Sharing clinical experiences from the front line

A clinician's perspective

A Practical approach to COVID 19

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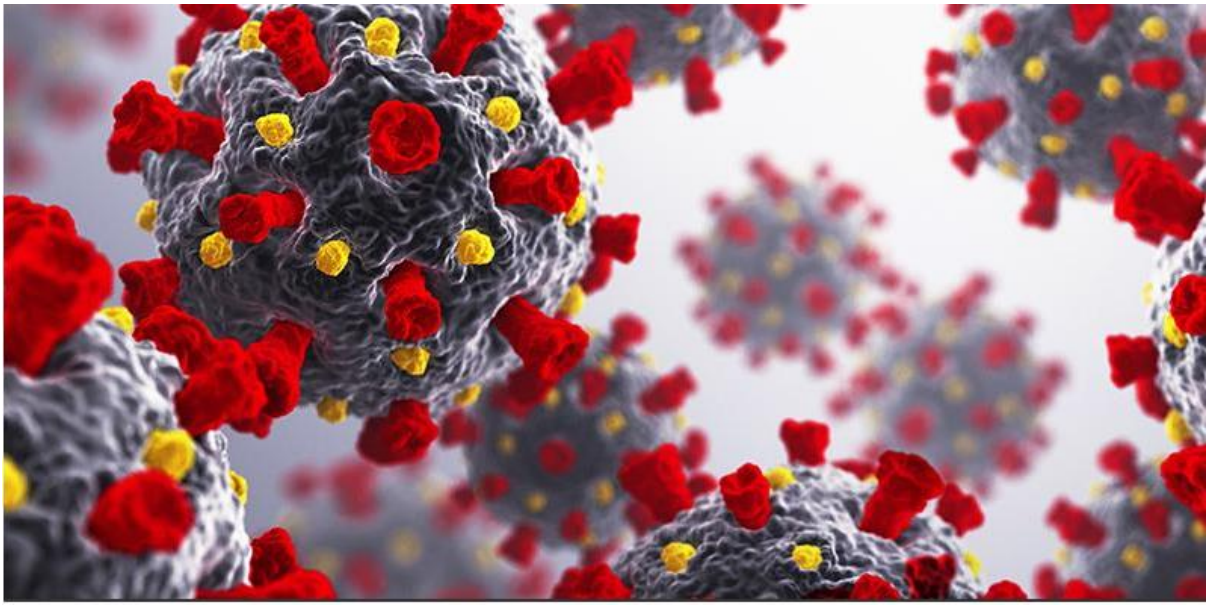

Abstract:

In December 2019, health authorities in Wuhan, China, identified a cluster of pneumonia cases of unknown etiology linked to the city's South China Seafood Market. Subsequent investigations revealed a novel coronavirus, SARS-CoV-2, as the causative agent now at the heart of a major outbreak. The rising case numbers have been accompanied by unprecedented public health action globally, alongside this has been a robust scientific response, including early publication of the pathogen genome, and rapid development of highly specific diagnostics. On March 11, 2020, the World Health Organization (WHO) declared the world-wide outbreak of COVID-19 a pandemic. This document summarizes the most recent knowledge regarding the biology, epidemiology, diagnosis, and management of COVID-19.

Biology:

SARS-CoV-2 is single-stranded RNA, enveloped virus that likely spread to humans from a zoonotic source, possibly bats or pangolins. It is believed to spread from **person to person** via **respiratory droplet nuclei**. Other routes of infection (e.g. contact, enteric) are possible as the virus can persist on surfaces and is shed in faces, but it is unclear if these are significant means of spread. There is evidence of transmission by asymptomatic individuals. The virus binds to the ACE2 receptor on type II pneumocytes. However, the role of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers (ARBs) as treatments or risk factors for disease is unclear. The reported incubation time is 3-12 days with a median duration of viral shedding of 20 days. There is evidence that the virus changes over time. There may be multiple strains of SARS-CoV-2 in circulation

Epidemiology:

Characteristics such as the **attack rate** (% of individuals in an at-risk population who acquire the infection), $\mathbf{R_0}$ (R naught, the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection), and **case fatality rate** (CFR, % of infected individuals who die) are contextual. That is, they depend on factors such as testing rate, population density, and control strategies that vary from location to location. These factors may also change over time.

