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Severe Acute Respiratory Syndrome Coronavirus 2

Michael Marks, Clinical Research Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom; and Hospital for Tropical Diseases, University College London Hospital, London, United Kingdom

Geraldine O'Hara, Department of Infection, Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

Catherine Houlihan, Department of Virology, University College London, London, United Kingdom

Lucy Bell, Department of Infection and Immunity, University College London, London, United Kingdom

Melissa Heightman, Department of Respiratory Medicine, University College London Hospital, London, United Kingdom

Nicholas Hart, Department of Respiratory Medicine, Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

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Introduction

In the latter half of December 2019 reports emerged of a new severe respiratory infection from Wuhan city, Hubei province in China. Early investigations identified a novel coronavirus as the causative agent (Li et al., 2020; Zhu et al., 2020). The virus is now referred to as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the resulting disease as coronavirus disease 2019 (COVID-19). Following the initial emergence of SARS-CoV-2 in Hubei the disease spread rapidly across China, in to Asia and then through a series of introductions across the rest of the world (Nie et al., 2020; Stokes et al., 2020; Wei, 2020). The World Health Organization (WHO) classified the emerging pandemic as a Public Health Emergency of International Concern (PHEIC) in early 2020.

In the absence of an established vaccine, international responses to SARS-CoV-2 have consisted of a number of interlinking public health control strategies which have been deployed to varying extents in differing regions. These strategies have included reducing or stopping air travel to avoid importations, quarantine of travelers on arrival, implementation of contact tracing and isolation strategies, widespread use of masks, and attempts to reduce social mixing through physical distancing, the shutting of non-essential services, and in some circumstances stay-at-home orders ("lockdown"). These strategies have had varying degrees of efficacy globally, likely reflecting different stages of the epidemic, variations in socioeconomic conditions between countries, and differing levels of compliance for each intervention (Cheng et al., 2020; Kissler et al., 2020; Okell et al., 2020; Pan et al., 2020).

Most evidence suggests that SARS-CoV-2 has a zoonotic origin (Andersen et al., 2020). Original reports were strongly associated with exposure to a seafood market in Wuhan where both live and slaughtered animals were sold for consumption (Huang et al., 2020). The current genetic evidence suggests that bats may have been the original host species although the possible role of an intermediate host remains unclear.

Transmission

Based on the available epidemiological data respiratory droplets represent the major route of transmission for SARS-CoV-2. As in all respiratory viruses the distinction between larger aerosols (droplets) and smaller aerosols is to some extent arbitrary, and there is undoubtedly at least some role for smaller “airborne” aerosols permitting transmission over a longer distance. Droplet transmission results from contact of an individual’s mucosa to infective droplets. SARS-CoV-2 may persist on surfaces for a relatively prolonged period, at least in experimental circumstances, and therefore indirect exposure via fomites may occur via direct or indirect contact with contaminated items in the environment (Ong et al., 2020). Some procedures (Aerosol Generating Procedures, AGPs) such as endotracheal intubation are thought to put individuals at an increased risk of exposure although the evidence for increased risk is variable.

Risk of onward transmission to a contact is related to the viral load of the index case, the duration of exposure and the distance between two individuals (Marks et al., 2020). A number of environmental factors including the degree of ventilation and the use of masks by both cases and contacts may also play a role in the risk of transmission. In keeping with most respiratory viral infections the risk of transmission is highly skewed with the majority of transmission appearing to occur from a minority of individuals. What drives the differential rates of transmission between these individuals remains unclear.

Although clinically children appear to be significantly less likely to develop symptomatic COVID-19 their role in transmission remains less clear. A small number of studies suggest that children may be infected at similar rates to adults and may also contribute to transmission but definitive data on their role in spread within the community is lacking at this time (Grijalva, 2020).

Following exposure, the median incubation period for SARS-CoV-2 infection before symptoms develop is estimated at 5 days with 97.5% of those who develop symptoms doing so within 12 days of infection (Lauer et al., 2020; Nie et al., 2020).

Virology

SARS-CoV-2 is a member of the Coronaviridae family, subfamily Coronavirinae. There are four genera of Coronavirinae: α , β , γ and δ , of which α and β predominantly infect mammals and contain the seven coronavirus types which infect humans. Between 10% and 30% of all “common colds” are caused by the α -coronaviruses 229E and NL63, and the β -coronaviruses OC43 and HKU1 (Paules et al., 2020). Two highly pathogenic β -coronaviruses have emerged in the past two decades in addition to SARS-CoV-2: SARS-CoV in 2002 and Middle Eastern Respiratory Virus (MERS-CoV) in 2012. SARS-CoV has a genome \sim 79% identical to SARS-CoV-2 and has resulted in more than 8000 cases with a fatality rate of 11% (WHO, 2003; Zhou et al., 2020a). MERS-CoV has a genome only \sim 50% identical to SARS-CoV-2 and caused fewer cases (2468 cases) but with a higher case fatality rate of 34% (WHO, 2019; Zhou et al., 2020a).

