Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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SARS 2 human coronavirus (COVID -19, SARS CoV2)

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Introduction

In December 2019, a cluster of patients diagnosed having severe lower respiratory tract febrile illness of unknown origin was reported in Wuhan City, Hubei Province, China. Test results ultimately revealed a novel strain of coronavirus isolated from the bronchoalveolar lavage of the patients, and was determined to be causative for the outbreak.[1–12] The pulmonary syndrome was very similar to SARS outbreak symptoms, and genetic study of the virus strain revealed an ~80% nucleotide similarity between the human coronavirus SARS (SARS CoV) and this novel strain. The pulmonary syndrome was later named coronavirus disease 2019 (COVID-19) by the World Health Organization. It has also been referred to as SARS CoV2 and SARS 2 CoV (Fig. 1).

Similar pulmonary syndromes have been recognized as being caused by other strains of the coronavirus family. The most notable examples are the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[11,13–15] The SARS outbreak has been contained, with no known human infection reported since the outbreak of 2003. However there continue to be small outbreaks of MERS reported.

Imaging is a critical component of the diagnostic workup, monitoring of disease progression, and follow-up in coronavirus-related pulmonary syndromes.[13–15] Imaging features in the acute and chronic phases of SARS and MERS as well as COVID-19 share similarities (Table 1).[11,13]

Epidemiology

Coronaviruses have been well known since first identified many years ago as primarily zoonotic pathogens, causative of diverse animal illness. However in the 1960′s, coronaviruses capable of causing human illness – usually consistent with “the common cold,” were identified. In more recent years newly identified human pathogen coronaviruses have caused three significant outbreaks since 2003. The first of these – SARS, emerged in 2003, though largely confined to Hong Kong, and Toronto. The second - MERS a decade later was mostly localized to the Middle East, although cases well beyond that region were diagnosed. The third is COVID-19.

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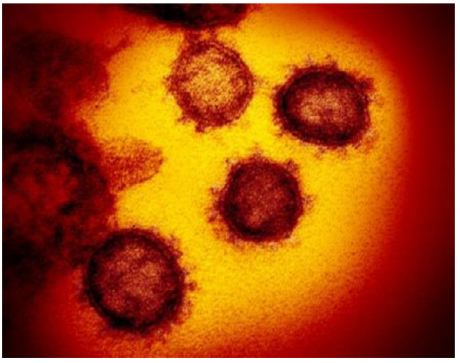

Fig. 1. Electron micrograph of SARS-COV2 (COVID −19)
From: National Institutes of Health/NIAID.

In December 2019 several cases of acute respiratory distress syndrome (ARDS) were reported in Wuhan City, China, the result of unknown etiology.[2,3,5,6,9] Early investigation noted these patients were linked to a local wet market (seafood markets, live animal markets), a common commercial source of food in China. Of concern, animal to human transmission, and ultimately human to human propagation of infections have long been associated with these wet markets over the years, including SARS.

During the ensuing investigation numerous samples of patients infected with what was to be designated as SARS2-COVID 19 suggested it came from animals sold in the wet markets.[2,3,5,6,9]

Further research identified the virus as a newly discovered human coronavirus, SARS 2 COVID-19 (COVID-19). Soon after it became clear COVID-19 is transmitted person to person. With a population of eleven million people, Wuhan City became the epicenter for the resulting COVID-19 outbreak, and ultimately starting point for the global pandemic.[3,5–10]

Since December 2019, according to World Health Organization (WHO) data, there have been approximately 7 million cases of COVID-19 reported worldwide. This is a dramatic increase in cases since March 2020. The rapidity of COVID-19 spread is significant.[3,16]

Against the backdrop of significant asymptomatic infection, determining the transmissibility factor, also referred to as the basic reproductive number (Ro) for COVID-19 remained a challenge. WHO initial estimates had Ro between 1.4 and 2.5.[17,18] Some regions report much higher numbers. Additional research suggests the Ro for COVID – 19 is between 1.5 and 6.68, with further calculations estimating Ro of 2.79 and 3.28.[17,19] The data suggest COVID −19 has a larger Ro than SARS.[20] Regardless of Ro 2 or 3, 4 +/− compared to influenza's lower Ro (<2), let it suffice this is a contagious virus in the context of questionable sustainable immunity and a highly vulnerable population.[21]

It should be noted Ro is dependent on several factors: i. different variables utilized; ii) different methods of modeling/calculating; and iii) different estimations.[17,20] Moreover, R0 is not a static number per se, or necessarily an intrinsic for a pathogen, albeit the general contagiousness of a pathogen based upon host-virus factors contributes to the transmissibility. Three key factors influence Ro: 1. the duration of contagiousness, 2. the likelihood of infection per contact between; 3. contact rate. Viral load, population density, economic, cultural-social and environmental factors also play a role.[17]

Regardless of Ro, currently there is no widespread vaccination against COVID-19 although two vaccines have received approval (the UK, and the US), with the issues such as population background immunity, and post infection immune protection currently being studied. Barring more definitive data, it must be assumed most populations are without immunity – herd or otherwise.

It appears the average incubation period for COVID-19 is ~5 days with a range of 2 – 14 days, although much longer periods have been reported in some cases.[1,2,7–9,22]

Table 1
Comparison of Clinical and Radiologic Features of SARS, MERS, and COVID-19 (7b, 32b)

Feature	SARS	MERS	COVID-19
CLINICAL SIGNS OR SYMPTOMS			
Fever or chills	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes
Malaise	Yes	Yes	Yes
Myalgia	Yes	Yes	Yes
Headache	Yes	Yes	Yes
Cough	Dry	Dry or productive	Dry (productive w/progressive illness)
Diarrhea	Yes	Yes	+/-
Nausea or vomiting	Yes	Yes	Less common
Sore throat	Yes	Uncommon	Less common/but possible
Arthralgia	Yes	Uncommon	Less common/but possible
IMAGING FINDINGS			
Acute phase			
Initial imaging			
Normal	15–20% of patients	17% of patients	15–20% of patients
Abnormalities			
Common	Peripheral multifocal airspace opacities (GGO, consolidation, or both) on chest XRay and CT scans	Diffuse findings similar to SARS	Diffuse findings similar to SARS and MERS; may be more diffuse early, or more rapidly progressive. B/L lung involvement to be expected
Rare	Pneumothorax	Pneumothorax	Pneumothorax
Not seen	Cavitation, lymphadenopathy	Cavitation, lymphadenopathy	Cavitation, lymphadenopathy
Appearance	Unilateral, focal (50%); Multifocal (40%); diffuse (10%) Bilateral, multifocal	Bilateral, multifocal basal airspace on CXR or CT (80%), isolated unilateral (20%)	Bilateral, multifocal, as well as basal airspace are common findings. Of note, a </=15% may present with normal CXR
Follow-up imaging appearance	Unilateral, focal (25%); Progressive (most common, can be unilateral and multi-focal or bilateral with multi-focal consolidation)	Extensive into upper lobes or perihilar areas, pleural effusion (33%), interlobular septal thickening (26%).	Persistent or progressive pleural airspace opacities
Indications of poor prognosis	Bilateral (like ARDS), four or more lung zones, progressive involvement after 12 d	Greater involvement of the lungs, pleural effusion, pneumothorax	Consolidation vs ground glass opacities (GGO)
	SARS	**MERS**	**COVID-19**
Chronic			**Data still being reviewed**
Transient reticular opacities (e)	Yes	Yes	
Air trapping	Common (usually persistent)		
Fibrosis	Rare	One-third of patients	Data still being reviewed

Acronyms: GGO = ground-glass opacity, ARDS = acute respiratory distress syndrome. aOver a period of weeks or months.

