The role of the allergist/immunologist in the COVID-19 pandemic: A Janus-faced presentation

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ABSTRACT

Background: *Following its initial description in December 2019 in Wuhan, China, coronavirus-2 (COVID-19) has rapidly progressed into a worldwide pandemic, affecting millions of lives. Although every specialty of medicine has been affected, the field of allergy/immunology holds a special place in the battle against this modern-day plague. Because of the specialized training in allergy and clinical immunology, and the familiarity with comorbid contributing conditions, the allergist/immunologist is uniquely poised to play a major role both in the delivery of specialized therapeutic procedures and practices that can improve the health of patients with COVID-19 as well as in the use of forthcoming vaccines for the prevention of its spread.*

Objective: *The purpose of this report is to examine the current body of evidence supporting the two phases of infection and inflammation that influence the pathogenesis of COVID-19 and to provide a classification of COVID-19 disease presentations and potential therapeutic targets with which the allergist/immunologist has particular expertise.*

Methods: *This article was based on a literature review of articles published in PubMed related to COVID-19 and the immune response, and the author's own research and clinical experiences in the field of immunology.*

Results: *Currently, the management of COVID-19 disease is being directed by a preventive strategy based on social distancing, quarantine, and facemasks to reduce the spread of the virus. Numerous clinical trials are being initiated to identify effective treatments for COVID-19 and are directed toward treatment of the two phases of infection and inflammation that influence the pathogenesis of COVID-19. An important resource for the allergist/immunologist is the COVID-19 Treatment Guidelines Panel (COVID-19 TGP), a National Institutes of Health sponsored panel of U.S. physicians, statisticians, and other experts, which has developed a set of continuously updated treatment guidelines intended for clinicians caring for patients during the rapidly evolving COVID-19 pandemic.*

Conclusion: *COVID-19 is unique among other infectious diseases because, in many cases, the host immune inflammatory response can cause greater harm to the individual who is infected than the pathogen itself. In this report, the pathogenesis of COVID-19 and the influence it has on COVID-19 presentations is reviewed, together with recommended potential therapeutic targets and treatment recommendations.*

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There can be no better opportunity to highlight "Immunologic advances that allergists need to know," the subject originally assigned to me for presentation at this year's Eastern Allergy Conference, than to focus on the immune response to COVID-19 and "The role of the allergist-immunologist in the COVID-19 pandemic." The global spread of the coronavirus-2 (severe acute respiratory syndrome coronavirus [SARS-CoV] 2), named COVID-19, has led to a devastation of social, economic, and health care systems, with a disruptive ripple effect on every aspect of human life, with dimensions not witnessed with any infectious disease in more than a century.[1] The pandemic has radically changed health priorities and has placed the health care systems of many countries under unprecedented stress. This has resulted in a disruption of health care systems and a reassessment of health delivery priorities by health care providers. Although every specialty of medicine has been affected, the field of allergy/immunology holds a special place in the battle against this modern-day plague. Because of the specialized training in allergy and clinical immunology, and the familiarity with comorbid conditions, such as asthma, chronic respiratory conditions, and immune deficiency disorders that place patients at increased risk for severe illness, the allergist/immunologist is uniquely poised to play a major role in the delivery of specialized procedures and practices that can improve the health of patients with COVID-19.[2,3] The goal of this presentation was to examine the current body of evidence that supports the two phases, infection and inflammation, that influence the pathogenesis of COVID-19 and to provide a classification of COVID-19

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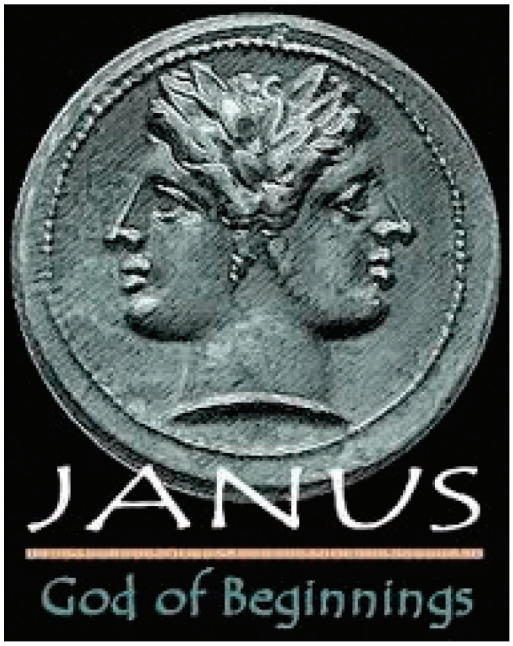

Figure 1. *Janus the Roman god of beginnings, gates, transitions, time, doorways, passages, and endings. He is usually depicted as having two faces because he looks both to the future and to the past.*

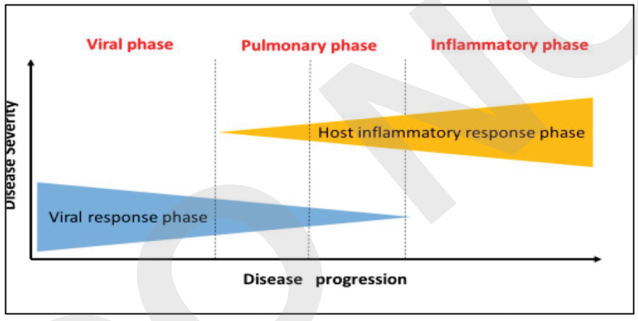

Figure 2. *Schematic representation of the two phases of coronavirus-2 (COVID-19) (modified and reproduced with permission from Ref. 4).*

states and potential therapeutic targets with which the allergist/immunologist has particular expertise.

THE PATHOGENESIS OF COVID-19: A "JANUS-FACED DISEASE OF TWO FACES": VIRAL INFECTION AND INFLAMMATION

In ancient Rome, Janus was the god of beginnings, gates, transitions, time, doorways, passages, and endings. He is usually depicted as having two faces because he looks both to the future and to the past (Fig. 1). In an analogous fashion, there are two distinct but overlapping pathologic faces of COVID-19, the first triggered by the virus itself and the second by the host immune response (Fig. 2).[4] This Janus-faced polarity of two disease phases sets the stage both for a discussion of the pathogenesis of COVID-19 and a basis for classification of related disease states and potential therapeutic targets.[5]

Viral Factors

Shown in Fig. 3 are the viral factors that initiate COVID-19. Bats are the reservoir of a wide variety of coronaviruses, including SARS-CoV like viruses.[6] COVID-19 is thought to originate from bats or other unknown intermediate hosts that cross the species barrier into humans. The virus-host interactions that affect viral entry and replication are shown in the upper panel of Fig. 3. COVID-19 is an enveloped positive single-stranded RNA coronavirus. Two-thirds of the viral RNA is located mainly in the first open reading frame (1a/b) and encodes 16 nonstructural proteins. The remaining part of the viral genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, together with several accessory proteins. The spike S glycoprotein is thought to be the main constituent that binds to angiotensin-converting enzyme 2 (ACE2) host cell receptors, which is a critical step for viral entry and an optimal target for therapy and prevention. The role that the other viral components that facilitate membrane invagination and endocytic entry of COVID-19 into the host cell and the role they play in pathogenesis is currently are under investigation.[6]

Host Factors

The host factors that influence susceptibility to infection with COVID-19 and disease progression are shown in the lower panel of Fig. 3.[6] Individuals who are more susceptible to severe disease include the elderly (>65 years of age) and those with underlying health conditions that place them at increased risk for severe illness, such as hypertension, chronic obstructive pulmonary disease, diabetes, cardiovascular disease, and immune deficiency disorders.[7] COVID-19 in individuals with these predisposing factors progresses to the most serious sequelae of infection, consisting of acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, coagulation dysfunction with hypercoagulability and thrombus formation, and multiple organ failure.