SARS-CoV-2 is a single strand positive sense RNA virus. Unusually, this large RNA virus has a proof-reading exoribonuclease which reduces errors. This replication fidelity somewhat limits genetic diversity but single nucleotide polymorphisms, insertions and deletions (though recombination events) make phylogenetic analysis still possible. Although the origin of SARS-CoV-2 is thought to be from bats, the sequences of the two most closely related bat coronaviruses are distinct enough to conclude that neither is an immediate ancestor (Zhou et al., 2020a). Much interest has been placed in mutations which have conferred virulence during the global spread of the virus but there is no genetic evidence to support this to date. Although the G614 variant of SARS-CoV-2 overtook the D614 variant in mid-2020, no alteration in severity of disease has been seen (Korber et al., 2020; The Royal Society, 2020).

The envelope of the spherically-structured SARS-CoV-2 is coated with spike (S) glycoproteins which protrude giving the virus the appearance of a crown when examined under an electron microscope (leading to the name “corona”). The S glycoprotein comprises S1 which mediates attachment to the host cell, and S2 which mediates fusion and entry to the cell. S1 comprises a receptor binding domain (RBD) which, in SARS-CoV-2 is more exposed and allows a 10 times increased binding affinity compared to SARS-CoV due to a unique addition of four amino acids in S1. SARS-CoV-2 enters human cells through the binding of S1 to human ACE2 which is expressed on cells in the respiratory tract, myocardial tissue, renal and intestinal cells. Other viral proteins produced during replication include open reading frames (ORF) 1a and 1b, envelope (E), membrane (M), nucleoprotein (N) and accessory proteins which are cleaved from polyproteins.

Pathogenesis and Immunology

Initial reports of COVID-19 described an intense inflammatory response accompanied by profound lymphopenia (Huang et al., 2020) and suggested that the magnitude of these phenotypes correlated with outcomes (Zhou et al., 2020b). Studies spanning

human immunology, animal models and in vitro experimentation have developed our understanding of the inflammatory and immune mechanisms underpinning COVID-19 pathogenesis.

Hyperinflammation and Immunopathology

Viral replication is decoupled from inflammation and clinical severity in the natural history of COVID-19. Peak viral titers are observed around symptom onset (He et al., 2020) but clinical deterioration is more closely correlated with rising inflammatory markers, typically at 7–10 days of illness (Huang et al., 2020). This prompted the hypothesis that unrestrained “hyperinflammation” drives COVID-19 disease. High levels of cytokines such as IL-6 and TNF α observed in early cohorts (Huang et al., 2020) led to the proposal that severe disease involved a “cytokine storm” with features of hemophagocytic lymphohistiocytosis (HLH) (Mehta et al., 2020). However, there is increasing consensus that COVID-19 hyperinflammation is a distinct entity from classical cytokine storm syndromes, involving less hypercytokinemia (Manson et al., 2020; McGonagle et al., 2020) and a specific phenotype of intravascular immunothrombosis (McGonagle et al., 2020). Specific pathogenic roles for different cytokines in COVID-19 have not been delineated. IL-6 is proposed as a disease driver as high levels are correlated with adverse outcomes (Zhou et al., 2020b), but clinical trials of IL-6 blockade have not demonstrated benefit to date (Campochiaro and Dagna, 2020). It is uncertain which cells are the principle producers of inflammatory cytokines (Wilk et al., 2020) although studies suggest these derive from cells at the site of disease rather than circulating leukocytes (Arunachalam et al., 2020). Post-mortem histopathology provides further evidence for tissue-localized inflammation in COVID-19, with leukocytic infiltrates accompanying diffuse alveolar damage (Carsana et al., 2020).

Innate Responses

While hyperinflammation may contribute to severe COVID-19, many individuals have mild or subclinical infections without significant inflammation, despite having viral loads of sufficient levels for transmission (Bai et al., 2020). One hypothesis for milder disease in these individuals is that they mount an effective innate immune response which contains the virus. Classic innate antiviral responses involve type I interferons (IFNs) which activate a broad range of antiviral defenses. In vitro and animal studies identify a muted type I IFN response to SARS-CoV-2, in comparison to other respiratory viruses (Blanco-Melo et al., 2020). Attenuated type I IFN responses are seen in patients with COVID-19 and correlate with severity (Hadjadj et al., 2020).