Microbiology

Coronaviruses are a diverse group of viruses. All are single stranded, zoonotic RNA viruses; they are among the largest known RNA viruses.[1,4,12,13,22,23] There are seven known coronaviruses that attack humans – HcoV-OC43, HCoV229E, SARS-COV, HCoV-HKU1, MERS-COV, HCoVNL63, and the most recently identified is SARS 2 COVID-19. In varying degrees of severity, and organ affinity, these seven are capable of causing a wide range of human illness, with symptoms ranging from minimal, as with one of the common cold causing CoV, to severe mul-

tisystem organ involvement as seen in COVID-19, including death.[1,4,12,13,22,23] SARS, MERS, and COVID-19 are considered highly pathogenic coronaviruses.

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B. COVID – 19: VIROLOGY INFLUENCE ON PATHOPHYSIOLOGY: An introductory overview

COVID-19, much like SARS, targets primarily the respiratory tract, resulting in a wide array of pulmonary illness – from asymptomatic or mild illness to interstitial pneumonia, progressive alveolar damage, and severe acute respiratory failure/acute respiratory disease syndrome (ARDS) (1-18). COVID-19 severity may require intubation and mechanical ventilation (1, 19), along with other aggressive interventions, including extracorporeal membrane oxygenation (ECMO), even hyperbaric oxygen therapy (HBOT) (20,21). Of note extrapulmonary disease including multisystem organ failure are associated with advancing COVID-19 related illness, and require intensive care management. Cardiac, liver, and kidney involvement are well documented (1-8). Conjunctivitis is noted in $\sim$ 1/3 of patients in a recent report, and gastrointestinal symptoms are also well documented, which include nausea, vomiting and diarrhea (1-8,11, 22-23).

ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2)

SARS-CoV-2 as noted earlier is primarily a respiratory pathogen, infecting the respiratory tract as well as gastrointestinal tract. Cell tropism for COVID-19 includes nasal epithelial cells, pneumocytes, and alveolar macrophages, as well as enterocytes (1,2,9-18).

Oral, and nasal mucosa, respiratory tract and alveoli, intestinal mucosa and human aqueous humor cells show high levels of the metallopeptidase angiotensin-converting enzyme 2 (ACE2), which is the functional receptor for COVID-19 S-host interaction and infectivity (Figures 1–3) 1, 2, 9 – 18). ACE2 is widely distributed with varying degrees of density across multiple organ

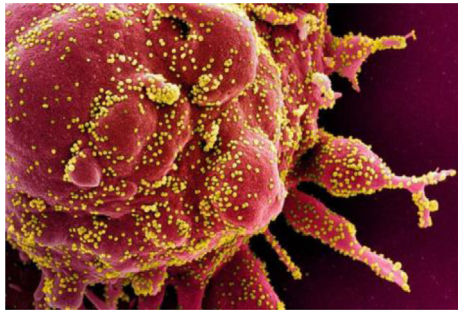

Figure 1. Scanning electron micrograph of a cell heavily infected with SARS-CoV-2, the virus that causes COVID-*19*. Image credit: National Institutes for Health (NIH) -NIAID

systems in the human body, which may explain the diversity of pulmonary and extrapulmonary involvement from COVID-19, and varying degrees of clinical severity (1,3, 6, 9, 11, 13, 22-24).

Studie from 2004 looking at ACE2 localization in response to the SARS outbreak revealed there was robust surface expression of ACE2 protein on lung alveolar epithelial cells, as well as enterocytes of the small intestine, in arterial and venous endothelial cells and the arterial smooth muscle cells in all organs examined during this research (Figure 4). The density of ACE2 in human lung epithelia and small intestine may give insight into the pathophysiology of COVID-19 and other highly pathogenic coronaviruses (9-11).

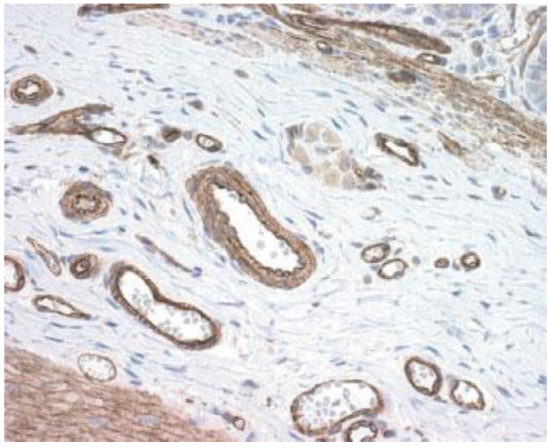

Figure 2. Strong staining is present in vascular endothelium (arrow) and vascular smooth muscle cells (arrow-head) (11).

The extrapulmomary disease noted with COVID-19 becomes more readily understood in the context of this wide ACE2 distribution given cell binding involves the viral S protein to host angiotensin-converting enzyme 2 (ACE2) receptors. Research has shown ACE2 seems to be required for both COVID- 19 and SARS infection (9-11).

Viral entry is accomplished in a complex process. Once the virus enters a host cell, virus complex is translocated to the endosome, where endosomal acid proteases then cleave the S protein, thus facilitating membrane fusion (9, 12, 14-16). The viral genome is subsequently released to then become part of the process whereby it is translated; viral replicase polyproteins PP1a and PP1ab, which are cleaved into functional proteins by viral proteases.

Further interaction between the host and virus is accomplished using subgenomic templates for mRNA synthesis and the translation of viral structural proteins (9-12, 14-17).

The viral genome replication process is mediated by a viral replication complex, which includes RNA-dependent RNA polymerase (RdRp), along with helicase, exonuclease N, and other accessory proteins. Subsequent assembly of viral nucleocapsids from these packaged genomes and translated structural proteins involves the host cell endoplasmic reticulum-Golgi. At then end of this process, virions are released from infected cells through a process known as exocytosis.

It is the various receptors, proteins, and processes that have become the target significant research into identifying and developing antivirals that can interrupt the virus life cycle somewhere in the chain of events, or a viable vaccine that prevents COVID-19 from effectively infecting the human host.