A JANUS TALE OF THE MANY FACES OF THE IMMUNE RESPONSE TO COVID-19: AN IMMUNOLOGIC IMBALANCE OF PRO- VERSUS ANTI-IMMUNOLOGIC IMMUNITY

The immune responses to COVID-19 is a source of profound complexity that involves components of both the innate and adaptive immune systems with both beneficial and detrimental rarely seen in other infectious disease.[8] Despite current limitations in treatment options for COVID-19, it is of value to draw on knowledge from

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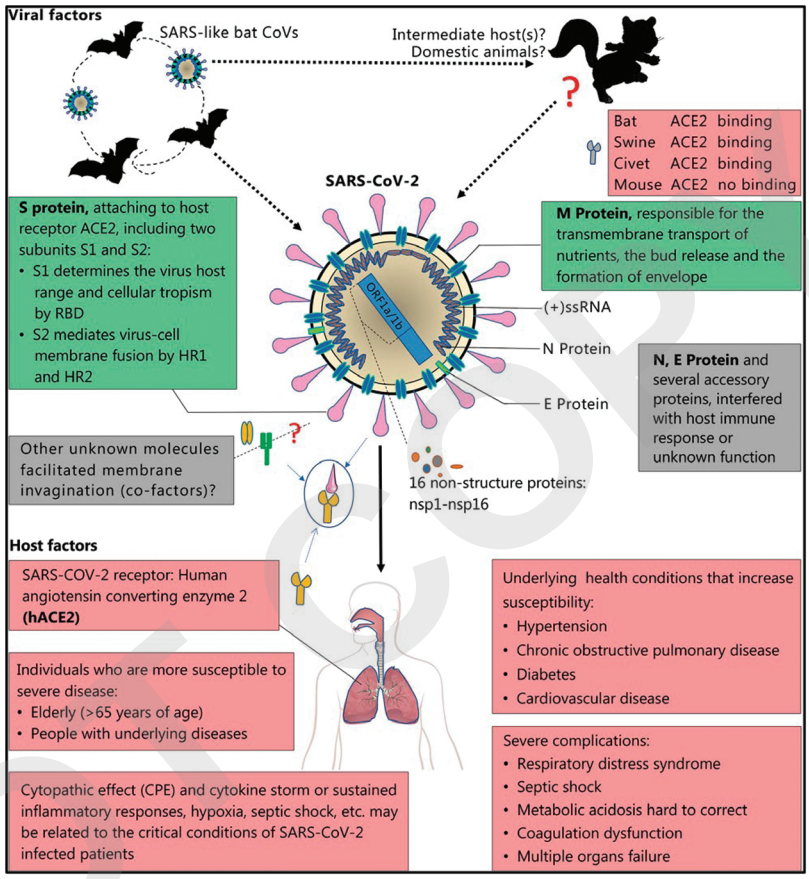

Figure 3. *Viral and host factors that influence the pathogenesis of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] (reproduced with permission from Ref. 6).*

years of fundamental research in viral immunology to gain an understanding of how elements of both innate and adaptive immune mechanisms can be involved in measures to treat and, ultimately, prevent this and future viral pandemics. In 1971, we put forth a hypothesis describing immunologic phenomena as an array of potential responses of the host concerned with the recognition and elimination of foreign substances and in which the immunologic mechanisms that are stimulated are dependent on both the degree and persistence as well as the efficiency of elimination of the foreign agent.[9] The hypothesis that was published in 1971 is provided in full in the Online Supplemental A, Table S1.

The hypothesis has been recently updated to include the most current components of the immune system and is shown in Fig. 4.[10] This framework lays down both a foundation for a discussion of the Janus-faced biphasic beneficial and/or detrimental responses of the innate and adaptive immune responses to COVID-19 as well as a basis for a current understanding of the fluctuating clinical course of the disease and for potential strategies for therapeutic intervention.

The primary response to COVID-19 is carried out by cells of the innate immune system, to counter a foreign configuration and include the functions of phagocytosis and inflammation (Fig. 4). Housed within the innate immune system are macrophages, neutrophils, mast cells and basophils, natural killer cells, innate lymphoid cells, and dendritic cells as well the biologic amplification systems of complement and the coagulation system.[10] All of these components are activated as part of the host's inflammatory response in COVID-19 and are responsible for many of the clinical and laboratory findings seen during initial phases of infection (*e.g.,* fever, anemia, thrombocytopenia, neutropenia, hyperferritinemia, hypercoagulopathy, elevated fibrinogen, D-dimer levels). During this initial phase of viral entry into and attachment of the virus to ACE2 receptors of cells in the host respiratory system, destruction of lung cells triggers a local immune response, recruiting macrophages and monocytes that respond to the infection, release cytokines, and prime the immune system for encounter with the second phase of the adaptive immune encounter with T and B cells (Fig. 5). Usually, in 80% of cases, this encounter with cells of the innate and immune system is capable of resolving the infection. However, in some cases, a dysfunctional immune response occurs, in which virus persistence leads to the third phase of the immune response in which the encounter is no longer beneficial and is associated with excessive release of proinflammatory cytokines and local and systemic tissue injury referred to as the cytokine storm (Fig. 4).

