Virology, Transmission and Pathogenesis of SARS-CoV-2

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Introduction

Since the emergence of SARS-CoV-2 in December 2019, there has been an unparalleled global effort to characterise the virus and the clinical course of disease. SARS-CoV-2 is an enveloped β-coronavirus, with a genetic sequence very similar to SARS-CoV (80%) and bat coronavirus RaTG13 (96.2%).[1] Coronavirus Disease (COVID-19), caused by SARS-CoV-2, has demonstrated a biphasic pattern of illness, which is likely due to a combination of an early viral response phase and an inflammatory second phase. Most of the clinical presentations are mild and the typical pattern of COVID-19 is more like an influenza-like illness that includes fever, cough, malaise, myalgia, headache, and taste and smell disturbance rather than severe pneumonia.[2] In this review, we provide a broad update on the emerging understanding of SARS-CoV-2 pathophysiology, including virology, transmission dynamics, and the immune response to the virus.

VIROLOGY

What we know about the virus itself (Figure 1)

Mutation rates in CoV are lower than other RNA viruses because they have the capacity for proof-reading during replication. As SARS-CoV-2 has spread globally, like other viruses, it has accumulated some mutations in the viral genome which contains geographic signatures that help researchers with virus characterisation and understanding of epidemiology and transmission patterns. In general, these mutations have not been attributed to phenotypic changes impacting viral transmissibility or pathogenicity. G614 variant in the S protein has been postulated to increase infectivity and transmissibility of the virus.[3] Higher viral loads were reported in clinical samples with virus containing G614 than previously circulating variant D614, although there was no association with severity of illness measured by hospitalisation outcomes.[3] However, these findings have yet to be confirmed in regards to natural infection.

Why is SARS-CoV-2 more infectious than SARS-CoV-1?

The modelling studies estimate that SARS-CoV-2 has a higher reproductive number (R_0) than SARS-CoV, indicating much more efficient spread.[2] Multiple characteristics of SARS-CoV-2 may help explain this enhanced transmission. While both SARS-CoV-1 and SARS-CoV-2 preferentially interact with the angiotensin-converting enzyme 2 (ACE2) receptor, SARS-CoV-2 has structural differences in its surface proteins, which allow stronger binding to the ACE2 receptor,[4] and greater efficiency at invading host cells.[2] SARS-CoV-2 also has

greater affinity for the upper respiratory tract and conjunctiva,[5] both of which are entry points for the virus, thus, infecting the upper respiratory tract and conducting airways more easily.[6]

Viral load dynamics and duration of infectiousness

Viral load kinetics could also explain some of the differences between SARS-CoV-2 and SARS-CoV-1. In the respiratory tract, peak SARS-CoV-2 load observed at the time of symptom onset or in the first week of illness with subsequent decline thereafter, indicating highest infectiousness potential just before or within the first 5 days of symptom onset (Figure 2).[7] In contrast, in SARS-CoV-1 highest viral loads were detected in the upper respiratory tract in the second week of illness, which explains it's minimal contagiousness in the first week after symptom onset, enabling early case detection in the community.[7]

qRT-PCR (which detects viral SARS-CoV-2 RNA) can remain detectable for a mean of 17 days (max 83 days) after symptom-onset in the upper respiratory tract.[7] However, detection of viral RNA by qRT-PCR does not necessarily equate to infectiousness and viral culture from PCR positive upper respiratory tract samples has been rarely positive beyond 9 days of illness.[5 7] This corresponds to what is known about transmission based on contact tracing studies which is maximal in the first week of illness, and no late transmission have been documented.[8] More severely ill or immune-compromised patients may have prolonged virus shedding, or some patients may have intermittent RNA shedding; however, low level results close to the detection limit may not constitute infectious viral particles. While asymptomatic individuals (those with no symptoms throughout the infection) can transmit the infection, their contribution to the spread seems to be limited.[9 10] Whereas pre-symptomatic transmission, 1-2 days before symptom onset, occurs and likely contributes to the spread of SARS-CoV-2. [10 11]

Route of transmission and transmission dynamics

Like the other CoVs, the primary mechanism of transmission of SARS-CoV-2 is via infected respiratory droplets, with viral infection occurring via direct or indirect contact with nasal, conjunctival or oral mucosa. Target host receptors are mainly found in the human respiratory tract epithelium, including the oro-pharynx and upper airway. The conjunctiva and gastrointestinal tracts are also susceptible to infection and may also serve as portals of entry.[6]