A mechanistic route to severe disease has been suggested in which an impaired type I IFN response allows uninhibited viral replication, in turn stimulating immune cells which amplify tissue-damaging inflammation (Hadjadj et al., 2020). While direct evidence for such an axis is lacking, there is strong supporting evidence for the importance of type I IFN in protection against SARS-CoV-2. Loss of function variants in genes encoding components of type I IFN pathways are found in a subset of patients with severe COVID-19 (Zhang et al., 2020). Compellingly, approximately 10% of patients with severe disease in a large cohort had neutralizing auto-antibodies against type I IFNs (Bastard et al., 2020). These were not found in patients with mild disease. While these defects in antiviral immunity are not ubiquitous in patients with severe COVID-19, they provide proof-of-concept that type I IFNs are critical for protection.

T-Cell Responses

Lymphopenia is a hallmark of COVID-19 (Zhou et al., 2020b) while lymphocyte infiltration is found at the site of disease in the lung (Carsana et al., 2020). Immunophenotyping of patients (Kuri-Cervantes et al., 2020; Laing et al., 2020; Mathew et al., 2020) has confirmed depletion of circulating T-cell subsets including helper (CD4+) and cytotoxic (CD8+) T-cells (Laing et al., 2020; Mathew et al., 2020). Heterogeneous activation patterns are seen in the remaining T-cell populations, with some patients displaying robust activation and others having no detectable activated cells (Mathew et al., 2020). It is unclear whether these profound alterations in T-cell biology are a precipitant or a product of severe COVID-19.

While T-cells may contribute to COVID-19 pathogenesis, T-cell mediated adaptive immunity is a critical component of protection against viruses. Characterizing the SARS-CoV-2 specific T-cell response has accordingly been a key focus of research (Grifoni et al., 2020; Ni et al., 2020; Sekine et al., 2020). T-cells targeting SARS-CoV-2 antigens including the Spike, M & N proteins are found in convalescent COVID-19 patients, including CD4+ cells polarized towards an IFN γ -producing Th1 phenotype and CD8+ cells expressing cytotoxic enzymes (Grifoni et al., 2020). It is unclear whether these cells protect against severe disease, as they are found in patients across the clinical spectrum.

Most individuals have prior exposure to circulating seasonal coronaviruses. Determining whether this provides cross-reactive T-cell immunity to SARS-CoV-2 is a key question. Investigation of SARS-CoV-2 naïve individuals identified cross-reactive CD4+ T-cells in 20–50% (Grifoni et al., 2020). Whether the presence of cross-reactive T-cells relates to variation in COVID-19 clinical presentation is yet to be established in prospective studies.

B-Cell and Antibody Responses

Although B-cells are not depleted to the same extent as T-cells in COVID-19, their population make-up is altered, with striking expansions of immature plasmablasts (Kuri-Cervantes et al., 2020; Laing et al., 2020; Mathew et al., 2020). Although the role of these immature B-cells in disease is unclear, plasmablast frequency correlates with severity (Laing et al., 2020) and they may have pathogenic potential through limitation of antibody diversity or production of immune complexes (Kuri-Cervantes et al., 2020).

Neutralizing antibodies are a key facet of antiviral responses. Seroconversion for SARS-CoV-2-specific IgM and IgG occurs in the second week of illness in most patients, and antibody titers in the acute phase are correlated with severity (Zhao et al., 2020). Convalescent patients have virus-specific antibodies which display neutralizing activity in vitro (Ni et al., 2020). The durability of the antibody response remains under investigation. Anti-SARS-CoV-2 antibody titers wane within 3 months in many patients, particularly after mild or asymptomatic infection (Ibarrondo et al., 2020; Long et al., 2020), but longer periods of serological follow-up are yet been reported.

Cross-reactive antibodies, assumed to be generated by prior exposure to seasonal coronaviruses, have been measured in SARS-CoV-2 unexposed individuals (Ng et al., 2020). Concerns have been raised about the prospect of antibody-dependent enhancement (ADE), in which cross-reactive antibodies may facilitate viral entry to cells (Iwasaki and Yang, 2020). The propensity of cross-reactive antibodies to confer protection, or aid pathogenesis via ADE, has not yet been determined.

Protective Immunity and Vaccine Development

It remains uncertain whether SARS-CoV-2 infection in humans leads to durable immunity which protects against reinfection. Evidence from seasonal human coronaviruses shows reinfection can occur and that antibody responses wane between episodes (Edridge et al., 2020). Conversely, a non-human primate model of SARS-CoV-2 infection showed that macaques developed effective adaptive immunity following primary infection, with rapid viral clearance and protection against clinical disease on re-challenge (Chandrashekar et al., 2020). While the correlates of protection against SARS-CoV-2 remain unclear, a diverse range of candidate vaccines are in late stage clinical trials. Many have been shown to be immunogenic in initial studies (Jeyanathan et al., 2020). Furthering our understanding of immune responses to SARS-CoV-2, particularly in the context of re-exposure and re-infection, will be critical in developing rational vaccination approaches.