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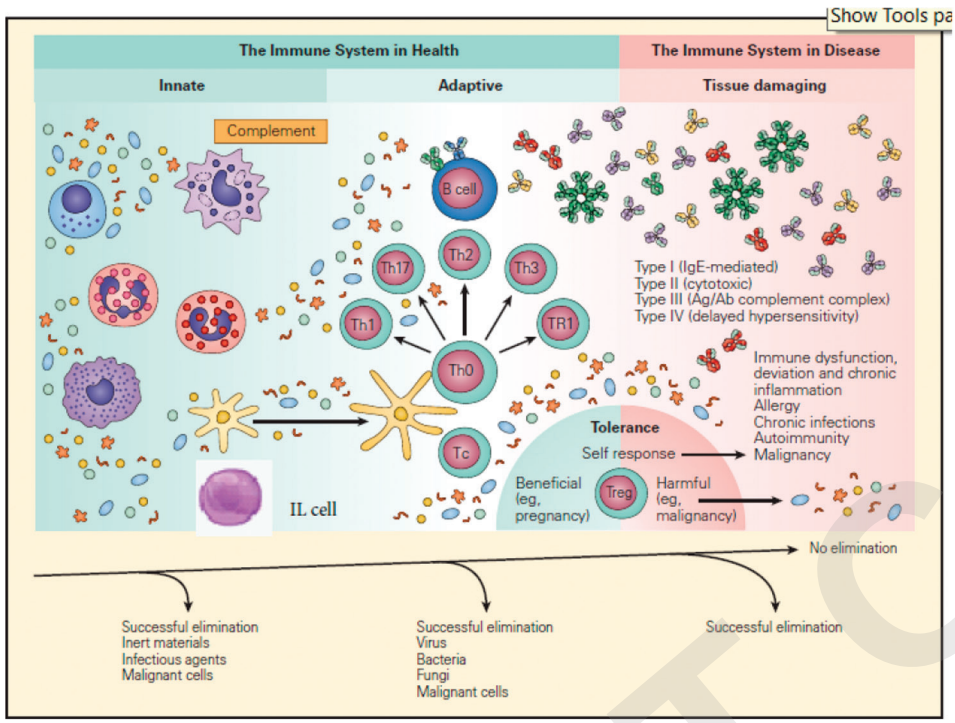

Figure 4. *Schematic representation of the total immune capability of the host based on efficiency of elimination of foreign matter. (reproduced with permission from Ref. 10).*

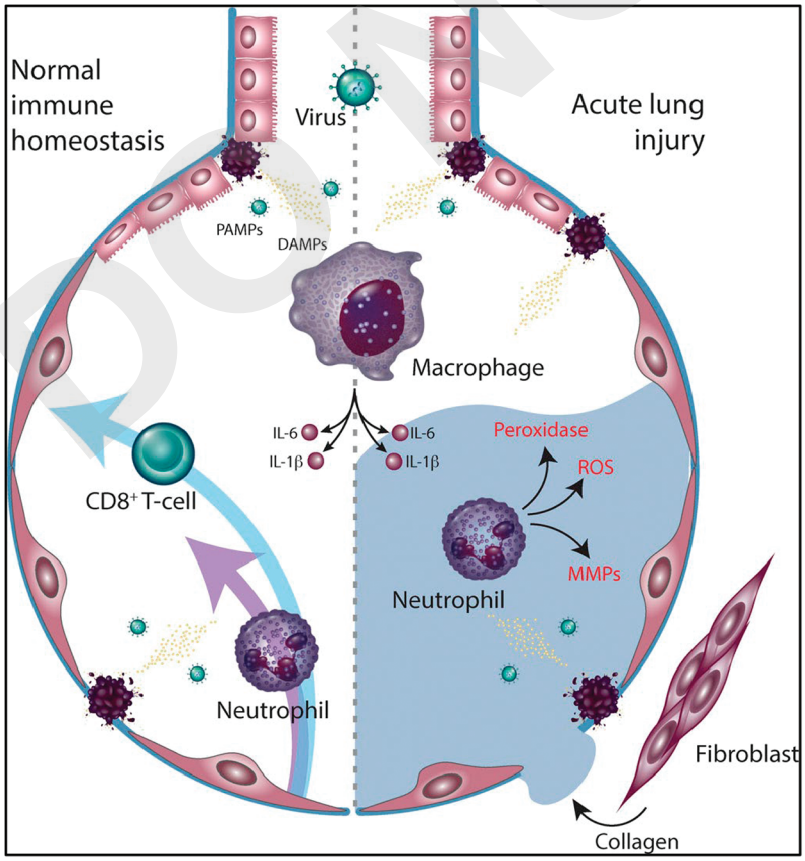

Figure 5. *Innate immune regulation of antiviral defense and tissue toxicity. Virally derived Damage-Associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs) activate tissue-resident macrophages. (reproduced with permission from Ref. 5). Downstream production of interleukin (IL) 6 and IL-1β recruit neutrophils and CD8⁺ T cells, which control viral growth* (left) *but also induce tissue damage, leading to alveolar flooding and fibrosis* (right). *MMP = matrix metalloproteases. ROS = reactive oxygen species.*

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Table 1 **Immune response to coronavirus-2 (COVID-19)*#**

Component	Function	Cell components
Innate immune response	Beneficial: viral control	Macrophages, monocytes, neutrophils, mast cells, basophils, natural killer cells, innate lymphoid cells and dendritic cells
Adaptive immune response	Beneficial: viral clearance	T cells; CD4 helper B cell function; CD8 cytotoxic function; B cells; antibody formation to key viral proteins, *e.g.*, the spike S glycoprotein.
Tissue damaging aspects of the immune response	Deleterious tissue injury	Cytokine storm with production of proinflammatory cytokine from macrophages and T cells

**Future protection induced by natural infection or vaccination relies on memory T cells and production of neutralizing antibodies by B Cells.*

Shown in Table 1 are some of the beneficial and deleterious elements of the innate and adaptive immune systems that participate in the immune responses to COVID-19. The initial control of COVID-19 is carried out by cells of the innate immune system that use a variety of molecular sensing receptors expressed on their cell membranes, *e.g.*, Pattern Recognition Receptors (PRRs), that detect Pathogen-Associated Molecular Patterns (PAMPs) expressed by the virus (Fig. 3). Subsequent viral clearance is mediated by the adaptive immune system carried out by T-cell responses that provide CD4 helper and CD8 cytotoxic functions, and B cell responses that lead to the formation of antibodies formed to key viral proteins, *e.g.*, the spike S glycoprotein. Classically, immunoglobulin M (IgM) antibody is produced first followed by IgG after B-cell class switching with T-cell help (Fig. 6).

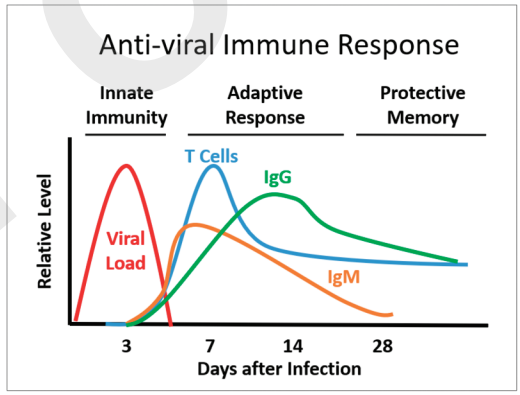

Figure 6. *Antiviral immune responses to coronavirus-2 (COVID-19). Sequential appearance of viral load, T cells and immunoglobulin M (IgM) and IgG antibody responses (kindly provided by Stuart Weisberg, M.D., Ph.D.).*