Table 1 summarizes reported epidemiologic characteristics of SARS-CoV-29.

Table 1: Reported epidemiologic characteristics of SARS-CoV-2.

Attack rate:	30-40% (community, in China)
Ro:	2-4 (lower with containment)
Case fatality rate	1.5% USA, 3.4% overall worldwide
Incubation time	3-14 days
Viral shedding	Median 20 days

Clinical Presentation:

Symptoms may vary from mild cough to fulminant respiratory failure. Positive tests have also been obtained from asymptomatic patients. Table 2 lists the estimated frequency of symptoms observed to date

Table 2: Frequency of Symptoms in COVID-19

Symptom	Percent of patients with symptom
Cough	50-80%
Fever	85% (only 45% febrile on presentation)
Fatigue	69.6%
Dyspnea	20-40%
URI symptoms	15%
GI symptoms (nausea, vomiting, diarrhea)	10%

Initial assessment:

COVID-19 is classified as an airborne high consequence infectious disease (HCID) in the UK. The cornerstone of management of all possible or confirmed cases is early triage and isolation.

Assessments should be carefully prepared for, including in primary care where many patients are likely to present. During initial assessment, precautions should be taken to minimise transmission including, where possible, initial consultation by telephone. An action plan should be developed in healthcare areas where assessments are likely to occur. The key principles are to identify potential cases as soon as possible; prevent potential transmission of infection to other patients and staff; avoid direct physical contact including physical examination and exposures to respiratory secretions; and to isolate the patient. Practitioners should obtain specialist advice, determine if the patient is at risk of COVID-19, and inform the local health protection team. Notably, if a history is elicited that suggests a possible case once consultation has already commenced, examination should be abandoned and the practitioner should leave the room, close the door, and wash their hands thoroughly with soap and water. The assessment can then be continued by telephone and the patient triaged appropriately and transfer arranged to an appropriate setting if indicated.

Prior to assessment of a patient identified as at risk of COVID-19, clinicians must isolate the patient with their belongings and waste in a single occupancy room, preferably a respiratory isolation room and ideally under negative pressure; positive pressure must not be used. Personal protective equipment (PPE) must be worn, comprising, as a minimum, a correctly fitted FFP3 respirator, gown, gloves and eye protection. Practitioners should be trained in the safe putting on and removal of PPE. Patients should be asked to wear a surgical facemask during transport to isolation.

Diagnosis:

Patients satisfying epidemiological and clinical criteria as specified at www.gov.uk/government/collections/wuhan-novel-coronavirus are classified as a possible case. If a patient meets the case definition, clinicians should consult the latest guidance from their public health authority. Diagnostic sampling must be undertaken only with appropriate infection control precautions and with discussion with local infectious diseases and public health teams. Testing of any samples should take place in a Biological Safety Level 3 laboratory. It is essential to inform the laboratory before sending samples. Early publication of the pathogen genome has allowed rapid development of a reverse transcription polymerase chain reaction (PCR) based test, and whole genome sequencing may also be carried out on positive samples to aid understanding of

transmission and mutations. Point-of-care test kits are likely to be made available shortly for home testing. Serological markers have also been identified but are not currently useful for clinical diagnostics

Laboratory Findings:

The following lab abnormalities have been observed in patients with COVID-1910: Complete blood count: normal WBC, **leukopenia**, **lymphopenia (80 %+)**, thrombocytopenia, Chemistries: elevated BUN/creatinine, elevated AST, ALT, and Total bilirubin, inflammatory markers: normal or low procalcitonin, high C-reactive protein and ferritin .Miscellaneous: elevated D-dimer, interleukin -6, and lactate dehydrogenase

Imaging:

Imaging findings are frequently absent on presentation and should not be used for diagnosis of COVID 19. Many patients have normal imaging at the time of presentation, but the following abnormalities have been reported (Figure 1): Chest X-ray: bilateral, peripheral, patchy opacities Chest CT scan: bilateral ground glass opacities, crazy paving, and consolidation. Not routinely recommended to avoid unnecessary exposure during transport .Point-of-care ultrasound: B-lines, pleural line thickening, consolidations with air bronchograms. Assessment of cardiac function is also useful

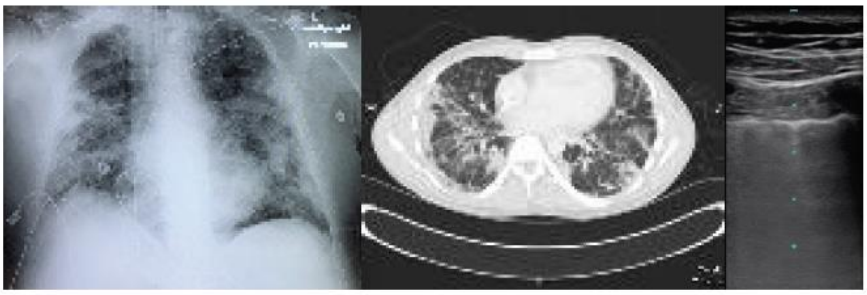

Figure 1: COVID-19 Imaging. (A) CXR showing bilateral peripheral opacities, (B) Chest CT showing diffuse ground glass with a peripheral predominance, (C) point of care lung ultrasound showing predominance of B-lines in patients with COVID-19. Images courtesy of Dr. Nick Mark.

Diagnostic Testing and Reporting:

Lack of availability has hampered COVID-19 testing not only in developing countries but also globally to date, but testing capacity is increasing rapidly. The following recommendations have been made regarding diagnostic testing and reporting. Send nasopharyngeal and or throat swab for SARS-CoV-2 polymerase chain reaction testing (RT-PCR). Check with your local facility regarding test characteristics, including sensitivity and specificity of the test

- Differentiating SARS-CoV-2 from other circulating respiratory viruses is important, particularly Influenza, therefore consider testing of usual respiratory pathogens. Co-infection has also been reported
- Do not order sputum induction
- Avoid bronchoscopy unless absolutely indicated If indicated, follow current recommendations for bronchoscopy in suspected COVID-19 patients as recommended by the American Association for Bronchology and Interventional Pulmonology

- PFTs or spirometry are not indicated in these patients. In addition, ATS and American College of Occupational and Environmental Medicine has recommended against doing routine outpatient PFTs for concerns of spread
- Notify your local health department of positive cases
- There are suggestion that false negative PCR rate is estimated between 25-35%

Isolation and Infection Control for Confirmed and Suspected Cases:

Recommendations for isolation and infection control are evolving as more is learned about the SARS-CoV-2 virus. Current best practices include:

Place all suspected patients in droplet masks during assessment and when in transit
If cohorting is required due to resource limitation, keep patients 2 meters apart in a single room
Restrict visitors
Try to avoid room entry unless essential; try to move equipment (e.g. IV pumps) out of the room
Hand hygiene: 20+ seconds with soap and or 60- 95% alcohol containing hand gel
Use appropriate PPE in the correct sequence, including: Standard precautions
Contact precautions
Droplet precautions with eye protection
PLUS airborne precautions for aerosolizing procedures such as intubation, extubation, non-invasive positive pressure ventilation (NIPPV), open circuit suctioning, bronchoscopy, and aerosol treatments
N95 masks must be fit tested

1. All Healthcare professionals must be trained in how to properly don, use, and doff PPE in a manner to prevent self-contamination
2. If available, consider powered air-purifying respirator (PAPRs) or controlled air purifying respirators (CAPRs). Use of tight-fitting respirators require fit testing, but use of loose-fitting respirators does not require fit testing

General Treatment Recommendations:

The following treatment strategies are recommended based on experience to-date. Of note, these are Suggestions and should not replace clinical judgement at the bedside.