Diagnostic Testing

Although this is a rapidly developing field, confirmation of infection with SARS-CoV-2 can be broadly considered in terms of viral RNA detection (molecular methods), detection of viral proteins (antigen detection) or detection of a humoral response to the virus (serological methods) (Fig. 1). The gold standard diagnostic is the identification of viral RNA by reverse-transcriptase polymerase

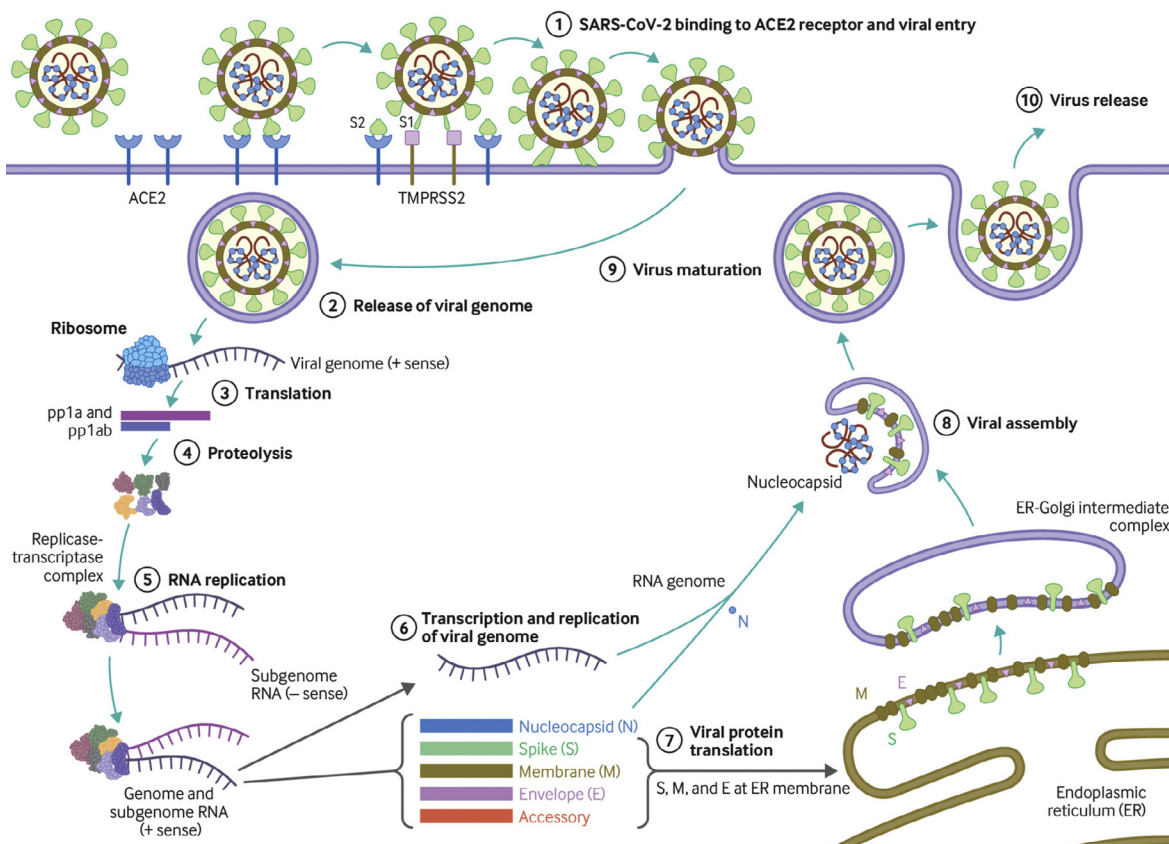


Fig. 1 Entry of SARS-CoV-2 and replication within the host cell.

chain reaction (RT-PCR) in a patient sample, most commonly a nasopharyngeal or oropharyngeal swab specimen. Nasopharyngeal specimens are more technically difficult to collect and considered more invasive but seem to have improved detection of virus over oropharyngeal specimens (Mohammadi et al., 2020). For public health surveillance and ease of collection, saliva is increasingly being recognized as an important diagnostic specimen (Wyllie et al., 2020). SARS-CoV-2 RNA has been detected in upper and lower respiratory specimens (sputum, endotracheal aspirate and bronchiolar lavage fluid), feces, blood, urine and breast milk, albeit with diminishing frequency (Diger et al., 2020; Jeong et al., 2020; Wang et al., 2020a). The highest diagnostic yield is seen in lower respiratory tract specimens (Mohammadi et al., 2020).