THE COVID-19 INFLECTION POINT OF ILLNESS

During COVID-19, elements of both the innate and the adaptive immune systems participate; first, with involvement of the innate immune system, followed by the adaptive immune response. Approximately 80% of patients infected with COVID-19 may be either asymptomatic or manifest active disease with fever and flu-like symptoms but will not express the cytokine storm and will have a relatively successful recovery. Shown in Fig. 7 is a schematic representation of the clinical course of illness for up to 20% of individuals with COVID-19 who will express clinical disease with fever and flu-like symptoms, and who will have the potential to develop the cytokine storm. As suggested by Chatham and Cron,[11] somewhere between 3 and 5 days after the onset of symptoms, some patients will actually feel somewhat better but will then reach an inflection point where two possibilities exist. A subset of patients can progress to a cytokine storm, with severe symptoms of respiratory distress and severity of illness, requiring hospitalization and oxygen requirements, and another subset in which the clinical trajectory can possibly be deflected with appropriate antiviral and anti-inflammatory therapy. Herein lies the challenge for the treatment of COVID-19; determination of what are the appropriate antiviral and anti-inflammatory therapies, and when should they be used is particularly important. As we shall see, some medications, such as the corticosteroids, which are beneficial in certain stages of the disease, can be harmful in other stages. The same is true with cytokine and anticytokine interventions, as cited in a very prescient article by Jamilloux *et al.*[12] with regard to cytokine and anticytokine interventions, entitled, "Should we stimulate or suppress immune responses in COVID-19?"

Cytokine Storm and Clinical Sequelae of COVID-19

One of the most serious immunologic sequelae of COVID-19 is the development of the cytokine storm,

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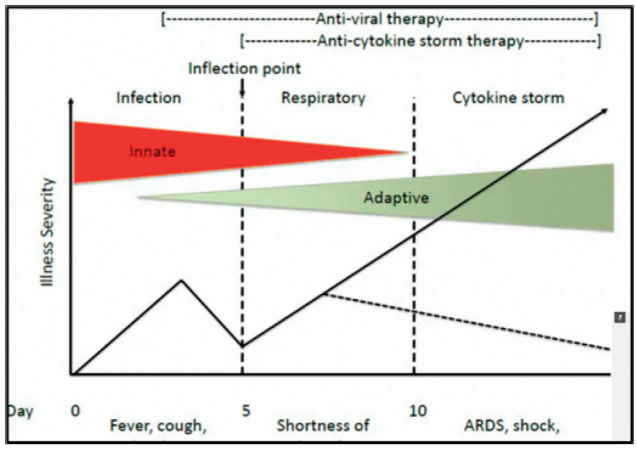

Figure 7. The coronavirus-2 (COVID19) Inflection Point of Illness2 (reproduced with permission from Ref. 11). A graphic depiction of the course of illness, for the up to 20% of individuals with COVID-19 who develop a cytokine storm syndrome (CSS) and respiratory distress that requires hospitalization, presents severity of illness along the Y-axis and time in days along the X-axis. ARDS = Acute respiratory distress syndrome; MODS = multiorgan dysfunction syndrome.

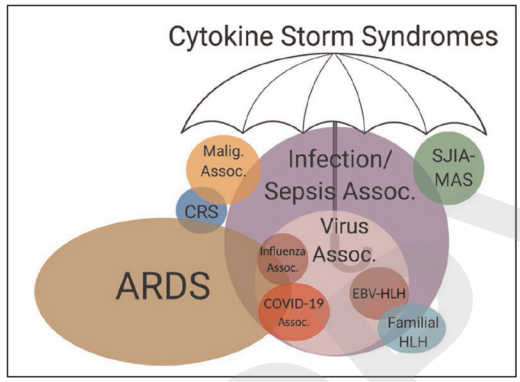

Figure 8. The family of conditions characterized by cytokine storm (reproduced with permission from Ref. 16). Malig. = Malignancy; Assoc. = associations; SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome; CRS = cytokine release syndrome; ARDS = acute respiratory distress syndrome; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis.

referring to a maladaptive release of proinflammatory cytokines that occurs in response to a variety of clinical conditions that progress rapidly, with a high mortality (Fig. 8).[13–17] Cytokine storm syndrome (CSS) is an umbrella term that encompasses a spectrum of potentially fatal hyperinflammatory conditions, such as the macrophage activation syndrome (MAS), hemophagocytic lymphohistiocytois, and cytokine release syndrome (CRS).[16] Shown in Fig. 8 is a schematic representation of some of the many associated disease states (*e.g.*, lupus and lymphoma) that are triggered by a variety of stimuli (*e.g.*, dengue virus and chimeric antigen receptor [CAR)] T-cell therapy). In a sense, the immune system loads the gun . . . and COVID-19 pulls the trigger.[17] Of particular relevance to COVID-19 is that several viral infections, including those caused by pandemic influenza strains, are common triggers. There are several pathophysiologic pathways that can result in CSS, but the best studied pathway is defective lymphocyte killing *via* the perforin pathway.[15] Although the search for a genetic predisposition for COVID-19 cytokine storm susceptibility remains elusive, the report by Schulert *et al.*,[18] who identified mutations in genes linked to hemophagocytic lymphohistiocytois and MAS in fatal cases of H1N1 influenza, might offer an interesting area for future research.

Irrespective of mechanism, CSS display features of inappropriately elevated proinflammatory cytokines (interleukin [IL] 1, IL-6, and interferon-γ) produced by a dysregulated host immune response, which results in multiorgan failure.[15] All CSS are not identical, however, and COVID-19–associated CSS has some unique features, including a tendency for early onset of ARDS and clotting while having elevated serum ferritin and lower IL-6 concentration than observed in other CSS.[14,17] Nonetheless, COVID-19 triggers a hyperinflammatory response in a substantial number of patients, who require hospitalization.

Different therapies have been used over the years for treatment of various CSS that include immunosuppressive therapies (*e.g.*, glucocorticoids, calcineurin inhibitors) and targeted immunomodulatory therapies (*e.g.*, anticytokines, Janus kinase [JAK] inhibitors).[14,17] Although several early studies of treating COVID-19–associated CSS that targeted IL-6 by using specific monoclonal anti–IL-6 products suggested some benefit with COVID-19, later publications have reported mixed results. As more U.S. studies are becoming available, however, this will require updating.[15] IL-1 is another proinflammatory cytokine being targeted to treat various CSS with anakinra (a recombinant human IL-1 receptor antagonist) improved survival in a subset of patients with sepsis and features of CSS.[15] Identification of the key role that these and other proinflammatory cytokines play in the pathogenesis of COVID-19 has launched a new era of therapy for this condition.[19]

THE COVID-19 TREATMENT GUIDELINES PANEL

The National Institutes of Health has established a panel of U.S. physicians, statisticians, and other experts, the COVID-19 Treatment Guidelines Panel (COVID-19 TGP), which has developed treatment guidelines for COVID-19. These guidelines[20], intended for health care

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Table 2 **List of the potential antiviral drugs under evaluation by the COVID-19 Treatment Guidelines Panel for the treatment of COVID-19*#**

