 candidate vaccines are in clinical evaluation for SARS-CoV-2 (Adenovirus Type 5 Vector; LNP-encapsulated mRNA; Inactivated; ChAdOx1; 3 LNP-mRNAs; DNA plasmid vaccine with electroporation) as of May 15, 2020. The Coalition for Epidemic Preparedness Innovations provides dynamic status updates (https://cepi.net).

***The thermal and chemical stability of single-domain antibodies (VHHs) position them as potential therapy for viral infections. Could this approach be applied in COVID-19?***

SARS-CoV, MERS-CoV and SARS-CoV-2 are zoonotic pathogens. SARS-CoV S-directed single-domain antibodies cross-react with SARS-CoV-2S and MERS-CoV. In recent research, immunization of llamas with perfusion-stabilized betacoronavirus S-proteins induced bivalent cross-reactive single-domain camelid antibodies that could neutralize SARS-CoV-2 pseudoviruses. Crystallography has revealed that single-domain antibodies impede viral penetration into cells. The favorable biophysical and potent neutralization properties support the possibility of therapeutic use.192 Human monoclonal antibodies may offer similar neutralization capacity with potential for better tolerability and a longer half-life.193

***Given that SARS-CoV-2 is predominantly a respiratory pathogen, could a nebulized vaccine be more effective in terms of bioavailability and function?***

Single-domain antibodies have been investigated as potential therapeutics for influenza, RSV and HIV in addition to coronaviruses. SARS-CoV-2 mainly targets the respiratory tract, hence the development of vaccines to be delivered to the respiratory epithelia and lung parenchyma using a nebulizer has been considered to maximize bioavailability and function.194 Although active research against respiratory viruses has focused on aerosolized plasmid DNA vaccines, other forms of vaccine administration are currently further advanced in clinical trials.191 Veterinary medicine commonly uses aerosolized coronavirus vaccines for chicken farms.195

***When will a SARS-CoV-2 vaccine be available?***

A new virus, and novel vaccine platforms, necessitate careful evaluation, ideally including toxicology in valid animal models. Early progress towards SARS vaccines has facilitated a “running start” but standards of care and safety must be maintained. Acceleration rather than omission of clinical trials is key. Preliminary data from Oxford University are anticipated mid-2020.191 Of note, a dose-escalation, single-center, open-label, non-randomized, phase 1 was conducted in 108 healthy individuals that received an Ad5 vectored COVID-19 vaccine. The vaccine was tolerable and immunogenic at 28 days post-vaccination. SARS-CoV-2-specific antibodies peaked at day 28 post-vaccination and specific T-cell responses were detected from day 14 post-vaccination.196

1. ***Epidemiology of COVID-19 and environmental factors***

***What are some characteristic aspects of the COVID-19 pandemic?***

An important aspect is that COVID-19-associated mortality is very high, almost unavoidable when the pandemic control fails. This is due to rapid community spread, high community virus, especially in the elderly and co-morbid, but also in younger non-comorbid persons, including healthcare workers, young adults and children. The COVID-19 pandemic also seems to be characterized by a significant number of asymptomatic spread.197-199

***The iceberg of COVID-19: are there asymptomatic cases below the water surface?***

The number of COVID-19 diagnosed patients may represent just the tip of the iceberg. To date, epidemiological studies that provide an accurate idea of asymptomatic cases are scarce.3,4,89 Most of the identified asymptomatic cases are diagnosed by random screening of healthcare workers, and individuals who had been in close contact to COVID-19 cases.48 In addition, there is a high number of asymptomatic individuals who have experienced COVID-19-like symptoms in their clinical histories without any diagnostic tests and hospital admission. Due to the nature of this disease, it is very difficult to identify asymptomatic virus carriers, which will be one of the reasons for difficulties in the containment of the pandemic.4 The real percentage of asymptomatic individuals and how long they carry the virus is unknown. Large screening studies for virus-specific IgM, IgG and IgA will be a decisive factor in controlling the pandemic, as it is the main indicator of the development of population immunity.