The spike S protein entry depends on S protein priming, and binding between the receptor binding domain (RBD) of this viral spike and the ACE2 receptor using TMPRSS2 and furin (1, 14, 16). Recall it is these spikes that give the halo or corona effect of coronaviruses, earning them their name. S is cleaved at S1/S2 and S2' sites, allowing fusion of viral and host cell membranes – which requires the S2 subunit (9, 11, 14-16). The SARS-S then engages with ACE2 as the viral entry receptor (REF ACE/Li), and utilizes a cellular serine protease TMPRSS2 for S protein

priming (REF 9-11, 17). Since SARS and SARS-2 (COVID-19) share similar identity, it is postulated the mechanisms and viral life cycle share similar characteristics. Further research conducted revealed that COVID-19 entry into host cells also depends on an entry complex similar to SARS CoV receptor ACE2, which is corroborated in research from others (7, 9-12), and may be blocked by an inhibitor of cellular serine protease TMPRSS2, which is also utilized by COVID-19 for S protein priming (7,9-12, 24,25).

It is postulated that the binding affinity between S protein and ACE2 receptors is a significant determinant of subsequent viral replication rates and even disease severity.

Given COVID-19 is primarily an airborne pathogen, the first ACE2 cells encountered by droplets are of the upper respiratory tract – goblet and ciliated cells in the nasal epithelium (1, 18).

ACE2 found in cardiomyocytes and coronary pericytes may play a role in the acute cardiac events associated with COVID-19 (1, 23).

ACE2 is involved in rennin-angiotensin system (RAS), and works in an important homeostatic effect with angiotensin converting enzyme (ACE). Both ACE2 and ACE have play a role in the complex regulatory mechanisms of the cardiovascular system. ACE2 negatively regulates RAS (1, 24). The mechanisms and influencers of those mechanisms that influence the balance between ACE and ACE2 remains incompletely understood.

What is well known is the expression of ACE2 in various organ systems. It is highly expressed in the lungs, and upper respiratory tract as well. Also ACE2 is highly expressed in the kidneys, especially proximal tubules, and is well expressed in the heart. In experimental models, ACE2 deficiency induces cardia fibrosis with aging and/or pressure overload, and post infarct adverse ventricular remodeling, along with hypertrophy in mice. It was noted that ACE inhibitors, AT1 receptor blockers can prevent or reverse this (1,25).

Cardiac biopsies were obtained from some SARS patients during the 2003 outbreak in Toronto. SARS-CoV viral RNA was found in 35% suggesting some cardiac tropism, and the potential a similar affinity for cardiac ACE2 exists in COVID-19, helping to explain at least in part why cardiovascular events are not infrequently reported in COVID-19 (1).

Another mechanism contributing to cardiac involvement during COVID-19 is the hypoxia experienced by patients moderately to severely ill by this coronavirus, which can exacerbate underlying cardiovascular disease. It has also been postulated that the hyperoxic treatments provided may contribute to elevated reactive oxygen species released in the circulation, which can result in tissue injury (1). Whether these contribute to COVID-19 associated cardiovascular effects remains to be further studied, but worth considering.

The aging effect likely contributes to the decline in some COVID-19 patients, as cardiovascular risk and frailty increase with age, with a higher prevalence in those over 80 (Moccia/Collard). To be sure not all persons over 65 are frail. In fact studies suggest the prevalence of physical frailty in that cohort is 4 – 17%, progressively increasing as one approaches or exceeds 80. The physiology of aging and cardiovascular disease is reasonably well described, and most clinicians understand this, along with the benefits of encouraging healthy lifestyles in older persons. Of note with respect to COVID-19, among aging patients, physiologically they their cardiovascular cells have impaired resilience to oxidative stressors, and at least some deficit in antioxidant mechanisms (1, 26).

Some have posited the notion that during COVID-19 in the treatment of the elderly attempts at restoring endothelial function could be useful. An example is activiating Nrf@ using propofol during mechanical ventilation (1, 27) or oltipraz, or other meds, as rescue agents of endothelial and cardiac cells in older patients (1,7,19). Also suggested for COVID-19, and studied in MERS is the potential for Ca2+ antagonists (1, 27). Further research is clearly needed but again a wide array of mechanisms and interventions are being explored to address both COVID-19 illness in general, and some of the cardiovascular effects specifically.

Much discussion about the role of ACE inhibitors and ARB agents – most commonly prescribed for hypertension and related cardiovascular disorders – in terms of enhanced risk or potential benefit with COVID-19 infection has emerged. To date, in the context of COVID-19 pandemic, the American Heart Association and the American College of Cardiology do not recommend abrupt cessation of these antihypertensive medications. Extensive research is underway evaluating the role, risk or benefit of ACE inhibitors and ARBs in terms of COVID-19.

In terms of Coronavirus and ACE2, research suggests the antibody responses against SARS CoV could at least partially protect against SARS CoV2 infection. Convalescent SARS patients have a neutralizing antibody response that was detectable ~24 months after recovery from infection. This response seems directed at the S protein. The capacity of SARS CoV immunity so many years after the outbreak remains to be seen, especially in terms of any cross protection against COVID-19. Moreover the larger question remains – the extent, sustainability, and effectiveness of recovery related immune response by patients who have survived COVID-19 infection. This is discussed in the next section (1, 11, 14, 16, 17).

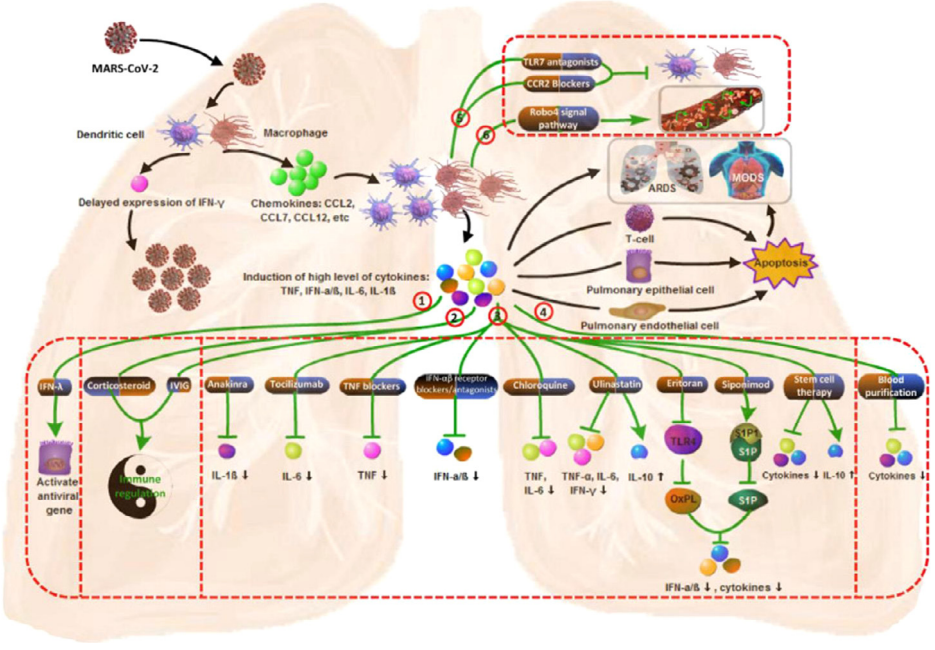

Figure 3. COVID-19 Mechanism of cytokine storm in COVID-19 and potential therapy(29). Also potential targets and associated mechanism of action for therapeutic intervention. These will be discussed in detail in the Therapeutics Section.