Summary Recommendations
There are no U.S. Food and Drug Administration approved drugs for the treatment of COVID-19
Definitive clinical trial data are needed to identify safe and effective treatments for COVID-19; in this table, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data
As in the management of any disease, treatment decisions ultimately reside with the patient and his or her health care provider
For more detailed information on the antiviral agents that are currently being evaluated for the treatment of COVID-19, see Tables 2a and 2b (20)
Remdesivir
Recommendations for Hospitalized Patients With Severe COVID-19
In situations in which remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated or on extracorporeal ECMO (BI)
The following recommendation statements for the use of remdesivir are currently being revised and will be updated soon:
The Panel recommends administering the investigational antiviral agent remdesivir for 5 days for the treatment of COVID-19 in hospitalized patients with oxygen saturation measured via pulse oximetry ≤ 94% on room air (at sea level) or those who require supplemental oxygen (AI)
The Panel recommends remdesivir for the treatment of COVID-19 in patients who are on mechanical ventilation or ECMO (BI)
Recommendation for duration of therapy for patients who have not shown substantial clinical improvement after 5 days of therapy
There are insufficient data on the optimal duration of therapy for patients who have not shown substantial clinical improvement after 5 days of therapy; in these groups, some experts extend the total remdesivir treatment duration to up to 10 days (CIII)
Recommendation for patients with mild or moderate COVID-19
There are insufficient data for the Panel to recommend either for or against the use of remdesivir for the treatment of patients with mild or moderate COVID-19
Chloroquine or hydroxychloroquine
The Panel recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (AII)
The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI)
Other antiviral drugs
The Panel recommends against using the following drugs to treat COVID-19, except in a clinical trial:
The combination of hydroxychloroquine plus azithromycin (AIII), because of the potential for toxicities
Lopinavir/ritonavir (AI) or other human immunodeficiency virus protease inhibitors (AIII), because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19

COVID-19 = Coronavirus-2; ECMO = membrane oxygenation.
**Rating of recommendations: A = strong; B = moderate; C = optional.*
#Rating of evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory end points; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion.

providers, are based on published and preliminary data and the clinical expertise of the panelists, many of whom are frontline clinicians caring for patients during the rapidly evolving pandemic. The guidelines are posted online[20] and are updated often as new data are published in peer-reviewed scientific literature and other authoritative information emerges. The guidelines consider two broad categories of therapies currently in use by health care providers for COVID-19 and which are the focus of this article. These include

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1.0, antivirals, which may target the coronavirus directly; and 2.0, host modifiers and immune-based therapies, which may target the virus or influence the immune response to the virus.

ANTIVIRAL DRUGS FOR COVID-19

Recommendations of the COVID-19 TGP for the Use of Potential Antiviral Drugs for the Treatment of COVID-19

Shown in Table 2 is a list of the potential antiviral drugs under evaluation for the treatment of COVID-19 by the COVID-19 TGP. Although there are currently no U.S. Food and Drug Administration (FDA) approved antiviral drugs available for the treatment of COVID-19, two groups of drugs have received recent media exposure: remdesivir and the chloroquine or hydroxychloroquine group of drugs, with or without azithromycin.

In a recent preliminary report of a National Institutes of Health supported study by Beigel *et al.*,[21] in a total of 1059 patients (538 assigned to remdesivir and 521 to placebo), the clinical effect of remdesivir was relatively modest, with a primary outcome of a reduction in time to recovery from a median of 15 days among recipients of placebo to 11 days among those who received remdesivir. A trend toward lower mortality among patients who received remdesivir (7.1%) than among those who received placebo (11.9%) was also observed, but the differences did not reach statistical significance. On May 1, 2020, the FDA issued an Emergency Use Authorization for remdesivir to treat adults and children with severe COVID-19. The conditions for use of remdesivir recommended by the COVID-19 TGP are shown in Table 2.

The scientific evaluation for the use of the chloroquine/hydroxychloroquine group of drugs has encountered a more ambiguous trajectory. The initial authorization for use of these drugs for COVID-19 by the FDA on March 28, 2020, under the Emergency Use Authorization for emergency use of oral formulations, was revoked on June 15, 2020, based on lack of effectiveness and potential adverse effects (*e.g.*, cardiac arrhythmias).

Host Modifiers and Immune-Based Therapies for COVID-19

Shown in Table 3 is a list of host modifiers and immune-based therapy under evaluation for treatment of COVID-19 under consideration by the COVID-19 TGP. Shown in Tables 3 to 9 are a list of the COVID-19 TGP's recommendations for use in the treatment of COVID-19 as of this writing but which will be updated as new data become available. The reader is referred to the recommendations of the COVID-19 Treatment Guide-lines Panel (COVID-19 TGP) for the current list of treatment regimens for COVID-19 (20).

Table 3 **Host modifiers and immune-based therapy under evaluation for treatment of COVID-19 by the COVID-19 Treatment Guidelines Panel**

- Blood Products
  - COVID-19 convalescent plasma and SARS-CoV-2 immune globulins
  - Non–SARS-CoV-2 specific intravenous immune globulin
- Interferons
  - Interferon alfa
  - Interferon beta
  - Interferon gamma
- Interleukin-1 inhibitors
  - Anakinra
- Interleukin-6 inhibitors
  - Sarilumab
  - Siltuximab
  - Tocilizumab
- Kinase inhibitors
  - Janus kinase inhibitors
    - Baricitinib
    - Ruxolitinib
    - Tofacitinib
  - Bruton tyrosine kinase inhibitors
    - Ibrutinib
    - Acalabrutinib
    - Zanubrutinib
- Corticosteroids
  - For patients critically ill with COVID-19
  - For patients on chronic corticosteroids

COVID-19 = Coronavirus-2; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

BLOOD PRODUCTS

Blood Products: Convalescent Plasma and SARS-CoV-2 Immune Globulin

Passive immunization or antibody therapy involves the administration of antibodies to a susceptible individual obtained from an individual who has recovered from an infectious disease or who has been immunized with a specific vaccine for the purpose of preventing or treating an infectious disease due to that agent.[22] Shown in Fig. 9 is a schematic representation of the use of convalescent sera for COVID-19 prophylaxis and therapy. In contrast, active immunity is usually defined as long-lasting immunity that is acquired through production of antibodies within the organism in response to an infectious agent or after immunization with a specific vaccine. The main advantage of

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Table 4 **Recommendations of COVID-19 Treatment Guidelines Panel for use of blood products in COVID-19***

Drug Name Blood products	FDA-Approved Indications	Preclinical Data, Mechanism of Action, Rationale for Use in COVID-19
COVID-19 convalescent plasma and SARS-CoV immune globulins	On August 23, 2020, the FDA issued an EMERGENCY USE AUTHORIZATION (EUA) of COVID-19 convalescent plasma for treatment of COVID-19 in hospitalized patients.[25]	Plasma donated from individuals who have recovered from COVID-19 includes antibody to SARS-CoV-2; similarly, SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19; both products may help suppress the virus and modify the inflammatory response
There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV immune globulins for the treatment of COVID-19		
Non–SARS-CoV specific intravenous immune globulin AII	Primary immune disorders; thrombocytopenic purpura; Kawasaki disease; motor neuropathy; prophylaxis of various bacterial and viral diseases	Currently, only a small percentage of the U.S. population has been infected with SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies.