***What are the reasons for striking differences in the COVID-19 infection rate among countries with similar climate, lifestyle and location at similar latitude?***

The differences are almost entirely due to timing and effectiveness of public health interventions. Countries that failed to control did too little, too late, and allowed SARS-CoV-2 to rip through their population, with catastrophic outcomes. Those that intervened early and effectively stopped transmission very effectively.200

***What is the basic reproduction number (R0) of SARS-CoV-2?***

It is difficult to determine as it varies greatly from country to country, depending on how well countries control their epidemics with widespread testing, case isolation and vigorous contact tracing, testing and isolation if positive. In countries that do this well, the R0 can be very low indeed. In countries that fail to control the R0 is high but unknown as SARS-CoV-2 spreads untested and therefore undetected. It has been estimated to be ~2.2.201

***What differentiates the previous epidemiological distribution of SARS- CoV-1 and MERS-CoV to the current SARS-CoV-2?***

SARS-CoV-2 transmits more readily than either SARS-CoV or MERS-CoV. The R0 of SARS-CoV-2 is controversial, but if left unchecked, it would be likely greater than 3-4. However, the R0 number cannot be precisely defined as no country has left it to spread completely unchecked. In any case, even when checked, the R0 of SARS-CoV-2 is higher than that of SARS-CoV (1.7-1.9) and MERS-CoV (<1).202 There is a considerable frequency of very mild COVID-19 patients as well as asymptomatic SARS-CoV-2-infected people. This makes transmission control more challenging than either SARS-CoV or MERS-CoV, where illness is frequently more severe.

***Are children at risk of SARS-CoV-2 infection?***

Children are at low risk of severe COVID-19 outcomes.203,204 Most patients in pediatric age with SARS-CoV2 infection presented with no or mild clinical manifestations, including fever, fatigue and dry cough. They were typically managed with supportive treatments only and they had generally a favorable prognosis with a recovery within 2 weeks.205,206

***Are children involved in SARS-CoV-2 transmission?***

Many children remain asymptomatic, even when they have radiologic pneumonia detected on screening.203 Given that children are effective transmitters of other respiratory viruses,207 it is expected that they will be just as good at transmitting SARS-CoV-2.

***Which animals in the nature have been so far shown to get infected with SARS-CoV-2?***

Bats are likely the natural reservoir of SARS-CoV-2. In addition, related coronaviruses have been identified in Malayan pangolins, which are considered as an intermediate host between bats and humans. SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but ferrets, cats and Rhesus macaques are permissive to infection.208

***What demographic factors are associated with severe COVID-19?***

Data on the characteristics of severe COVID-19 patients are uniformly showing a correlation with age. According to CDC National Vital Statistic System on COVID-19 fatal outcomes, death rate doubles with each decade after 45 years (National Vital Statistics System). Comorbidities have also been associated with more severe disease. In Italy209 and China210 hypertension (OR 2.36), chronic respiratory disease (OR 2.46), cardiovascular disease (OR 3.42) and diabetes (OR 2.05) show a positive correlation with severity. Gender and ethnicity have also been shown to impact COVID-19 severity (**see below**).

***Does ethnicity influence the prevalence of SARS-CoV-2 infection?***

Data on ethnicity and COVID-19 are scarce and further research on ethnicity and COVID-19 outcomes is clearly needed.211 However, the data available show a disproportionate number of COVID-19 deaths in Black, Asian and minority ethnic backgrounds. In fact, one third of UK ICU admissions are reportedly from them.212 In the USA, African Americans had more COVID-19 diagnoses and deaths, after adjusting for age, poverty, comorbidities, and epidemic duration. These disparities are also seen in the Hispanic and Asian communities.213

***Are pregnant women at risk of COVID-19 infection?***

Pregnant women may be at risk of bad COVID-19 outcomes because they have deficient IFN-α and IFN-λ responses to viral infections.214 However, reported pregnancy outcomes in COVID-19 are reassuring as maternal outcomes appear similar to non-pregnant adult females.215

***Are there specific treatments for pregnant women in case of severe COVID-19?***

Testing treatments is problematic because pregnant women are excluded from most trials.216 It is known that azithromycin doubles innate IFN production from virus-infected lung cells.217 It is safe for all trimesters of pregnancy218 and has been shown effective in high quality clinical trials of virus-induced lung disease.219,220

***Are males at a greater risk of SARS-CoV-2 infection?***

Males seem to have less potent innate antiviral responses as compared to female counterparts.221 As a consequence, outcomes in COVID-19 are much worse (~1.5-4 times worse) in terms of mortality, ICU admissions, hospitalisations91,222,223 and case identifications224 for males than for females. Mortality in females is lower by 30% up to age 60, then it levels off between sexes (National Vital Statistics System).