Molecular Methods

Reverse-transcriptase PCR assays detect the presence of SARS-CoV-2 RNA by first generating a complementary DNA strand (cDNA) followed by amplification using a template sequence specific to the virus (called an oligonucleotide). All commercial and in-house RT-PCRs for SARS-CoV-2 target either one or several regions specific to this virus, usually within the N, E, or S genes, the Open Reading Frame ORF-1, or the RdRp gene. Larger amounts of virus in a sample leads to faster multiplication times and an earlier positive signal (cycle threshold or Ct). This allows an element of quantification of the virus although with the caveat of operator dependence on both sample collection and laboratory analysis. Nevertheless, the resulting Ct value from RT-PCR correlates reasonably well with infectivity of the virus in cell culture (Walsh et al., 2020). SARS-CoV-2 RNA is detected 48 h before symptoms and usually not beyond 14 days (Fig. 2) (Walsh et al., 2020). The limit of detection of most commercial RT-PCRs is impressive at 1–10 copies per reaction (or 100 copies/ml) with sensitivity over 92% (99% for the majority), and specificity over 95% in analysis of patient samples (FIND, 2020).

The major drawbacks of RT-PCR lie in the level of skill required of laboratory staff, laboratory infrastructure, and the minimum time requirement of 4 h from sample processing to result. Rapid tests employing nucleic acid amplification similar to RT-PCR but which require minimal laboratory skill and infrastructure have emerged. The Xpert Xpress SARS-CoV-2 (Cepheid, CA, USA), CovidNudge (DnaNudge, UK) and ID Now SARS-CoV-2 (Abbott, Chicago, IL, USA) are single-use cartridge assays which demonstrate sample-to-result in under an hour (15 min in the case of ID Now) mostly with impressive sensitivity/specificity of 100%/100% (Wolters et al., 2020), 94%/100% (Gibani et al., 2020), 76.8%/99.6% (Dinnes et al., 2020) respectively in field tests.

An important additional method for rapid molecular diagnosis is reverse-transcriptase loop-mediated isothermal amplification (RT-LAMP). This sub one-hour method amplifies cDNA using a combination of 6 primers and takes advantage of the newly generated strand “looping” back to hybridize to the inner strand. This reaction continues exponentially without the need for the temperature change as in a traditional PCR reaction. The method has been combined with rapid nanopore sequencing (LAMPore) to allow a more specific diagnosis in addition to the potential for sequencing for epidemiological investigation, although supportive data are currently lacking.

Antigen Detection

Rapid diagnostic antigen tests (Ag-RDTs) for SARS-CoV-2 are predominantly near-patient tests, requiring little skill in their use and interpretation. Lateral flow assays (LFA) are the most common type in development and have a background of successful widespread use for the diagnosis of other major public health infectious diseases such as HIV and malaria. The LF assay contains a nitrocellulose strip encased in a plastic cassette. The strip is impregnated with antibodies to viral proteins, usually N protein for SARS-CoV-2 and a further two strips of fixed antibodies which will demonstrate a color change in the presence of (1) the conjugated target antigen and (2) a conjugated control. A sample (nasopharyngeal swab, oropharyngeal swab or saliva) is placed in a well at

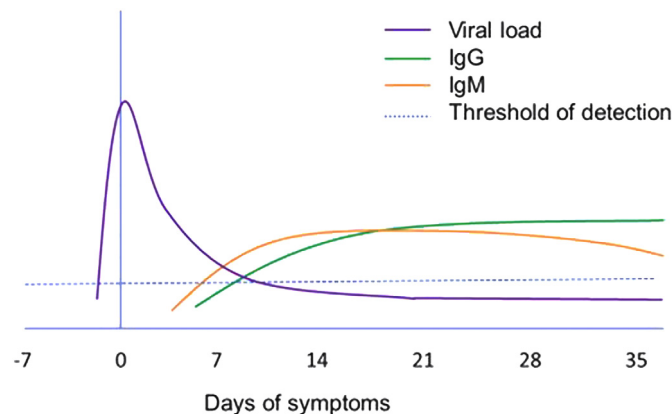


Fig. 2 Timing for detection of viral RNA and host antibody responses in relation to infection. Cevik M, Kuppalli K, Kindrachuk J, and Peiris M (2020) Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ* 371. <https://doi.org/10.1136/bmj.m3862>.

one end of the kit along with the provided buffer and the kit is usually readable in under 30 min. WHO have specified the minimum performance requirement for these SARS-CoV-2 Ag-RDTs: sensitivity $\geq 80\%$ and specificity $\geq 97\%$ when compared to a gold-standard nucleic acid amplification reference (WHO, 2020). Independent validation of three of these (to date) by the NGO Foundation for Innovative New Diagnostics (FIND) reveals a high specificity but a low sensitivity in field testing, with only 80% sensitivity or above being achieved at higher viral loads (lower Ct) in oro- or nasopharyngeal specimens (FIND, 2020). The use of saliva in these Ag-RDTs is ideal from a public health perspective but leads to a further lowering of sensitivity, leading to limited use for patient diagnosis (Nagura-Ikeda et al., 2020).