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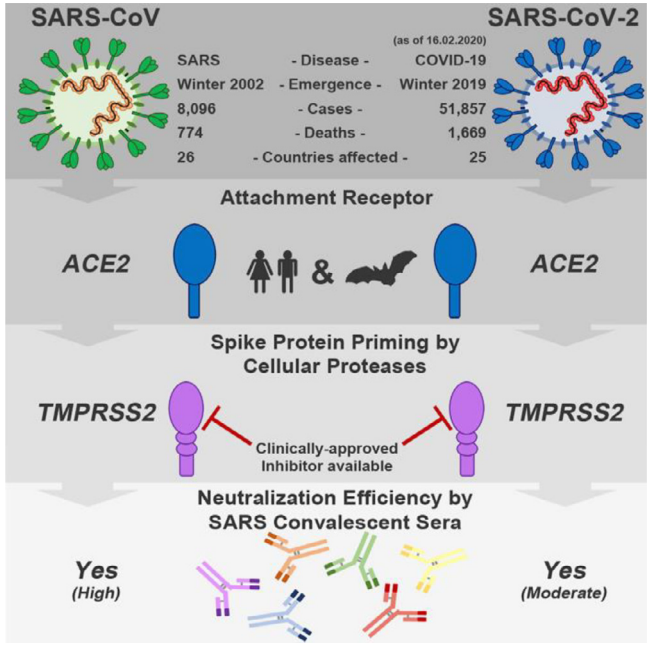

Figure 4. (From Hoffman, et al - 14) SARS and COVID-19 Infectivity/Response Comparisons.

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C. COVID – 19: THE HUMAN IMMUNE SYSTEM AND VIRUSES

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The immune system relies upon multiple protective mechanisms and pathways (1-8). It is a complex and dynamic interplay between the various immune responses and invading pathogen, often with rapid return to health, but sometimes associated with both positive and deleterious effects.

Humans are protected by the innate immune system, and the adaptive immune response (1,2).

The innate immune system (ISS) includes mature functional forms of germ line genes, and physical barriers. For example epithelial cell layers with tight cell-cell junctions, mucosal layer

that secretes protective fluid, epithelial cilia that brush away mucus, allowing constant refreshing of this barrier (1). The innate system includes bioactive molecules found in biological fluids such as complement proteins, defensins, and ficolins, or agents released from cells as they are activated such as cytokines which regulate the function of other cells, chemokines that attract inflammatory leukocytes, lipid mediators of inflammation, reactive free radical species, and other amines or enzymes that contribute to tissue inflammation (NIH). The IIS also includes membrane bound receptors and cytoplasmic proteins that may bind on the surfaces of infecting pathogens. Some of the defenses listed above are consistently active, such as the cilia covering epithelia, while others are activated when host-pathogen interaction occurs (1,2).

The adaptive immune response (AIR) system shows specificity for target antigens (1,2). It is based on antigen specific receptors expressed on the surface of T and B lymphocytes. These antigen specific receptors are encoded and assembled in a complex cascade that forms intact T cell receptor and immunoglobulin B cell antigen receptor Ig genes. These initial few hundred gene elements can cascade to form millions of different antigen receptors, each potentially having unique specificity for a different antigen (2).

Both systems usually act together; the innate system is considered the first line of host defense, and days after infection the adaptive response takes prominence by the time antigen specific T and B cells have undergone what is referred to as clonal expansion. Of note parts of the innate system help activate the antigen specific cells.

As discussed earlier, interferons, TNF, various interleukins and other response agents are released.

A robust immune response relies upon subsets of leukocytes. These differentiate from hematopoietic stem cells. Myeloid cells can develop into various forms of granulocytes, megakaryocytes, platelets, and erythrocytes. Granulocytes as part of the immune system, include monocytes, macrophages, neutrophils, eosinophils, basophils, and mast cells. Neutrophils produce reactive oxygen species cytotoxic to bacteria, play a role in tissue repair, and are phagocytic for microbes and particles. These various cells work in various proportions against a variety of pathogens. The challenge of course is to identify and distinguish pathogen, infected cells, and healthy ones.

Most clinicians are familiar with illnesses that result from a hyperimmune response against normal tissue, and the need for immune modulators. COVID-19, like other viral illnesses poses unique challenges for the human immune system, including an associated hyperimmune response – cytokine storm (3, 9).

The interaction between the human immune response systems (innate and adaptive immunity) and COVID-19, as well as other highly pathogenic coronaviruses continues to be studied. In patients where more severe illness occurs it appears there is a timing mismatch between the two forms of immune response (1). Researchers theorize that the adaptive immune response of COVID-19 patients is more likely to come before the peak of viral load, while this is not seen for influenza patients. The result is that in the influenza patient viral clearance is enhanced, while it may be delayed in COVID-19 patients, and with it other complications (1).

Various theories concerning pharmacological interventions to alter the timing of various components of and intensity associated with the immune system to enhance viral clearance and attenuate some of the deleterious effects of the immune response, as pertains to COVID – 19, such as cytokine storm, and perhaps the possible mismatch phenomenon posited by some researchers, all of which remain to be studied (1, 3, 9).

It is well known that the immune response to viruses in general and COVID-19 specifically is complex, is predicated on host factors, comorbidities, whether immunosuppressive therapies, and biologic disease modifying agents are being utilized for preexisting illness, and coronaviruses' ability to adapt, mutate, and evade host defenses. Beyond the scope of this current paper, nevertheless the astute clinician will be aware of the complexities in the host-COVID-19 immune response, and that it contributes to clinical benefit, and in some cases clinical deterioration.

Moreover, the persistent question why a majority of COVID-19 infected patients tend to survive with minimal effect, compared to a not insignificant proportion of patients require aggres-

sive health care facility management remains to be answered. Whether there are some differences in immune response – adaptive or innate, as of yet unidentified, poorly understood, or waiting for further characterization, between persons progressing to moderate or severe illness compared to the majority of individuals infected with COVID-19 who remain minimally symptomatic or asymptomatic remains to be seen.

Perhaps as some studies suggest there is a perfect storm combination of effects – host immunity, viral load, age, and underlying comorbidities. However, this does not address the previously well, younger (under 65) patient who gets profoundly ill, or dies. To be sure outliers occur in any illness but this does not seem to be the case (3-7, 9).

The host-virus response, and protective immunity in COVID – 19 continue to be studied.

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C1 COVID – 19: IMMUNOLOGY – GENERAL CONSIDERATIONS

Based on extensive research, the immune response to coronaviruses is complex, owing to their ability to adapt, mutate, and mechanism of infection. This seems especially true for COVID-19.