COVID-19 = Coronavirus-2; FDA = U.S. Food and Drug Administration; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; AIII = strong, expert opinion.
**The COVID-19 Treatment Guidelines Panel recommends against the use of non-SARS-CoV specific intravenous immune globulin (IVIG) for the treatment of COVID-19, except in the context of a clinical trial (AIII); this should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.*

passive immunization is its immediacy of action, its main drawback is its short period of duration. Experience from previous outbreaks with other coronaviruses, such as SARS-CoV-1, shows that such convalescent sera contain neutralizing antibodies to the relevant virus.[23]

Although the use of non–SARS CoV-2 specific intravenous (IV) immunoglobulin has been suggested as a possible therapy, because only a small proportion of the U.S. population has been infected with COVID-19, gamma globulin prepared from the plasma of donors who have not had COVID-19 is not likely to contain SARS-CoV-2 antibodies and, therefore, the use of this product is not recommended by the COVID-19 TGP.

In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy mediates protection is by viral neutralization. However, other mechanisms may be possible, such as antibody-dependent cellular cytotoxicity and/or phagocytosis. Possible sources of antibody for SARS-CoV-2 are human convalescent sera from individuals who have recovered from COVID-19 or who have been immunized with an upcoming COVID-19 vaccine, bv monoclonal antibodies prepared *in vitro* by hybridoma technology or by preparations generated in certain animal hosts, such as genetically engineered cows that produce human antibody.[24] Although many types of blood products are currently available or under development, the only antibody preparation that is currently available for immediate use is that found in human convalescent sera (Fig. 9). As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase.

Recommendations from the COVID-19 TGP for the use of blood products in COVID-19 are shown in Table 4. Convalescent plasma has several limitations, including batch-to-batch variability and requirement for blood type matching. Samples must also be screened for bloodborne pathogens, including hepatitis viruses, human immunodeficiency viruses, and parasites. Monoclonal antibody administration is an alternative to convalescent plasma. Multiple techniques now allow the rapid recovery of antiviral monoclonal antibodies or antibody derivatives.

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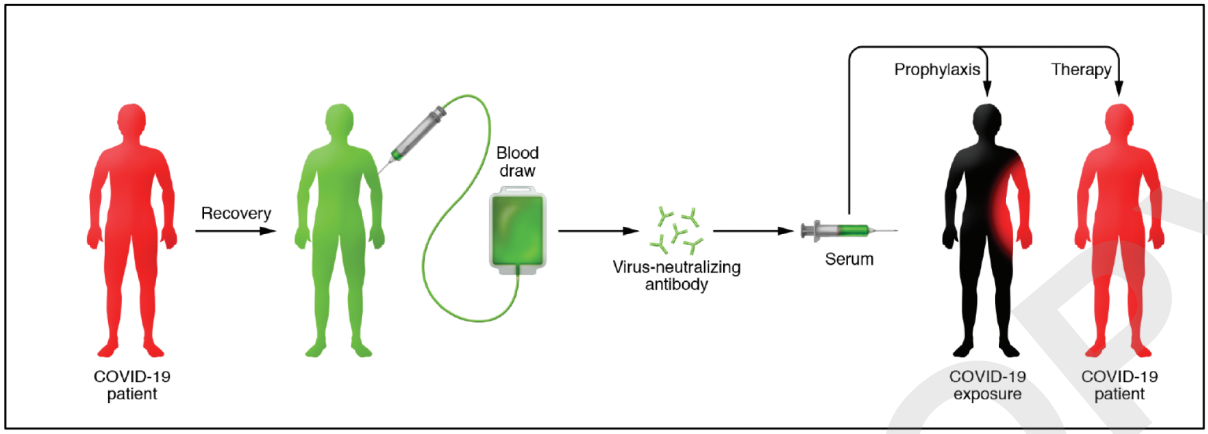

Figure 9. *Schematic representation of the use of convalescent sera for coronavirus-2 (COVID-19) prophylaxis and therapy (reproduced with permission from Ref. 22). An individual who is ill with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies. After identification of those with high titers of neutralizing antibody, serum that contains these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infection in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. In addition, convalescent serum could potentially be used in the therapy of individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than in the treatment of established disease.*

INTERFERONS

Interferons are a family of cytokines with antiviral properties that have been suggested as a potential treatment for COVID-19 because of their *in vitro* and *in vivo* antiviral properties (Table 5). Interferon-β used alone and in combination with ribavirin in patients with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) failed to show a significant positive effect on clinical outcomes. In a retrospective observational analysis of 350 patients who were critically ill with MERS from 14 hospitals in Saudi Arabia, mortality rates were higher among the patients who received ribavirin and interferon (β-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.[26] A randomized clinical trial that included 301 patients with ARDS[27] found that, compared with placebo, IV interferon β-1a had no benefit, as measured by ventilator-free days over a 28-day period (median of 10.0 days versus 8.5 days) or mortality (26.4% versus 23.0%). Interferon-alfa-1b, which is not available in the United States, has been used in patients with COVID-19 in China, but it has been primarily used by atomization inhalation, and the clinical data have not yet been presented. The COVID-19 TGP, therefore, recommends against the use of interferons for the treatment of COVID-19, except in the context of a clinical trial.

IL-1 AND IL-6 INHIBITORS

Shown in Table 6 are recommendations of the COVID-19 TGP or use of IL-1 and IL-6 inhibitors.

IL-1 INHIBITORS

The rationale for use of IL-1 inhibitors is based on elevated levels of IL-1 in patients with COVID-19 and other conditions, such as severe CAR–T-cell mediated CRS (Table 6). There are case reports and series[20] that describe a favorable response with anakinra in these syndromes, including the survival benefit in sepsis and reversing a cytokine storm in adults with MAS after tocilizumab failure. Although a number of clinical trials for the treatment of COVID-19 are currently underway with anakinra, there are currently insufficient data to recommend either for or against the use of IL-1 inhibitors, *e.g.*, anakinra, for the treatment of COVID-19.