***How long will it take to generate robust and reliable data on COVID-19 prevalence?***

There is reasonably robust data of COVID-19 deaths in hospitals because most people who die in hospital are tested. Deaths outside hospitals are likely underestimated, as people dying in care homes, where mortality approaches ~40%,225 may die without being tested and diagnosed. It is difficult to determine prevalence as testing practices vary so much from country to country. Seroprevalence studies will help to collect these data.

***Is COVID-19 prevalence higher in industrialized countries?***

COVID-19 was introduced early to many industrialized countries as a result of air travel. Most of Europe and the USA probably did not react in a timely and efficient manner, resulting in rapid spread and high mortality. In light of the devastating situation in many European countries and USA states, less industrialized countries prepared better to control the pandemic.226 An important factor for prevalence studies is the percentage of the population that has undergone a diagnostic test, which seems to be at low levels in developing countries.

***Will the summer weather decrease SARS-CoV-2 spread?***

Respiratory viruses spread less readily in summer than in winter for reasons that are not well understood. Dry air and higher temperatures are slowing down the spread of respiratory viruses. Absence of school attendance, more time outdoors, greater household ventilation, warmer temperatures facilitating virus inactivation and higher vitamin D levels all likely play a part. Although social distancing measures are being applied with SARS-CoV-2, the summer should play a role in hampering spread. However, based on the analogy of previous influenza pandemics, it is unlikely that summer, on its own, could stop transmission of a new virus.227,228

***Is a second wave of COVID-19 expected to occur?***

It largely depends on the SARS-CoV-2 seroprevalence developed in each country, which is still awaited. Countries that have had widespread transmission may get second waves, but less severe. In contrast, countries that effectively controlled the pandemic are at high risk of major second waves if those controls are relaxed, because they have not had widespread transmission and active immunization is not available.

***What is the evidence suggesting that SARS-CoV-2 could become a seasonal infection rather than a transient pandemic?***

SARS-CoV-2 has spread worldwide in humans, causing mild or no disease in most cases. It is very likely that it will continue circulating as other human coronaviruses do (229E, HKU1, NL63, OC43), and it may well become an endemic, seasonal virus.229

***What is the most efficient strategy to prevent SARS-CoV-2 infection?***

The main route of SARS-CoV-2 transmission is via respiratory droplets and aerosols.230-232 Avoidance of high virus loads, acquired through aerosol and droplet transmission, is paramount to prevent severe outcomes. Consequently, social distancing, mask and hand sanitation are undoubtedly effective because they prevent the droplet-and surface contact-associated initial high virus load and the increased risk of severe disease.233,234 If social distancing is combined with widespread testing, case isolation, vigorous contact tracing and personal protection, it should control the COVID-19 pandemic. Indeed, severe and critical illness among Chinese health care workers before January 10th (when personal protection was likely not in place) was 45%. In contrast, after February 1st (when personal protection measures were in place), this dropped to 8.7%.235

***What is the relative risk to contract SARS-CoV-2 infection through surfaces?***

SARS-CoV-2 remained viable in aerosols throughout a 3 hour duration in one experiment, with a ~10-fold reduction in infectious titre.236 SARS-CoV-2 was more stable on plastic and stainless steel than on copper and cardboard; viable virus was detected up to 3 days after application to plastic and 2 days to stainless steel, on each surface the virus titer was reduced nearly ~100-fold.236 Therefore, it is convenient to minimize contact with surfaces touched by others (even before SARS-CoV-2 existed), for example when using public transportation.

***What is the duration of viral shedding?***

In 248 COVİD-19 patients, the estimated median time from symptom onset to viral clearance in the nasal swabs was 11 days, while in asymptomatic cases it was 2 days.237 In patients that recovered, the median duration of viral shedding was ⁓20 days, while in non-survivors it was detected until death. The longest duration of viral shedding in survivors was 37 days.91 In addition, non-SARS-CoVs have been shown to be carried in the human respiratory tract without any current infection;238 this type of carrier may serve as a silent reservoir of SARS-CoV-2, thus contributing to its transmission.