The transmission risk depends on many factors such as contact pattern, environment, infectiousness of the host and socio-economic factors, as described elsewhere.[11] The majority of transmission occurs through direct close contact (15 min face to face or within 2

metres), especially efficient spread has been seen within households, family and friend gatherings.[11] Household attack rates ranges from 4-35%.[11] While sleeping in the same room or being a spouse increases the risk of infection, isolation of the infected case away from the family is related to lower risk of infection.[11] In addition, dining in close proximity or sharing food and group activities such as board games identified as high-risk activities.[11] The infection risk significantly increases in enclosed environments compared to outdoor settings.[11] Although aerosol transmission can still factor in during prolonged stay in crowded, poorly ventilated indoor settings (meaning transmission could occur at a distance), in the absence of aerosol-generating procedures, the data are inconsistent with regards to aerosols being a major route of transmission. [11] [12]

The role of faecal shedding in SARS-CoV-2 transmission and the extent of fomite (through inanimate surfaces) transmission also remains to be fully understood. Both SARS-CoV-2 and SARS-CoV-1 remain viable for many days on smooth surfaces (stainless steel, plastic, glass) and at lower temperature and humidity (i.e. air-conditioned environments).[13] [14] Thus, transferring infection from contaminated surfaces to the mucosa of eyes, nose and mouth via unwashed hands is a possible route of transmission. This route of transmission may contribute especially in facilities with communal areas, with increased likelihood of environmental contamination. However, both coronaviruses are readily inactivated by commonly used disinfectants, emphasising the importance of surface cleaning and handwashing. While SARS-CoV-2 RNA has been found in stool samples and RNA shedding often persists for longer than in respiratory samples,[7] virus isolation has rarely been successful from the stool.[5] [7] There are no published reports of faecal-oral transmission. In SARS, faecal-oral transmission was not considered to occur in most circumstances; but, one explosive outbreak was attributed to aerosolization and spread of the virus across an apartment block via a faulty sewage system.[15] An indirect evidence of similar transmission has been reported for SARS-CoV-2 in China, although no direct evidence has been presented, except for the positive surface samples in the bathrooms.[16] It remains to be seen if this is a common occurrence.

PATHOGENESIS

Viral entry and interaction with target cells

SARS-CoV-2 binds to heparin sulphate[17] and ACE2, the host target cell receptor, which is principally expressed in the airway epithelial cells, vascular endothelial and intestinal epithelial cells among others.[2] Active replication of the virus and release of virus in the lung cells leads to non-specific symptoms such as fever, myalgia, headache and respiratory

symptoms.[2] In an experimental hamster model, the virus causes transient damage to the cells in the olfactory epithelium, leading to olfactory dysfunction, which may explain temporary loss of taste and smell commonly seen in COVID-19.[18] The distribution of ACE2 receptors in different tissues may explain the sites of infection and patient symptoms. For example, the ACE2 receptor is found on the epithelium of other organs such as the intestine and endothelial cells in the kidney and blood vessels, which may explain gastrointestinal symptoms and cardiovascular complications.[19] For example, overexpression of human ACE2 was associated with SARS-CoV-2 neuroinvasion in a mouse model, suggesting that neurological presentation seen in some patients might be related to direct viral invasion of central nervous system.[20] Lymphocytic endothelitis has been observed in post-mortem pathology examination of the lung, heart, kidney, and liver as well as liver cell necrosis and myocardial infarction in patients who died of COVID-19.[2 21]

Much remains unknown. Are the pathological changes in the respiratory tract or endothelial dysfunction due to direct viral infection, cytokine dysregulation, coagulopathy or is it multifactorial? And does direct viral invasion or coagulopathy directly contribute to some of the ischemic complications such as ischaemic infarcts? These and more, will require further work to elucidate.

Immune response and disease spectrum (Figure 2 and Box 1)

After viral entry, the initial inflammatory response attracts virus-specific T cells to the site of infection, where the infected cells are eliminated before the virus spreads, leading to recovery in most patients.[22] In patients who develop severe disease, SARS-CoV-2 elicits an aberrant host immune response.[22 23] For example, post mortem histology of lung tissues of patients who died of COVID-19 have confirmed the inflammatory nature of the injury, with features of bilateral diffuse alveolar damage, hyaline-membrane formation, interstitial mononuclear inflammatory infiltrates, and desquamation consistent with acute respiratory distress syndrome (ARDS), and is similar to the lung pathology seen in severe MERS and SARS.[24 25] A distinctive feature of COVID-19 is the presence of mucus plugs with fibrinous exudate in respiratory tract, which may explain the severity of COVID-19 even in young adults.[26] This is potentially due to the overproduction of pro-inflammatory cytokines that accumulate in the lungs eventually damaging the lung parenchyma.[22]