IL-6 INHIBITORS

IL-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells. Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with SARS-CoV-2 infection. COVID-19–associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein, D-dimer, and ferritin.[28,29]

There are several commercial anti–IL-6 inhibitors in clinical trials for COVID-19. Sarilumab is a recombinant humanized anti–IL-6 receptor monoclonal

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Table 5 **Recommendations of the by the COVID-19 Treatment Guidelines Panel for IFNs***

Drug Name INF alfa and INF beta	FDA-Approved Indications	Preclinical Data, Mechanism of Action, Rationale for Use in COVID-19
INF alfa	IFN alfa-2b: leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C; IFN alfa-1b is not available in the United States.	Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types
INF beta	Multiple sclerosis (IFN β-1a, IFN β-1b)	Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function); among IFN subtypes, IFN β-1b shows greatest *in vitro* inhibition of MERS-CoV; *in vitro* activity against MERS-CoV in lung cells
IFN-γ	An IFN-γ blocking antibody indicated for the treatment of patients with primary hemophagocytic lymphohistiocytosis	An open-label, randomized trial that is currently underway in Italy is comparing intravenous (IV) anakinra to IV emapalumab (an IFN-γ–blocking antibody) for the treatment of COVID-19

COVID-19 = Coronavirus-2; IFN = interferon; FDA = U.S. Food and Drug Administration; MERS-CoV = MERS-coronavirus; IV = intravenous; AIII = strong, expert opinion.
**The COVID-19 Treatment Guidelines Panel recommends against the use of IFNs for the treatment of severely and critically ill COVID-19 patients, except in a clinical trial (AIII).*

antibody that is approved by the FDA as a subcutaneous formulation for use in patients with rheumatoid arthritis, but it is not currently approved for CRS (Table 6). An ongoing placebo-controlled clinical trial is evaluating the use of an IV formulation administered as a single dose for COVID-19. Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and is approved by the FDA for use in patients with Castleman disease as an IV infusion. Tocilizumab is a recombinant humanized anti–IL-6 receptor monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by CAR–T-cell therapy. Tocilizumab can be dosed for IV or subcutaneous injection. Because there insufficient data from clinical trials on the use of IL-6 inhibitors in patients with COVID-19, the COVID-19 TGP cannot recommend either for or against the use of IL-6 inhibitors (*e.g.*, sarilumab, siltuximab, tocilizumab) for the treatment of COVID-19.

Kinase Inhibitors

There are two types of kinase inhibitors that are being evaluated for the treatment of COVID-19: (1) the JAK inhibitors, and (2) the Bruton tyrosine kinase (BTK) inhibitors (Table 7).

The JAK inhibitors function by inhibiting the JAK signal transducer and activator of transcription pathway. Baricitinib is a potent anti-inflammatory with activity against interferon-associated inflammation that has also been postulated to have an antiviral effect. Baricitinib is approved by the FDA to treat rheumatoid arthritis and can ameliorate the chronic inflammation seen in interferonopathies.[7–9] Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies and prevent chronic graft-versus-host disease in recipients of stem cell transplantations.[15] Based on results from a small case series, ibrutinib has been theorized to improve inflammation and protect against ensuing lung injury in patients with COVID-19. Ibrutinib, a BTK inhibitor, and a related drug, acalabrutinib, are showing promise in human clinical trials.[30] The COVID-19 TGP recommends against the use of JAK inhibitors (*e.g.*, baricitinib) for the treatment of COVID-19, except in the context of a clinical trial.

Corticosteroids

Because of their potent anti-inflammatory effects, corticosteroids have been proposed as a potential therapeutic agent for suppressing cytokine-related lung injury in patients with COVID-19 (Table 8). Based on the preliminary unpublished results of the Randomized Evaluation of COVid-19 thERapY (RECOVERY) Trial. The COVID-19 TGP recommends

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Table 6 **Recommendations of the COVID-19 Treatment Guidelines Panel for IL-1 and IL-6 inhibitors***

Drug Name	FDA-Approved Indications	Preclinical Data, Mechanism of Action, Rationale for Use in COVID-19
IL-1 inhibitor		
Anakinra#	Rheumatoid arthritis; cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease; intravenous formulation is not approved for use in the United States	Competitively inhibits IL-1 binding to the IL-1 type I receptor
Interleukin-6 inhibitors§		
Sarilumab	Rheumatoid arthritis	Human recombinant monoclonal antibody; IL-6 receptor antagonist
Siltuximab	Multicentric Castleman disease	Human-mouse chimeric monoclonal antibody; IL-6 antagonist
Tocilizumab	Cytokine release syndrome (induced by CAR T-cell therapy); rheumatoid arthritis; giant cell arteritis; polyarticular juvenile idiopathic arthritis systemic juvenile idiopathic arthritis	Recombinant humanized monoclonal antibody; IL-6 receptor antagonist

COVID-19 = Coronavirus-2; IL = interleukin; FDA = U.S. Food and Drug Administration; CAR = chimeric antigen receptor.
**Although there are a number of clinical trials and reports of favorable reports to IL-6 inhibitors, there are insufficient data to recommend either for or against IL-6 inhibitors for the treatment of COVID-19.*
#Although there are a number of clinical trials and reports of favorable reports to anakinra, there are insufficient data to recommend either for or against interleukin-1 (IL-1) inhibitors, such as anakinra, for the treatment of COVID-19.
§IL-6 levels when elevated may an important mediator when severe inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.

dexamethasone 6 mg daily for up to 10 days in patients with COVID-19 who are on mechanical ventilation or those who require supplemental oxygen but who are not on mechanical ventilation. The COVID-19 TGP recommends against using dexamethasone to treat patients with COVID-19 who do not require supplemental oxygen. The guidelines[20] note that the COVID-19 TGP may modify these recommendations based on the final published results of this and other ongoing studies. Before initiating dexamethasone, clinicians should review the patient's medical history and assess the potential risks and benefits of administering corticosteroids to the patient.

For patients who receive corticosteroids for diseases that require chronic use (*e.g.*, primary or secondary adrenal insufficiency, rheumatologic diseases), these should not be discontinued. On a case-by-case basis, supplemental or stress-dose steroids may be indicated. The COVID-19 TGP recommends that inhaled corticosteroids that are used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19. The recommendations for using corticosteroids in patients with COVID-19, therefore, vary, depending on the severity of illness as well the underlying medical condition, as described in Table 8.

COVID-19 VACCINES AND THE ALLERGIST/IMMUNOLOGIST

Several articles appeared recently that have addressed practical considerations for the allergist/immunologist in dealing with the COVID-19 pandemic, which have included contingency planning for the allergy/immunology clinic and other social-medical measures to deal with the pandemic.[31–35,37] Although no vaccines have been approved for the prevention of COVID-19 as of this writing, there are currently >137 candidates undergoing preclinical development and 23 in early clinical development, according to the World Health Organization.[36]

An ideal vaccine against COVID-19 should have the following attributes: effectiveness after one or two vaccinations; protection for susceptible target populations, such as older adults, individuals who are immuno-

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Table 7 **Recommendations of the COVID-19 Treatment Guidelines Panel for kinase inhibitors***