Serological Methods

Testing for the presence of a humoral response to SARS-CoV-2 infection involves detection of the presence of IgG, IgM or IgA to one of the viral proteins. These are predominantly within spike (S, S1, S2 or RBD) and nucleocapsid proteins. The format of serological tests includes enzyme-linked immunosorbent assays (ELISA), chemiluminescence immunoassays (CLIA), and point-of-care lateral flow assays. Neutralization tests examine the ability of antibodies in patient serum to prevent viral infection in cell culture but these tests are not feasible for clinical practice and serve mostly to validate serological tests. The most common assays in large-scale use are the Elecsys Anti-SARS-CoV-2 assay (Roche, Switzerland) and the Abbott SARS-CoV-2 IgG (Abbott Diagnostics, USA) which both measure antibodies to nucleoprotein and test either IgG and IgM (Roche) or only IgG (Abbott). Sensitivity of these assays in clinical sample validations is reported as 93% and 97% respectively, with both demonstrating 100% specificity, although criticism has been raised at the unexpected high sensitivity in asymptomatic individuals (Ainsworth et al., 2020; Rosadas et al., 2020). The timing of antibody testing is key: sensitivity of most IgG/M combination assays in the first 2 week ranges from 30% to 72% but increases to over 90% after 14 days (Fig. 2) (Deeks et al., 2020). There is potential waning of antibody responses over time, but further evaluation is anticipated.

Clinical Features of COVID-19

Asymptomatic Infection

Asymptomatic infection with SARS-CoV-2 is recognized but has not been systematically studied. The presymptomatic phase mean individuals asymptomatic at the time of diagnosis (i.e., positive RT-PCR test) may go on to develop symptoms at any time up to 6 days after the initial positive RT-PCR test (Arons et al., 2020; Kimball et al., 2020; Sakurai et al., 2020). Furthermore, putative asymptomatic infection may result in clinically unapparent radiological abnormalities. Small studies of asymptomatic individuals demonstrate abnormal CT chest findings (ground glass opacification, patchy infiltrates and other abnormalities) in the majority of individuals (Hu et al., 2020; Wang et al., 2020b). Thus defining asymptomatic infection is challenging and likely best done retrospectively.

Symptomatic Infection

The spectrum of symptomatic infection ranges from mild to critical but the vast majority of infections are not severe and do not require hospitalization.

In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories. However, the criteria for each category may overlap and/or clinical status may change over time.

- Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19.
- Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) $\geq 94\%$ on room air at sea level.
- Severe Illness: Individuals who have $SpO_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg, respiratory frequency > 30 breaths per minute, or lung infiltrates $> 50\%$.
- Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Symptoms of COVID-19 are multi-system in nature; 370,000 confirmed COVID-19 cases in the United States reported symptoms including cough (50%), fever (subjective or $> 38^\circ\text{C}$, in 43%), myalgia (36%), headache (34%), dyspnoea (29%), sore throat (20%), gastrointestinal symptoms such as diarrhea and nausea/vomiting (20%) and disorders of smell and taste in 10% (Stokes et al., 2020). Older patients, especially those with dementia may present with relatively non-specific findings such as poor appetite, falls or hypoactive delirium, which underlines the difficulties associated with defining asymptomatic infection (Davis et al., 2020). Symptomatic infection in children and adolescents is relatively uncommon; when it occurs, it is usually mild, although a small proportion (e.g., 1–2%) experience severe disease (Stokes et al., 2020).

Severe illness can occur in healthy individuals of any age, but predominantly occurs in older adults or adults with co-existing medical conditions (Wu and McGoogan, 2020). It is apparent some individuals who initially present with disease at the mild end of the spectrum experience a deterioration approximately 7–10 days into the illness and may require critical care interventions (Huang et al., 2020; Wang et al., 2020b). Some patients with severe COVID-19 exhibit persistent fever, elevated inflammatory markers (e.g., CRP, D-dimer, ferritin), and elevated proinflammatory cytokines consistent with a persistent overactive inflammatory response; this can occur relatively late in the illness, and appears associated with higher mortality (Huang et al., 2020).

Patients with milder initial infections also frequently have prolonged symptoms however systematic evaluation of the long-term sequelae of COVID-19 in mild, moderate and severe disease remains ongoing. Patients who were critically ill with COVID-19 are at risk for persistent impairments in cognition, mental health, and/or physical function following survival of critical illness (post intensive care syndrome).

Older age is clearly associated with increased mortality with the risk of death among individuals over 80 years in age was 20-fold that among individuals in the 50–59 years age group (Williamson et al., 2020). Similarly in China case fatality rates in hospitalized individuals with COVID-19 were 8 and 15% among those aged 70–79 years and 80 years or older, respectively, in contrast to the 2.3% case fatality rate across all age groups (Wu and McGoogan, 2020).