***Do some COVID-19 patients act as “superspreaders”?***

The individual variation in the transmission of an infection is described by a factor called “dispersion factor or *k*”. The lower the value of “*k”* is, the more transmission comes from a small proportion of individuals acting like superspreaders. Superspreading clusters have been observed in past coronavirus outbreaks (SARS/MERS), where a small number of infected individuals was responsible for a large proportion of secondary transmissions, with an estimated “*k”* of about 0.16 for SARS and 0.25 for MERS.239 It is unclear whether superspreading clusters have contributed to COVID-19 outbreak. A simulation of early outbreak trajectories estimated that “*k*” for COVID-19 is higher than for SARS and MERS.239 However, in a recent preprint study, the estimate of “*k*” for SARS-CoV-2 was around 0.1, suggesting that around 10% of infected patients may have been responsible for 80% of secondary transmissions.240 Individual variation in infectiousness is difficult to measure, as it is mostly empirical, but the identification of any SARS-CoV-2 superspreading will be of primary importance for pandemic control.

***Are COVID-19-dedicated hospitals useful to limit SARS-CoV-2 infections and optimize the healthcare resources during the COVID-19 pandemic?***

Designation of COVID-19-dedicated wards and personnel within hospitals is useful to limit nosocomial SARS-CoV-2 infections. It also allows other non-COVID-19 conditions to be treated using normal healthcare resources more safely. Maintaining such separation requires intensive SARS-CoV-2 testing in view of the high asymptomatic infection rate.241

***Is a community-based strategy more effective, in comparison to a hospital-based one, to limit SARS-CoV-2 infections and optimize healthcare resources during the COVID-19 pandemic?***

Community based strategies are clearly effective at controlling transmission of SARS-CoV-2. Australia, Hong Kong, Japan, Singapore, South Korea, and New Zealand have all controlled effectively. Their cumulative COVID-19 mortality is >100-fold less than that in France, Italy, Spain and the UK, countries which have shown failure to adequately control the pandemic.242,243

***May the elimination of the live animal market reduce the risk of future viral outbreaks?***

Closing live animal markets is likely to reduce the risk of future viral outbreaks although this is not a practical way, for multiple reasons including social and economic, to prevent viral outbreaks.

***Are new technologies (geolocation, phone apps, etc.) useful to track people during quarantine?***

This is an evolving area with a rapidly expanding interest. Many countries around the world are considering or are developing mobile phone apps capable of supporting rapid contact tracing as well as supporting and monitoring social distancing.244 Their usefulness is yet to be proven, and there are privacy and ethical considerations that require careful planning.245

***What kind of lifestyle factors play a role in the COVID-19 pandemic?***

Lifestyle factors that may influence SARS-CoV-2 infection susceptibility and COVID-19 severity include smoking, stress, diet and alcohol intake, among others. For example, smoking has been shown to increase the susceptibility to respiratory tract infections and its severity,246 and it is a risk factor for severe COVID-19.247 Moreover, alcohol consumption may impair anti-viral immunity;248 *in vitro* studies with human monocytes have shown that both acute and prolonged alcohol exposures inhibit type I IFN induction on Toll-like receptor-8 and -4 stimulation249. Dietary habits may also play a role as obese patients have been shown to have a higher risk of developing severe COVID-19.250 Furthermore, there are bioactive food compounds with antiviral activity, such as resveratrol,251 although the amount of them obtained through the diet is unlikely to play a relevant role in COVID-19.

***Could the higher cleaning and disinfectant exposure during the pandemic increase the allergy prevalence in the general population?***

It is well-established that epithelial barrier defects and/or damage favor the development of Th2 immunity.252,253 Increased hygiene, in general, as well as overexposure to epithelial barrier opening molecules, such as detergents, can promote the onset of allergic disease.254 To date, there is no evidence linking the COVID-19 protective measures (gloves, often use hand-sanitizers, *etc.*) with increased allergy prevalence. In that regard, multifactorial epidemiological studies are needed. These studies should consider the impact on allergic disease of virus-specific type 1 responses and psychosocial and environmental changes caused by the pandemic and efforts to content it.