Among the key issues associated with this new viral pathogen are the following:

1. Why the broad but consistent range of symptoms – the majority of persons infected with COVID-19 have mild or no symptoms, yet ~ 20% progress to more severe illness?
2. What is the role of human protective antibody IgG?, the T cell response?
3. Does infection with COVID – 19 confer sustained immunity against reinfection?
4. What factors contribute to a COVID-19 immune response, or prevent an adequate one?
5. Do all survivors develop similar immune protection if a protective immune response occurs?
6. If immune protection does develop – vaccine or natural infection, how potent, how fast, how long does it last?
7. Does prior infection with other human coronaviruses provide some cross protection against COVID – 19?

8. Have we asked all the important questions?
9. Are there more optimal ways to optimize infection control that are not utilized?
   a. Barriers to implementing?
10. What has COVID-19 yet to teach us?

These are some of the most important questions yet to be answered, with significant public health implications. They also influence vaccine development strategies.

C2 COVID – 19: IMMUNE RESPONSE - AN OVERVIEW

As discussed earlier, COVID-19 can induce a severe acute respiratory syndrome, with manifestations including pneumonia, ARDS, diarrhea, lymphopenia, and pro-inflammatory cytokine production (1-7). The immune response contributes to the clinical evolution – in both positive and potentially deleterious ways.

Just as SARS caused significant pulmonary disease, with a high case fatality rate just under 10%, SARS – CoV2 (COVID-19) also results in severe respiratory illness and death. Research confirms the immune response contributes to the clinical progression, for example lung tissue damage induced by a strong inflammatory response (cytokine storm), macrophage, and neutrophil activation (1, 2, 5 - 10).

Early studies have revealed some persons who tested positive from molecular testing did not have detectable levels of IgG (8). Among hospitalized paitents levels of neutralizing antibodies were low, or not detectable (8 – 10). Questions remain about the protective immunity levels and characteristics among those who are infected but either asymptomatic or minimally symptomatic.

An interesting finding seems to have emerged concerning T cell related immunity. COVID-19 can cause lymphopenia, and delay T cell pathway activation in the initial days of infection, with early research showing after two weeks of symptoms COVID-19 specific memory T cell phenotypes (central memory for CD4 lymphocytes, and effector memory for CD8 lymphocytes) start to emerge in peripheral blood. The extent of resulting protective immunity remains to be further elucidated. This could have important implications for vaccine development, and provide greater insight into the value of convalescent plasma, and the protective immunity against COVID-19 in general. Further research is underway (10).

Moreover it is worth noting that an absence of IgG detection is not necessarily the same thing as lacking protective immunity. An example of this is hepatitis. In the context of vaccination in patients in which no antibody detection was noted, memory T cells can be activated and confer protection from reinfection (11, 12). Changes in protective immunity of viral diseases in which no antibody detection was noted may therefore not relate to protective capability (9-13).

As coronaviruses have demonstrated, they undergo viral mutations. Such induction of these mutations may contribute to COVID-19's ability to evade the immune system. This virus may reduce B cell activity.

The human immune response is a complex and dynamic interplay of multiple pathways and effector cells. The further development and subsequent deployment of additional testing assays designed to determine the various immune cellular responses, in addition to neutralizing antibodies testing warrants consideration (9, 14). For example lymphocyte T cell assays are relatively highly specific and sensitive (11 -13). Some posit the notion that such testing may reveal both a lack of IgG but also presence of T cells post infection, which may be sufficient for immune protection.

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C3 COVID – 19: IMMUNE SYSTEM AND CYTOKINE STORM

The phenomenon of cytokine storm refers to an excessive immune response; it can develop rapidly, and cause serious illness, including death. Some studies suggest the rapid and severe clinical deterioration of patients is in part related to cytokine storm (1-8). It is considered contributory to the acute respiratory distress syndrome (ARDS) and multisystem organ failure among moderately to severely ill COVID-19 patients. It is posited that clinical improvement and enhanced survival can result if the cytokine storm can be prevented or attenuated. Currently research is underway to study both the cytokine storm in COVID-19 and ways to interrupt the development/progression of this immune response (1, 3).

During viral infection, cytokines are a component of the immune response, and also Immunopathology that results. As discussed earlier both innate and acquired immunity play a role in human defense against viral infections, and COVID – 19 is no exception (1, 6-8). The innate immune response is tasked as the first defense against viruses. Unfortunately some viral illnesses result in a dysregulated and/or excessive immune respone that can prove damaging (7, 9-11).

Not surprisingly increased serum levels of proinflammatory cytokines have been reported in other highly pathogenic coronaviruses 1, 4-6, 9-11)

Human coronaviruses are associated with proinflammatory responses. In in vitro studies, it has been demonstrated there is a delyed release of cytokines and chemokines in the respiratory

epithelial cells, dendrites and macrophages in the early stage of SARS. Cells will then secrete low levels of antiviral factors – interferons, and high levels of proinflammatory cytokines (interleukins 1b and 6, TNF and chemokines. MERS caused a delayed but elevated level of proinflammatory cytokines ad chemokines – it infects human airway epithelial cells, THP1 cells (monocyte cell), human peripheral monocyte derived macrophages and dendritic cells. Plasmacytoid dendritic cells are induced to produce large amount of interferons. Not surprisingly patients with severe MERS had significantly higher levels of serum cytokine and chemokines than patients with milder or moderate disease. Of note, elevated cytokine and chemokines levels are related to high numbers of neutrophils and monocytes in lung tissues as well as peripheral blood. It is this high level of inflammatory mediators that is posited as contributory to the lung pathology experienced in highly pathogenic coronaviruses (1, 4-8).

Interferon gamma primarily activates epithelial cells, reduces mononuclear macrophage mediated proinflammatory activity of interferons alpha and beta, and inhibits recruitment of neutrophils to the site of inflammation, activates antiviral genes, and aids in antiviral activity without causing a hyperimmune response. This has been the basis for early administration to reduce viral load and in some cases improve clinical symptoms. It has not demonstrated consistent success against COVID-19 as a monotherapy, nor has it demonstrated an ability to reduce mortality overall, but as part of a therapeutic cocktail may confer benefit. Further study is required, and prior experience suggests interferons need to be administered early in treatment (1-3, 5, 12).

Other approaches, in addition to convalescent plasma, such as anti TNF, IL1 blockade, glucocorticoids, and other interventions have been tried against cytokine storm, sepsis, coronaviruses, including COVID-19 (12 – 17).

In COVID-19 patients, high levels of inflammatory cytokines - IL-1B, IFN gamma, IP-10 and monocyte chemo-attractant protein 1 (MC P1) were detected. This may active at T helper 1 response. TH1 activation is an essential component in specific immunity. Interestingly, COVID-19 patients differ from SARS infected persons in terms of their levels of T helper 2 (TH2) secreted cytokines (IL4 and IL10). These inhibit the inflammatory response (1,4,5, 10 – 17).

Moreover, in patients with COVID-19 severity of illness seems to correlate with levels of IL2R and IL6. A study revealed patients with COVID-19 treated in the ICU compared with non ICU patients, had increased serum levels of granulocyte colony stimulating factor, IP-10, MCP1, macrophage inflammatory protein 1A, and TNF alpha. It seems consistent that cytokine storm is correlated with disease severity in at least some patients (1, 4-6).