Drug Name	FDA-Approved Indications	Preclinical Data, Mechanism of Action, Rationale for Use in COVID-19
JAK inhibitors		
Baricitinib	Rheumatoid arthritis	JAK inhibitor selective for JAK1, JAK2, and TYK2, relative to JAK3; theoretical direct antiviral activity through inhibition of kinases (AAK1 and cyclin G-associated kinase) that regulate viral endocytosis in pulmonary AT2 epithelial cells, which may prevent SARS-CoV-2 entry into and infection of susceptible cells; dose-dependent inhibition of IL-6 induced signal transducer and activator of transcription 3 phosphorylation
Ruxolitinib	Myelofibrosis; polycythemia vera; steroid-refractory acute graft-versus host disease	JAK inhibitor selective for JAK1 and JAK2; theoretical antiviral properties through inhibition of AAK1 which may prevent viral entry into and infection of pulmonary AT2 alveolar epithelial cells; inhibition of IL-6 *via* JAK1/JAK2 pathway inhibition
Tofacitinib	Rheumatoid arthritis; psoriatic arthritis; ulcerative colitis	JAK inhibitor selective for JAK1 and JAK3 with modest activity against JAK2; blocks signaling from gammachain cytokines (IL-2, IL-4) and gp 130 proteins (IL-6, IL-11, IFNs); shown to decrease levels of IL-6 in rheumatoid arthritis
BTK inhibitors		
Ibrutinib	Chronic lymphocytic leukemia/small lymphocytic lymphoma; mantle cell lymphoma; marginal zone lymphoma; Waldenström macroglobulinemia; chronic graft-versus-host disease in stem cell transplant recipients	First-generation oral BTK inhibitor; inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways; potential modulation of signaling that promotes inflammation and cytokine storm
Acalabrutinib	Chronic lymphocytic leukemia/small lymphocytic lymphoma; mantle cell lymphoma	Second-generation oral BTK inhibitor; inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways; potential modulation of signaling that promotes inflammation and cytokine storm
Zanubrutinib	Mantle cell lymphoma	Second-generation oral BTK inhibitor; inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways; potential modulation of signaling that promotes inflammation and cytokine storm

COVID-19 = Coronavirus-2; JAK = Janus kinase; TYK2 = Tyrosine kinase 2; AAK1 = Adaptor-associated protein kinase 1; AT2 = Alveolar type 2; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; IL = interleukin; IFN = interferon; BTK = Bruton tyrosine kinase; AIII = strong, expert opinion.

**The Panel recommends against the use of JAK inhibitors for the treatment of COVID-19, except in the context of a clinical trial (AIII).*

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Table 8 **Recommendations of the COVID-19 Treatment Guidelines Panel for corticosteroids**

Drug Name	FDA-Approved Indications	Preclinical Data, Mechanism of Action, Rationale for Use in COVID-19
The Corticosteroids (Including Dexamethasone) section is a new subsection of Immunomodulators Under Evaluation for Treatment of COVID-19; this new section is based on the Recommendations for Dexamethasone in Patients with COVID-19 section that was released on June 25, 2020. The Panel continues to recommend the use of dexamethasone in patients who are mechanically ventilated (AI) and in patients who require supplemental oxygen but who are not mechanically ventilated (BI). The new Corticosteroids (Including Dexamethasone) section also discusses the clinical data on the use of other corticosteroids in patients with COVID-19, the potential adverse effects of corticosteroids, other considerations when using corticosteroids, and recommendations for the use of dexamethasone in pregnant patients		
For patients critically ill with COVID-19		
The Panel recommends using dexamethasone in patients who are mechanically ventilated (AI) and in patients who require supplemental oxygen but who are not mechanically ventilated (BI)		
The Panel recommends against using dexamethasone to treat patients critically ill with COVID-19 who do not require supplemental oxygen (AI)		
For patients on chronic corticosteroids		
Oral corticosteroid therapy that was used before COVID-19 diagnosis for another underlying condition (*e.g.*, primary or secondary adrenal insufficiency, rheumatologic diseases) should not be discontinued (AIII); on a case-by-case basis, supplemental or stress-dose steroids may be indicated (AIII)		
Inhaled corticosteroids that are used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 (AIII)		

COVID-19 = Coronavirus-2; AI = strong, one or more randomized trials with clinical outcomes and/or validated laboratory end points; BI = moderate, one or more randomized trials with clinical outcomes and/or validated laboratory end points; AIII = strong, expert opinion.

compromised, and those with comorbidities; provision of protection for a minimum of 6 months; and prevention of secondary transmission of the virus from patients who are immunized to contacts.

Shown in Online Supplemental B, Table S2**,** is a list of candidate COVID-19 vaccines being developed, These include an assortment of the following: (1) DNA inactivated vaccines; (2) live attenuated, nonreplicating vector-based vaccines combined with COVID-19 DNA; (3) protein subunit and replicating viral vaccines; and (4) RNA candidate vaccines.[38] Of the vector-based vaccines that primarily use nonreplicating adenoviral vectors expressing the SARS-CoV-2 spike protein, two vaccines, one from AstraZeneca, PLC, Cambridge, UK (AZD1222) and the other from CanSino Biologics Inc.TEDA West District, Tianjin, PRC (Ad5-vectored COVID-19 vaccine), have shown promising results against COVID-19 in phase I/II and phase II studies, respectively. Results for both were published recently in *The Lancet* and phase III studies are planned for both candidate vaccines.[39,40] The interim results of clinical trials of both vaccines showed that the vaccines were tolerated and generated robust neutralizing antibody to the COVID-19 spike protein. A third recent study conducted a phase I, dose-escalation, open-label trial, which included 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, a candidate messenger RNA–1273 vaccine in a dose of 25 μg, 100 μg, or 250 μg.[41] The vaccine induced anti–SARS-CoV-2 immune responses in all the participants, and no trial-limiting safety concerns were identified. These findings also support further development of this vaccine in phase III trials.

To interpret more fully the degree of potential protective immunity that could be achieved in these studies, it would be desirable for the investigators to report not only the production of anti-spike neutralizing antibody that is achieved by these candidate COVID-19 vaccines but also the degree of stimulation of T cells and natural killer cells, key immune cells for destroying COVID-19 infected cells, The projected phase III trials that will be performed with each of these three candidate vaccines that will compare the degree of protective immunity in cohorts of subjects who received each of the putative COVID-19 vaccine(s) with those receiving placebo will ultimately provide the answer to this important question of protective immunity. Finally, the allergist/immunologist will play a significant role in addressing the myriad of hurdles that will be involved in the distribution, prioritization, and administration of the final approved COVID-19 vaccine, not the least of which will be the resistance that will be encountered from the antivaccine movement.[42]

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CONCLUSION

COVID-19 has become a uniquely challenging pandemic, with disruptive ramifications on human life unlike any other infectious disease in modern times. In this report, the two-phased mechanism of infection and inflammation that identify the pathogenesis of COVID-19 was reviewed, together with the influence it has on COVID-19 disease presentation and potential therapeutic targets. Numerous clinical trials are being conducted to identify the most effective treatments for COVID-19. An important resource for the allergist/immunologist is the COVID-19 TGP, which is critically reviewing the results of these and are continuously updating treatment guidelines for clinicians caring for patients during the rapidly evolving COVID-19. The recommendations of the COVID-19 TGP provide a useful guide in helping to choose the most appropriate current treatment modalities that will be approved for COVID-19 as well as those that inevitably will apply for the use of the forthcoming COVID-19 vaccines. Although every specialty of medicine has been affected, the field of allergy/immunology holds a special place in the battle against this modern-day plague. Because of the specialized training in allergy and clinical immunology, the allergist/immunologist is uniquely poised to play a major role both in the delivery of specialized therapeutic procedures and practices that can improve the health of patients with COVID-19 as well as in the use of forthcoming vaccines for the prevention of its spread.

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