***The COVID-19 pandemic has reduced fossil fuels and environmental pollution. Could this change the exposome in the long term and alter the cause of allergic and other respiratory diseases?***

Although a significant change in pollution parameters occurred, unfortunately this reduction in pollution is transient and consequently unlikely to be significant. The exposome-related allergy and asthma risk is multifactorial. It includes climate change, biodiversity, the microbiome and nutrition among others, which have not changed during the pandemic.255 In addition, although pollution levels have dropped, climate change still occurs at an accelerated pace. Lifestyle changes during lockdown256 with weight gain and increased exposure to indoor allergens and pollutants may even increase the incidence in the long-run.

**Conclusion**

With the rapid spread of COVID-19 at pandemic sizes, we were overwhelmed and drowned with a pollution of information even unfortunately coming from worldwide political leaders. A worldwide fight to content the pandemic has started in which, we needed international solidarity and prompt sharing of accurate scientific information. We strongly support the implementation of an open data concept for all COVID-19 and SARS-CoV-2 studies, which should be performed with full transparency. A global strategy to reduce the burden of COVID-19 must be established. It is well known that these action plans can only be successful by the combination of efforts of all stakeholders: WHO, governments, researchers, physicians, patient organizations, economists, pharmacists, industry, and policy makers. Our Academy, the EAACI has immediately taken action on developing and disseminating knowledge and developing statements43,102,109,146 on how to handle allergy and asthma patients. It is now needed that global and regional COVID-19 guidelines on all aspect of this disease should be developed and implemented.

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**Authorship**

**Tables**

**Table X. Recommendations for AIT during COVID-19 pandemic (Based on EAACI-ARIA guideline)**

|  |  |
| --- | --- |
| Continue SCIT or SLIT: | Non-infected individuals   * Asymptomatic patient without suspicion for SARS-CoV-2 infection and/or contact to SARS-CoV-2 positive individuals   Patients recovered after COVID-19 infection   * Patient with negative test result (RT-PCR) * Patient after an adequate quarantine * Patient with serum IgG to SARS-CoV 2 without virus-specific IgM. |
| Stop SCIT or SLIT | * Symptomatic patients with exposure or contact to SARS-CoV-2 positive individuals * Patients with positive test results (RT-PCR). |

AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; RT-PCR, real time polymerase chain reaction.