Some patients also experience septic shock and multi-organ dysfunction.[22] For example, the cardiovascular system is often involved early in COVID-19 disease and is reflected in the release of highly sensitive troponin and natriuretic peptides.[27] Consistent with the clinical context of coagulopathy focal intra-alveolar haemorrhage and presence of platelet-fibrin

thrombi in small arterial vessels is also seen.[25] Cytokines normally mediate and regulate immunity, inflammation and haematopoiesis; however, further exacerbation of immune reaction and accumulation of cytokines in other organs in some patients may be causing extensive tissue damage, and in some patients, a cytokine release syndrome (cytokine storm), resulting in capillary leak, thrombus formation and organ dysfunction.[22 28]

The mechanisms underlying the diverse clinical outcomes

Clinical outcomes are influenced by host factors such as older age, male gender and underlying medical conditions, [29] as well as factors related to the virus (such as viral load kinetics), host-immune response, and potential cross-reactive immune memory from previous exposure to seasonal coronaviruses. (Box 1)

Gender related differences in immune response has been reported revealing that that male patients had higher plasma innate immune cytokines and chemokines at baseline.[30] In contrast female patients had significantly more robust T cell activation than male patients and among male participants T cells activation declined with age, which was sustained among female patients. These findings suggest that T cell response is important in defining the clinical outcome.

Increased levels of pro-inflammatory cytokines correlate with severe pneumonia and increased ground-glass opacities within the lungs.[28 31] In cases with severe illness, increased plasma concentrations of inflammatory cytokines and biomarkers were observed compared to those with non-severe illness.[28 32]

Emerging evidence suggests there may be a correlation between viral dynamics, the severity of illness, and disease outcome.[7] Longitudinal characteristics of immune response showed a correlation between the severity of illness, viral load and IFN- α, IFN-γ and TNF-α response.[30] In the same study many interferons, cytokines, and chemokines were elevated early in disease for patients who had severe disease and higher viral loads. This emphasizes that viral load may drive these cytokines and the possible pathological roles associated with the host defence factors. This is in keeping with the pathogenesis of influenza, SARS, MERS whereby prolonged viral shedding was also associated with severity of illness.[7 33]

Given the substantial role of immune response in determining clinical outcomes, several immunosuppressive therapies aimed at limiting immune-mediated damage are currently in various phases of development (Box 2). For instance, glucocorticoids (dexamethasone).

suppress immune response by inhibiting lymphocytes including a range of cytokines, and the RECOVERY trial has demonstrated mortality benefit in patients with hypoxemia especially among those admitted to ICU or with >7 days of symptoms.[34] Although early evidence suggested host-targeted therapeutic options, such as inhibition of human cytokine interleukin-6, Tociluzumab may have survival benefit, [35] a press release suggests no survival benefit demonstrated by the COVACTA study, though the findings have not been formally published.[36]

Immune response to the virus and its role in protection

COVID-19 leads to an antibody response to a range of viral proteins, but the spike (S) protein and nucleocapsid are those most often used in serological diagnosis. There is little detectable antibody in the first four days of illness, but patients progressively develop antibody with most achieving detectable response after 4 weeks.[37] A wide range of virus neutralizing antibodies (nAb) have been reported, and emerging evidence suggests nAbs may correlate with severity but wane over time. [38] The duration and protectivity of antibody and T cell responses remain to be defined through studies with longer follow up. CD-4 T cell responses to endemic human coronaviruses appear to manifest cross-reactivity with SARS-CoV-2, but their role in protection remains unclear.[39]

Unanswered questions

Further understanding the pathogenesis for SARS-CoV-2 will be vital in developing therapeutics, vaccines, and supportive care modalities in the treatment of COVID-19. More data is needed to understand the determinants of healthy versus dysfunctional response and immune markers for protection and the severity of disease. Neutralising antibodies are known correlates of protection, but there may be other protective antibody mechanisms. Similarly, the protective role of T cell immunity and duration of both antibody and T cell responses and the correlates of protection need to be defined. In addition, optimal testing systems and technologies to support and inform early detection and clinical management of infection will be needed. It is worth noting that any of the mechanisms and assumptions discussed in the article and in our understanding of COVID-19 may be revised as further evidence emerges.

Authors contributions

MC, KK, JK, MP drafted the first and subsequent versions of the manuscript and all authors provided critical feedback and contributed to the manuscript.