ARDS reflects pulmonary and interstitial tissue damage related to inflammatory cell infiltration and excessive release of cytokines, resulting in advanced clinical deterioration. Not surprisingly the ARDS of COVID-19 is related to inflammatory cytokine storm. Serum levels of cytokines are significantly elevated in ARDS, and correlates with severity and mortality. Of note, cytokine storm is also an important determinant of clinical progression in the COVID-19 extrapulmonary illness, and multisystem organ failure often seen in advanced cases (1,2).

COVID-19 clearly presents multiple challenges in the medical management of infected patients, especially those progressing to moderate or severe illness. Addressing cytokine storm is an important consideration, and should be part of a comprehensive strategy to treat the COVID-19 infected patient.

Many therapeutic approaches have been suggested (1, 3, 12-27). TNF can trigger cytokine storm. Inhibition has been shown to confer benefit with sepsis, and atherosclerosis, but to date evidence is lacking in the treatment of human coronaviruses (1, 16, 17). Other possible approaches have been suggested ranging from the use of beneficial interferon (1, 4), to interferon inhibition, the use of corticosteroids (1, 4, 18), immunoglobulin (IVIG) (1 -3, 12), interleukin antagonists (1), chloroquine (1, 3, 21, 22), stem cell therapy (1), neutralizing antibodies (1, 12), blood purification treatments (1, 26) (plasma exchange, filtration, artificial liver technology), and other approaches in an attempt to remove or reduce inflammatory factors), natural anti-inflammatory substances such as ulinastatin (1, 23, 24), and other therapeutics have been suggested, several of which are discussed in the **Therapeutic Section** of this article.

As with SARS and MERS, COVID-19 associated cytokine storm usually is associated with worsening illness, and higher mortality. The ability to predict which COVID-19 infected patients will progress to cytokine storm, based on early laboratory testing, could lead to earlier interventions, and better clinical outcomes. Traditionally cytokine storm has been associated with hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS). This may not always be the case with CS associated with COVID-19, and therefore the HLH 2004 or MAS criteria may not provide the same clinical value.

Recently Temple University Medical researchers (28) conducted a pilot retrospective study of over 500 COVID-19 confirmed patients. Their early results suggest the COVID 19 CS group had higher levels of ferritin, CRP, trigylcerides and decreased levels of albumin signs of systemic inflammation. Also significantly elevated levels of Il-6; of note this is elevated in most COVID-19 patients. Also neutrophils and monocytes were significantly increased in CS group reflective of innate immunity, but lymphocytes were decreased. Markers of tissue damage were significantly higher in CS ALT, AST, D Dimers, LDH and troponin I, along with elevated creatinine, BUN, and their ratio were noted in their study. Differences in the Temple University pilot compared to HLH or MAS criteria suggest in some cases of COVID-19 CS may have different types of inflammation. Recent report suggests LDH, CRP, and low lymphocytes are associated with higher mortality in patients with COVID-19 (29).

These are offered as additional information to consider, with the caveat this was a pilot study involving a small number of patients, at only one medical center.

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COVID – 19: IMMUNE SYSTEM AND BRADYKININ STORM

Unlike most influenza viral illness, which coronaviruses, especially this latest highly pathogenic version, seem to be compared to in terms of preparedness and public health measures, COVID-19 has revealed a far more complex clinical picture, as well as proven to be difficult to contain, as well as treat. There are currently no equivalent therapeutics for coronaviruses that are analogous to the role oseltamivir, zanamivir, or peramivir play in the treatment of COVID-19, or any of the highly pathogenic coronaviruses (SARS, MERS).

Treatment of the various permutations of COVID-19 are dependent upon many factors, including time to presentation, initial symptoms, degree and speed of pulmonary and extrapulmonary involvement, general host factors, such as the role of the immune system, and specific patient characteristics, such as comorbidities, and their underlying severity at the time of infection. Moreover a treatment may have a therapeutic window, where it must be administered within a specific set of clinical and temporal conditions, or carries a higher risk/benefit ratio.

Among the general patient characteristics we have been discussing is host immune response. By better elucidating the various pathophysiological pathways involved in COVID-19 infection, new therapies and treatment approaches can be developed, older, existing meds can be repurposed, and better management delivered.

As discussed earlier, coronaviruses, except for the highly pathogenic strains, tend to cause mostly respiratory illness. Clinical experience throughout 2020 has demonstrated COVID-19 is able to cause a complex cascade of pulmonary and extrapulmonary illness with varying degrees of severity.

Numerous hypothesis have been posited trying to determine who will progress from mild to severe disease, and what are the cause/s of both the often severe respiratory illness, as well as hematologic, cardiac, renal, gastrointestinal, neurological and other system involvement.

Mounting evidence suggests host immune response is contributory to the severe forms of disease progression in all the highly pathogenic coronaviruses, and is associated with increased morbidity, intensive care unit treatment, as well as mortality (1 – 7).

Cytokine storm has been increasingly well characterized, as discussed above. But there are other contributors of the hyperimmune response (1 – 7) that are being posited (Figure 1) (1).

An example of this is the increased levels of granulocyte colony stimulating factor (G-CSF), intrerferon gamma induced protein 10 (INF GP10), monocyte chemo attractant protein 1 (MCP1) macrophage inflammatory protein 1 alpha, and tumor necrosis factor alpha (TNF a), in ICU patients, compared to levels obtained in non-ICU patients. Interleukin 2 (IL2) receptor, IL 6, IL8, IL 10, were found to be lower in COVID-19 compared to those who recovered from the illness (7,8).

These inflammatory responses found in COVID-19 patients, as discussed earlier, are associated with the "cytokine storm," which has characterized severely ill patients. This hyper-inflammatory response contributes to the severity, and possibly longer term injury. The pathophysiology of progressive lung involvement, for example, including respiratory failure, reveals hyaline membrane formation, inflammation, infiltration with multinucleated syncytial cells, and cytokine release (8,9).

Recently scientists at Oak Ridge National Laboratory reported findings on their gene expression analysis looking at the bronchoalveolar lavage fluid from COVID-19 patients initially utilized to sequence the new virus, as well as control subjects (1).

They discovered a critical imbalance in the rennin-angiotensin system (RAS); decreased expression of angiotensin converting enzyme (ACE) in association with increases in angiotensin converting enzyme 2 (ACE2), rennin, angiotensin, selected RAS receptors, kinogen, and several kallikrein activating enzymes, along with both bradykinin receptors. This pattern of the RAS is posited to elevate bradykinin levels on a multi-system, multi-tissue basis, resulting in vascular dilation, and vascular permeability, leading to hypotension (1).

These findings convey a similar picture of cytokine storm effect on some COVID-19 patients.

Differentially expressed genes: red ovals indicate genes upregulated in COVID-19, blue are downregulated, colors are scaled to the $\log_2$-fold-change values for COVID-19. The overall effect is to shift the system to production of $Ang_{1\text{-}9}$ and AGTR2-driven sensitization of BK receptors.