**Table X**: Convalescent plasma studies in Covid-19 patients as of 21thMay 2020

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Subjects | Design | Dose | Outcomes |
| Duan K, *et al.180*    China | 10  Severe disease, ICU no MV | Pilot study, single center. Compared to historic control group. | 200 ml CP with neutralizing antibody titers >1:640 | Increase in neutralizing antibodies. Improvement of symptoms Increase in oxyhemoglobin saturation at d3 d. Decrease CRP. No severe side effects. Reduction of deaths compared to historic control (p 0.001) |
| Shen C, *et al.257*    China | 5  Critical disease, all in ICU + MV | Uncontrolled Case series, single center. | 400 ml CP with titer > 1:1000 and neutralizing antibody titer >40 | 4/5: ARDS resolved within 12d  5/5: Pao2/Fio2 increased within 12 days  5/5: SARS-CoV-2 RNA load negative at d12  3/5: discharged from hospital at date of publication (51-55 d post infusion) |
| Zhang B, *et al.258*    China | 4  Critical disease, ICU + MV | Uncontrolled Case series | 200- 400 ml CP  (does not specify neutralizing antibody titer) | 4/4 clinical improvement and able to extubate  3/4 discharged from hospital at date of publication (24-33 d post infusion) |
| Ahn JY, *et al.259*    South Korea | 2  Critical disease, ICU + MV | Case series | 250ml, 2 doses 12h apart, (does not specify neutralizing antibody titer) | Radiological and clinical improvement  Decrease in viral load. |
| Ye M, *et al.260*    China | 6  Non-critically ill | Case series | 200- 600 ml CP  (does not specify neutralizing antibody titer) | Radiological and clinical improvement |
| Zeng QL *et al.261*    China | 21 ICU patients    6: active CP  15: controls | Case series Non-randomized. Controls did not have a match for CP | 200- 400 ml CP  (does not specify neutralizing antibody titer) | Increase in viral clearance in the CP vs. controls. [CP 5/5, Controls 3/14 (p 0.005)]  Increase survival period in CP patients (p 0.029) but there was  high mortality in both groups, [CP 5/6, controls 14/15] |
| Schulman K. (PI)    USA | Estimated enrollment: 206 patients visiting the ED. | Phase 2 trial. Randomized, double blinded, controlled. CP vs. placebo in adults with COVID-19 in an ED. | 200-600 ml CP with neutralizing antibody titers >1:80 | Stanford University.  Ongoing  NCT04355767 |
| Shoham S. (PI)    USA | Estimated enrollment: 150 subjects exposed to COVID-19. | Phase 2 trial. Randomized, triple blinded, controlled. CP vs. placebo. Adults in close contact exposure to a person with COVID-19 within 96h of enrollment (and 120h of receipt of plasma). | 200 ml CP with neutralizing antibody titers >1:64 | Johns Hopkins University.  Ongoing  NCT04323800 |
| Perotti C. (PI)    Italy | Estimated enrollment: 46 COVID-19 patients with moderate-severe ARDS for < 10 days and need for MV | Longitudinal non-randomized non-controlled | 250-300 mL of CP 3 times/d over 5 days  (neutralizing antibody titer not specified) | Foundation IRCCS San Matteo Hospital    Ongoing    NCT04321421 |
| Menichetti F. (PI)    Italy | Estimated enrollment: 126 COVID-19 patients hospitalized due to pneumonia with PaO2/FiO2 ratio 200-350 but not in MV | Phase 2 Trial. Multicenter prospective randomized open-label trial (CP vs standard therapy | 200 mL of CP  (neutralizing antibody titer not specified) | Azienda Ospedaliero, Universitaria Pisana    Ongoing    NCT04393727 |

**ARDS**, Acute respiratory distress syndrome; **CP**, Convalescent plasma; **CRP**, C- reactive protein; **d**, days; **ED**, Emergency department; **h**, hours; **ICU**, Intensive Care Unit; **PI**, Principal investigator; **MV**, mechanical ventilation.

**Table X.** The percentage of lymphocytes is decisive for prognosis at the first and second visits. Adapted from Azkur *et al*.48



**Figure Legends**

**Figure 1**. SARS-CoV-2 attachment, internalization and replication cycle in epithelial cells and the main effect of antiviral agents. Attachment of SARS-CoV-2 spike protein (S) to angiotensin-converting enzyme 2 (ACE2) mediates endocytosis of the virus into the host cell. The cell entry of the virus depends on both the binding of viral S proteins to cellular receptors and priming S protein by the serine protease transmembrane protease / serine (TMPRSS) 2. Cepharanthine / human recombinant ACE2 and camostat mesylate are the viral entry inhibitors, which prevent the binding of S protein to ACE2 and priming, respectively. In uncoating stage, virions are internalized by receptor-mediated endocytosis that the low pH in the endosome triggers the fusion of viral and endosomal membranes and the ssRNA (+) viral genome is released into the cytoplasm. Arbidol, chloroquine, hydroxychloroquine, mefloquine block this uncoating stage. Transcription of the viral genome and proteolytic cleavage of the replicase polyprotein and resulting translating proteins are processed into the viral RNA-dependent RNA polymerase (RdRp). Lopinavir, ritonavir, remdesivir and favipiravir prevent proteolysis and activity of RdRb. Non-structural and structural proteins, including nucleocapsid proteins are expressed as sub-genomic RNAs. Salemectin and resveratrol may inhibit viral helicase activity, viral mRNA synthesis, and the expressing of nucleocapsid proteins. Assembly and budding of viral proteins and nucleocapsid occur at membranes of the endoplasmic reticulum (ER), the ER-Golgi intermediate compartment (ERGIC), and/or the Golgi complex. Selamectin may inhibit viral assembly via impede to viral cargo. New SARS-CoV-2 virions released by exocytosis.

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