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Figures

Figure 1 legend: The viral envelope is coated by spike (S), a glycoprotein, envelope (E) and membrane (M) proteins. Host cell binding and entry are mediated by the S protein. In SARS-CoV2 the S2 subunit is highly preserved and is considered a potential antiviral target. The S1 subunit of S protein contains the receptor binding domain (RBD) that binds to the peptidase domain (PD) of angiotensin-converting enzyme 2 (ACE2). The first step in infection is virus binding to a host cell through its target receptor and it likely follows these steps. The virus binds to binds to heparin sulphate and ACE2 as the host target cell receptor in synergy with the host's TMPRSS2 (1) which principally expressed in the airway epithelial cells and vascular endothelial cells, which leads to membrane fusion and releases the viral genome into the host cytoplasm (2). Viral replication requires following steps in the viral cycle (3-7) and finally reaching final stages of viral assembly, maturation and virus release. (This figure is created by the authors based on available literature about SARS-CoV-2 considering viral cycle of CoVs)

Figure 2 legend: After the initial exposure, patients typically develop symptoms within 5-6 days (incubation period). SARS-CoV-2 generates a diverse range of clinical manifestations, ranging from mild infection to severe disease accompanied by high mortality. Often in patients with mild infection, initial host immune response is capable of controlling the infection, but in others there is a risk of severe disease. In severe and critical patients, excessive immune response leads to organ damage, necessitating ICU admission. In addition, the viral load peaks in the first week of infection, declines thereafter gradually, while the antibody response gradually increases and often detectable by day 14. (This figure is created by the authors with Biorender.com Figure adapted using DOI: 10.1016/j.cell.2020.04.013; DOI:https://doi.org/10.1016/S2213-2600(20)30230-7.)

Boxes

a) What You Need to Know

1. SARS-CoV-2 binds to the host cell through ACE 2 that is mainly expressed in the upper and lower respiratory epithelium, primarily leading to respiratory symptoms and generalized systemic illness.

2. The predominant driver of viral transmission is droplet transmission. Viral particles cause infection by either direct or indirect contamination of mucous membranes (nose, eyes, mouth).
3. While increased risk of infection has been observed in crowded indoor settings, in the absence of aerosol-generating procedures, the data is inconsistent with aerosol transmission being a major route of transmission
4. Most of the clinical presentations are mild and the typical pattern of COVID-19 is a flu-like illness rather than a severe pneumonia.
5. The mechanisms underlying the diverse clinical outcomes are unclear but may be related to infectious dose, viral load kinetics, dysfunctional immune responses, older age and underlying medical conditions.

b) How patients were involved in the creation of this article

No patients were involved in the creation of this article

c) Education into practice

Why SARS-CoV-2 is more infectious and capable of community spread compared to SARS-CoV-1?

How would you describe to a patient why the symptoms of cough, anosmia and fever occur in covid-19?

d) How this article was created

Authors searched PubMed from 2000 to 18th July 2020, limited to publications in English. Our search strategy used a combination of key words including “COVID-19” “SARS-CoV-2” “SARS” “MERS” “Coronavirus” “Novel Coronavirus” “Pathogenesis” “Transmission” “Cytokine Release” “immune response” “antibody response”. These sources were supplemented with systematic reviews. We also reviewed technical documents produced by the Centers for Disease Control and World Health Organization technical documents.

e) Questions for Future Research

1- What is the the role of the cytokine storm and how it could inform the development of therapeutics, vaccines, and supportive care modalities.
2- What is the window period the patients are most infectious?
3- Why some patients develop severe disease while others, especially children, remain mildly symptomatic or do not develop symptoms?
4- What is the determinants of healthy versus dysfunctional response, and biomarkers to define immune correlates of protection and disease severity for the effective triage of patients?
5- What is the protective role of T cell immunity and duration of both antibody and T cell responses and the correlates of protection need to be defined?

f) Additional Educational Resources

g) Information Resources for Patients

h) Practical boxes

Practical box 1:
Risk factors associated with the development of severe disease, ICU admission, and Mortality

Underlying condition	Presentation	Laboratory markers
Older age	Higher fever (≥39 °C on admission)	Neutrophilia/lymphopenia
Hypertension	Dyspnoea on admission	Raised Lactate and LDH
Cardiovascular disease	Higher qSOFA score	Raised CRP
COPD		Raised Ferritin
Diabetes		Raised IL-6
Obesity		Raised ACE2
Malignancy		D-dimer > 1 µg/mL

Practical box 2:
Therapeutics currently under investigation

Entry to the cell	Viral replication	Host immune response
ACE receptor inhibitors	**RNA polymerase inhibitors**	**Immunomodulators**
Angiotensin II receptor blockers	Remdesivir	Tociluzumab
Fusion inhibitors	Ribavirin	Sarilumab
Iminefovir	Favipravir	Adalimumab (TNF inhibitor)
Baricitinib	**Protease inhibitors**	IFN
	Lopinavir	Corticosteroids
	Darunavir	

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