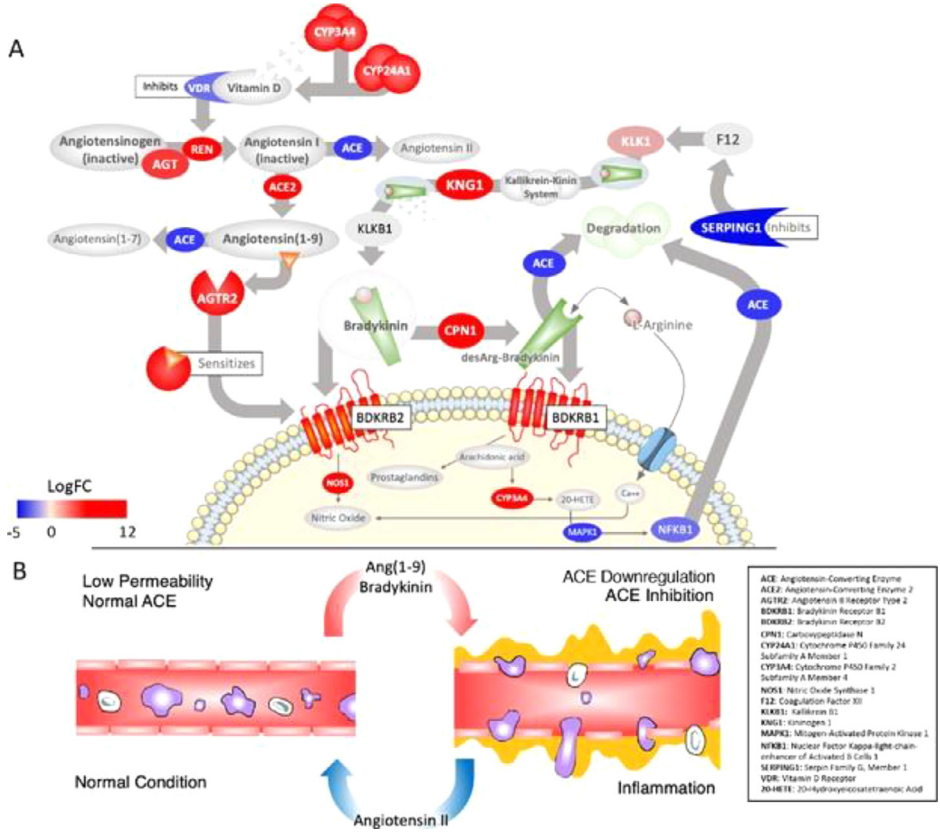

Figure 1. Critically disrupted RAS and Bradykinin pathways COVID-19 BAL samples.(1)

According to the researchers, these bradykinin related events may contribute to many of the symptoms associated with COVID-19 (1).

The authors reference Chinese researchers studying fluid and cells from COVID-19 patients noted decreased levels of ACE in lung cells, and increased levels of ACE2 resulting in increased amounts of bradykinin. Referring to it as bradykinin storm, it was noted to induce pain, cause expansion of blood vessels, increased permeability of these vessels, as well as an increase in hyaluronic acid (HA) production. Of note they discovered a decrease in enzymes that can degrade HA. These researchers suggest the combination of Bradykinin Storm fluid leakage, along with excess hyaluronic acid prevent efficient gas exchange (oxygen, carbon dioxide) within the lungs.

Garvin et al, suggest bradykinin storm may be responsible for more severe COVID-19 related illness.

Bradykinin System (BK)

Bradykinin is a component of the RAS. It induces vasodilation, natriuresis, and hypotension. ACE has a high affinity for ACE receptors. In situations where ACE levels are low, the balance towards BK mediated hypotension can occur (1, 10, 11).

BK is part of the complex inflammatory response cascade as well. It is associated with heightened pain, neutrophil recruitment, and vascular hyperpermeability.

In COVID-19 patients, degradation enzymes appear to be down-regulated. The researchers also note BK receptors are expressed in COVID – 19 patients studied, but at near undetectable levels in control subjects.

Wang et al, also note that COVID-19 contacts ACE2 recpetpr, causing imbalance of the ACE2-RAS- bradykinin axis, cytokine storm, all contributing to progression of illness (1,12). They note in some clinical experience symptomatology including hemoptysis, progressive pulmonary hypertension, and right heart failure, associated with ACE2 associated pulmonary vascular endothelium as contributory to pathophysiology, in some COVID-19 patients (1,12).

Associated with this bradykinin influence is significant down regulation of the genes that encode for HA degradation in severely ill COVID-19 patients, whereas there is an upregulation for genes associated with HA synthesis. (13, 14). This is posited to cause in increase in HA in the bronchoaleveolar space (Figure 2). The effect of hyperpermeability and increased HA associated with BK can cause intrapulmonary fluids, some refer to as a "hydrogel," that impair gas exchange (13 – 15). Other studies have shown increased HA in BAL fluid is associated with acute respiratory syndrome (ARDS), with a negative impact on pulmonary oxygenation index (13,15).

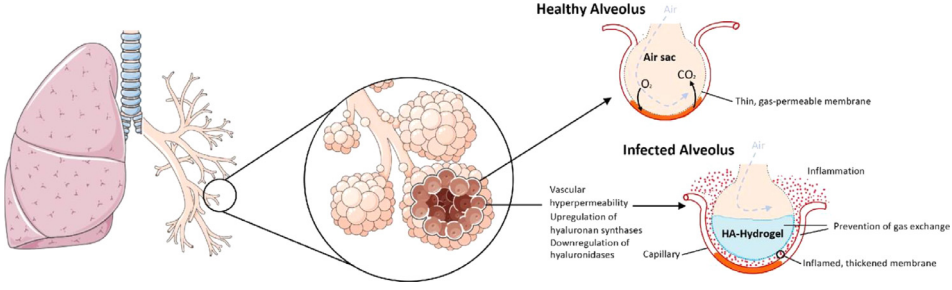

Figure 2. The upregulation of hyaluronan synthases and downregulation of hyaluronidases combined with the BK-induced hyperpermeability of the lung microvasculature leads to the formation of a HA-hydrogel that inhibits gas exchange in the alveoli of COVID-19 patients (1, 16,17).

Adachi, and others report organizing hyaline membranes in the early stages of the alveolar lesions, and exudative phase associated with alveolar damage (16, 17).

Increased levels of BK is associated with hypokalemia, which, if severe enough, can cause dysrhythmia, and cardiac arrest – also reported in COVID-19 patients.

Loss of ACE2 may lead to further activation of plasma kallikrein kinin system resulting increased bradykinin formation. BK is associated with angioedema; it is suggested many of the associated symptoms for COVID-19 – myalgia, fatigue, nausea, vomiting, diarrhea, anorexia, headaches, decreased cognitive function, are similar to elevated BK pathophysiology (18).