Co-Morbidities

Certain co-morbidities appear to be associated with severe disease including:

- Chronic obstructive pulmonary disease
- Cardiovascular disease (e.g., heart failure, coronary artery disease, or cardiomyopathy)
- Type 2 diabetes mellitus
- Obesity (body-mass index, ≥ 30)
- Sickle cell disease
- Chronic kidney disease
- Immunocompromised state from solid-organ transplantation
- Cancer

Older patients with co-morbidities appear to be particularly susceptible to severe COVID-19 and have higher rates of mortality (Docherty et al., 2020; Garg et al., 2020; Wu and McGoogan, 2020). A number of risk prediction scores have been developed for COVID-19. The ISARIC-4C Mortality and Deterioration scores have been validated in extremely large patient populations (Gupta et al., 2020; Knight et al., 2020) and can be completed using a relatively small number of variables including age, gender, number of co-morbidities, respiratory rate, oxygenation, Glasgow Coma Scale, urea and CRP.

Demographics

Demographic features including male sex and membership of black and minority ethnic groups have been associated in some studies with increased severity of COVID-19 death (Garg et al., 2020; Price-Haywood et al., 2020; Williamson et al., 2020). The effects of ethnicity is likely to be at least partially related to underlying disparities in the social determinants of health.

Laboratory Abnormalities

Common laboratory findings among hospitalized patients with COVID-19 include lymphopenia, elevated inflammatory markers (e.g., ferritin, C-reactive protein, and erythrocyte sedimentation rate), elevated liver enzymes, elevated lactate dehydrogenase levels and elevated D-dimer levels (Goyal et al., 2020; Liao et al., 2020; Pereyra et al., 2020). Severe lymphopenia and markedly elevated D-dimer levels appear to be associated with severe COVID-19 and increased mortality (Huang et al., 2020).

Radiology

Chest radiographs may be normal in early or mild disease; abnormal findings may include consolidation and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions (Wong et al., 2020). Computed tomography (CT) of the chest is more sensitive than chest radiograph and often shows patterns suggestive of COVID-19; however, no radiological findings are diagnostic of COVID-19. Chest CT in patients with COVID-19 most commonly demonstrates ground-glass opacification with or without consolidative abnormalities, consistent with viral pneumonia (Bao et al., 2020). Radiological findings may evolve over the course of the illness; consistent with clinical deterioration and peak at 10–12 days after the onset of symptoms.

Treatment of COVID-19

Treatment of COVID-19 depends on the stage and severity of disease. Patients who have mild illness can recover at home, with supportive care though the possibility of deterioration during later illness must be explicitly discussed and recognized. Patients

who have moderate disease should be monitored closely and hospitalized particularly if identified as being in vulnerable groups at risk of developing severe COVID-19; those with severe disease should be hospitalized.

SARS-CoV-2 replication is believed to lead to many of the clinical manifestations of COVID-19 thus antiviral therapies are being investigated as treatment options. These drugs variably inhibit viral entry, viral membrane fusion and endocytosis, and the RNA-dependent RNA polymerase. Because viral replication is greatest just before or soon after symptom onset, antiviral medications (e.g., remdesivir and antibody-based treatments) are likely to be most effective when used early. Later in the disease, a hyperinflammatory state or coagulopathy are thought to lead to clinical complications and it is postulated anti-inflammatory medications, immunomodulators, anticoagulants, or a combination of these treatments may be more effective than antiviral agents. There are no approved treatments for COVID-19 but some medications have been shown to be beneficial. Consideration must be given to administering unproven or novel therapeutics outside of clinical trials.

Antivirals

Remdesivir is an investigational nucleotide prodrug of an adenosine analog that has activity against SARS-CoV-2 in vitro. Viral replication is inhibited via binding to the viral RNA-dependent RNA polymerase, causing premature termination of RNA transcription.

As data emerges from comparative, randomized trials in patients with severe infection it appears remdesivir does not reduce mortality among the overall hospitalized patient population, but there may be a mortality benefit for select patients with severe disease who only require low-flow supplemental oxygen (Beigel et al., 2020; Wang et al., 2020c). In patients with moderate disease no clear benefit was observed between those randomized to a 5- or 10-day course of remdesivir compared with standard care (Spinner et al., 2020).

Remdesivir can cause gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time.

Immunomodulators

It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects of a COVID-19 associated systemic inflammatory response. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, randomized, open-label trial in hospitalized patients with COVID-19, demonstrated lower mortality rate in patients randomized to receive dexamethasone compared to those who received the standard of care. Notably this benefit was not observed in patients not requiring supplemental oxygen at enrollment (RECOVERY Collaborative Group et al., 2020).

At present there is no evidence supporting use of a myriad of compounds (both novel and repurposed) with in vitro activity against SARS-CoV-2 such as chloroquine, hydroxychloroquine, azithromycin or ivermectin. Large clinical trials are ongoing utilizing either monoclonal antibodies against specific structural proteins or convalescent plasma. At the time of writing published data are not yet available to inform clinical practice (Gandhi et al., 2020).