Implications for therapeutics

"Bradykinin storm," and "cytokine storm," may both be triggered, linked as part of the immune pathway and contributory to disease severity in COVID-19 patients. As such, this information may provide yet an additional opportunity to intercede in the disease cascade of patients infected with COVID-19.

For example, prior research has suggested persons who have vitamin D deficiency may be at greater risk for ARDS, with limited research showing an association with severity of illness in COVID-19 (19). Putative mechanism may be the role vitamin D plays in regulation of RAS, but further research is necessary, given an association is not synonymous with causative.

Researchers at Oak Ridge suggest FDA approved therapeutics that may be able to increase ACE, decrease BK, or block BK2 receptors could be repurposed to treat COVID-19 patients (Table 1), in the hope of rudcing vascular hyperpermability, and hyaluronan (1).

Icatibant

Recently a small case control study was resulted, looking at a Kinin B2 Receptor (BK2R) antagonist in patients infected with COVID- 19 (2). Nine COVID-19 patients were matched to eighteen controls. Most were men. Nine patients were given icatibant, a bradykinin 2 receptor antagonist – most were in a non ICU hospital room, while one was recently transferred out of the intensive

Table 1
Potential therapeutic interventions, their targets, and predicted effect (1).

Drug	Target	Predicted Effect
Danazol, Stanozolol	SERPING1	Reduce Bradykinin production
Icatibant	BKB2R	Reduce Bradykinin signaling
Ecallantide	KLKB1	Reduce Bradykinin production
Berinert,Cinryze,Haegarda	SERPING1	Reduce Bradykinin production
Vitamin D	REN	Reduce Renin production
Hymecromone	HAS1,HAS2, HAS3	Reduce hyaluronan
Timbetasin	TMSB4X TMSB4X	Increase fibrinolysis

care unit on high flow oxygen. In all nine patients who received icatibant, all showed a significant need for oxygen supplementation over the course of initial therapy. Among the control patients, three showed a spontaneous reduction in O2 supplementation required. The researchers noted that there were three patients who received icatibant required resupplementation with oxygen.

The researchers note based on their study that icatibant associated improvement in oxygenation suggesting benefit targeting the kallikrein - kinin system especially in the early stage of disease in hospitalized patients when they start becoming hypoxic. The authors suggest for the patients requiring resupplementation that contributory might be that Icatibant has a short half life (t 1/2) of ~2 hrs. The study design does not lend itself to answering this.

Although an interesting, and additional potential opportunity to assist patients infected with COVID-19, the study had limitations.

To date larger clinical trials are needed to address the role of specific bradykinin storm focused therapeutics in the treatment of COVID-19 patients (1). Nevertheless, gaining greater clarity into the various contributors to the complex interplay between COVID-19, host immune response, and multisystem involvement can only assist in better treating our patients, and pursuing potentially more effective therapeutic interventions.

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COVID-19: CLINICAL ILLNESS – A Brief Overview

The clinical illness associated with SARS 2 COVID-19, especially referable to the pulmonary manifestations, are similar to those of the earlier highly pathogenic human coronaviruses SARS and MERS (Table 1) (1- 20). Most commonly among the advanced disease from COVID-19, multiple systems can become involved – starting with respiratory illness, as well as extrapulmonary disease - gastrointestinal, cardiovascular, and neurological systems can become involved, resulting in a diverse cascade of symptoms (1,3-5).

Extrapulmonary illness, can be extensive, severe, and contribute to the morbidity and mortality of COVID-19.

Both pulmonary and extrapulmonary illness can be complex, and requires an aggressive, multidisciplinary approach. This is a brief overview. Other sections also provide insights into the pathophysiology, as well as general medical and non medication intervention strategies.

As discussed earlier, most patients (~80%) experience mild if any symptoms, which usually resolve in a week or less. But for a small, but seemingly stable percent of patients (~20%) will

advanced to moderate or severe illness, and within this group hospitalization, even intensive care unit management (ICU) may be necessary (3-8).

Respiratory tract involvement is usually one of the presenting symptoms owing to the route of entry for COVID-19, pulmonary tropism, and likely abundance of ACE2 in pulmonary tissue.

A high index of suspicion concerning COVID-19, and providing early testing remain important for both the benefit of patients, and for public health surveillance. Given the potential for multiple organ involvement, coagulation study, and broad hematology evaluation, along with cardiac, liver, and kidney function testing are encouraged, along with COVID-19 testing. Ruling out potential other respiratory pathogens, including influenza are warranted. Early XRay and CT evaluations are encouraged, as is aggressive management in the hope of preventing rapid clinical deterioration. Close attention to early deterioration, as well as underlying comorbidities are critical. Further details on the medical management are in the Case Definition/Medical Management Section.

Symptomatic patients infected with COVID-19 appear to manifest clinical illness after an incubation period of ~5 – 6 days for most people with a range of 2 – 14 days (8 – 10, 20). The data are relatively stable, and form the basis for general quarantine suggested times of 14 days with exceptions on individual basis. The time from symptoms to death has been reported between 6 – 41 days, with a 14 day average (9,10, 20). This depends upon the underlying health of the patient, comorbid conditions that may influence ACE-2 receptor density and/or overall immune status, age, and other factors, such as medications, with several of these variables currently under investigation in terms of their contribution to COVID-19 susceptibility, and severity of illness. It has been well described that the time to illness is typically faster for patients over 70 years of age, who are at greater risk for more serious illness. People with underlying pulmonary, cardiac, and renal disease also are at greater risk (3-5), as are persons who are obese.

Early commonly noted symptoms include fatigue, cough, and fever. Ageusia/dysgeusia (alteration in taste) occurs in a not insignificant proportion of patients (see Gastrointestinal Section). Hemoptysis, headache, productive sputum, diarrhea, and dyspnea have also been reported. Early dyspnea should always alert the clinician to rapid progressive of underlying illness – whether COVID-19 or other etiology. Early blood testing often reveals lymphopenia. In advancing disease clinical features consistent with acute respiratory distress syndrome (ARDS), and acute cardiac injury may be present.

Pulmonary illness can deteriorate rapidly – and result from a complex cascade of physiologic and virus related influences. These are discussed in greater detail in the WHO management guidelines section.

Extrapulmonary disease can be extensive and involve virtually every major organ system. Blood clots have been reported and contribute to the deterioration of patients. Cardiovascular, gastrointestinal, and renal manifestations are not uncommon. These will be covered in more detail in their respective chapters. The range of COVID-19 related illness and management are covered more in depth in the subsequent sections, including the THERAPEUTICS, as well as WHO Management Guidelines Section. Diagnostics and medical management protocols must be adapted to the range of pulmonary and extrapulmonary illness present, and aggressively anticipate recruitment of systems and progression of severity. Table 1 From Hosseiny et al. (1).

Information on special populations such as women who are pregnant and children are still being studied in terms of potential risk or protective factors in the context of COVID-19. These will be discussed further in the COVID-19 General Management Considerations, Radiological Testing, and Extrapulmonary (GI and Nephrology) Sections that appears elsewhere in this edition.

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