Antimicrobials

Empiric utilization of antimicrobials in patients diagnosed with COVID-19 should be avoided unless there is a high index of suspicion for bacterial co-infection. As the clinical features of COVID-19 may initially be difficult to distinguish from bacterial pneumonia, empiric treatment for community-acquired pneumonia is reasonable while the diagnosis is confirmed but consideration should be given to cessation of antimicrobials. If there is clinical suspicion for hospital-acquired pneumonia in patients with COVID-19 (e.g., new fever after defervescence with new consolidation on chest imaging) empiric antimicrobials may be started but attempts should be made to obtain respiratory specimens to enable narrowing of antibiotic spectra. Procalcitonin has typically been used in such patient groups but elevated procalcitonin has been described in COVID-19, particularly late in the course of illness, thus may be of limited diagnostic value (Guan et al., 2020; Wang et al., 2020b; Zhou et al., 2020b).

Palliative Care

Often overlooked in the midst of outbreaks it is essential that focus on novel therapeutics does not lead the clinician into failing to recognize the dying patient. Many patients with severe COVID-19 experience distress including physical symptoms such as dyspnea but equally importantly psychological ones such as isolation and fear of dying. Holistic care for patients is vital and palliation of suffering is an important part of care irrespective of prognosis. Early recognition of patients not suitable for intensive care allows pre-emptive planning for deterioration. Good communication with patients and families is essential “conveying hope that treatments will help needs to be sensitively balanced with explicit acknowledgement that patients are sick enough to die” (Ting et al., 2020). Infection prevention and control remains paramount but bedside visiting in PPE may be facilitated or utilization of novel technologies such as video calling to permit contact between patients at the end of life and loved ones (Life Lines Team Comprising, 2020).

Intensive Care

Among hospitalized patients a large proportion of individuals will require supportive care in a high-dependency or intensive care unit (ICU). Given the epidemic nature of SARS-CoV-2 there is a significant risk of exceeding ICU bed capacity. Early surge planning and expansion of both staff and bed base capacity are therefore critical.

High quality ventilatory support is the mainstay of ICU management but renal replacement, inotropic and nutrition support may also be required. There is currently no specific trial evidence to guide optimal ICU management but best practice from other causes of ARDS should be adopted including appropriate ventilation strategies and consideration of proning. In some circumstances Extracorporeal Membrane Oxygenation (ECMO) may be necessary.

Mortality rates have varied significantly from country to country reflecting overall ICU admission criteria and bed pressures. In the United Kingdom, the overall mortality in ICU is approximately 20–25% (ICNARC, 2020) and is associated male sex, older age, increased BMI and rising numbers of co-morbidities.

Recovery From COVID19

Most individuals feel fully recovered 2–3 weeks after onset of COVID19 infection. There is, however, growing concern re the prevalence of longer-lasting symptoms reported in others. Definitions for this syndrome are continuing to evolve but emerging terms include persistent COVID for ongoing symptoms lasting up to 12 weeks, while symptoms persisting beyond 12 weeks are described as the post-COVID syndrome. The term “Long-COVID” has been adopted by patient groups.

There remains limited data on long term outcomes following COVID-19. In a study in the United Kingdom 4.5% of patients had symptoms for more than 8 weeks and 2.3% for more than 12 weeks (Sudre et al., 2020). In this study increasing age, BMI and female sex increased the likelihood of long-lasting symptoms but in clinical practice many previously very fit individuals of younger age are also affected. The symptoms study suggests individuals who experience more than five symptoms during the first week of illness have a significantly increased risk of post COVID syndrome.

Patients requiring ICU experience a number of well recognized complications from SARS-CoV-2. These include an increased risk of post-traumatic stress disorder and other mental health problems and post critical illness myopathy and neuropathy. Some individuals with severe SARS-CoV-2 will develop a post-infectious organizing pneumonia and may be at increased risk of pulmonary fibrosis.

Services for patients with post-COVID syndrome are evolving. At the time of writing there are no established disease modifying agents for use in the post-COVID recovery phase. Assessment requires multi-specialty and multi-professional input and support from physiotherapy and psychology services. Patients require a holistic assessment aiming to address three broad categories of health issues. Firstly, identify patients with develop early complications such as venous thromboembolism, which have a high incidence even in patients not admitted to hospital. Secondly, to identify persisting organ-based inflammation resulting in ongoing symptoms. To date most apparent examples of this relate to myocarditis (evident on cardiac MRI), ongoing lung inflammation (with features of organizing pneumonia on HRCT thorax) or neurological symptoms with abnormalities on CNS imaging, autonomic dysfunction or neuropsychiatric presentations. Finally, some patients struggle with a myriad of other less clearly defined symptoms which typically start in the early weeks following infection and then persist beyond 12 weeks. In this case patients can be considered to have a post-COVID syndrome. These symptoms can be reported with or without identifiable evidence of organ-based damage.

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