- Fluid-sparing resuscitation
- Empiric antibiotics if suspicion for secondary infection
- Due to concerns for aerosol spread, nebulizers should be converted to MDIs
- WHO has not recommended against the use of Non-steroidal anti-inflammatory agent Clinicians should consider alternatives if concerns exist
- Initiating or discontinuing ACE-I and ARBs have been an area of intense discussion. The American College of Cardiology, American Heart Association and Heart Failure Society of

America's joint statement recommends against discontinuing ACE-I and ARBs in patients with COVID-19

- Monitor for and treat cardiomyopathy and cardiogenic shock which have been reported as a late complication of COVID-19. Point-of-care ultrasound may be useful in identifying patients with this complication
- Corticosteroids are not recommended except when required for other indications such as asthma or COPD exacerbations, refractory shock or evidence of cytokine storm

Specific clinical management:

At present, there are no recommended antivirals for COVID-19 and management is as per best supportive care for any respiratory disease. Several clinical trials are actively recruiting patients worldwide

Considerations for patients with severe acute respiratory illness include the early use of empirical antimicrobials and neuraminidase inhibitors to cover for alternative (or coexisting) diagnoses. A systematic review of interventions for the management of SARS-CoV patients found no definite benefits for ribavirin, with possible harm due to haemolytic anaemia and impaired liver function (raised alanine aminotransferase), while data on the combination of lopinavir 400 mg with ritonavir 100 mg orally every 12 hours was inconclusive due to study design, despite prior supportive *in vitro* findings. However, a randomised controlled trial of lopinavir/ritonavir for COVID-19 has already been initiated in Wuhan. There was no definite benefit for corticosteroids in SARS-CoV patients as a group, and some studies found possible evidence of harm, such as delayed viral clearance, psychosis, diabetes and avascular necrosis. Evidence from management of MERS-CoV also suggests corticosteroids may delay viral clearance. However, other indications for corticosteroids such as exacerbation of asthma could potentially supervene. Remdesivir, a novel nucleotide analogue prodrug with activity against MERS-CoV in mouse models has been given to one COVID-19 patient in the USA on a compassionate basis without adverse events, and randomised controlled trials formally investigating its use in COVID-19 infection have already been registered.

Detailed guidance intended for the management of COVID-19 cases developing severe acute respiratory illness has been published by the World Health Organization (WHO) and is available online at www.who.int/emergencies/diseases/novel-coronavirus-2019; it is likely to be regularly updated and is therefore not reproduced here.

Management of Hypoxemic Respiratory Failure:

Again, these are *suggestions* and should not replace clinical judgement at the bedside.

Oxygen by nasal cannula OR simple mask OR non-rebreather masks
Consider early intubation to avoid use of aerosolizing NIPPV and emergent intubations
Use rapid-sequence intubation. Avoid bag-mask valve if possible due to risk of droplet spread
Avoid direct laryngoscopy to distance provider from patient. Use video laryngoscopy where possible
Connect suction and capnography in advance to avoid circuit breaks
Minimize circuit breaks and use high-efficiency particulate air (HEPA) filters between endotracheal tubes and CO2 detectors
Use lung-protective ventilation strategies per ARDSnet protocol. Prone and paralyze as needed
Patients will likely require a prolonged duration of mechanical ventilation

Extracorporeal Membrane Oxygenation (ECMO) can be considered but is associated with a high mortality rate. Monitor for and treat **cardiomyopathy** and cardiogenic shock which have been reported as a late complication of COVID-19. Point-of-care ultrasound as well as BNP levels may be useful in identifying patients with this complication. In a recent case series from Washington, 33% of patients developed cardiomyopathy.

Investigational Therapies:

Information on registered clinical trials for COVID-19 in the United States is available at: https:// clinicaltrials.gov/

No US Food and Drug Administration (FDA)-approved drugs specifically for the treatment of patients with COVID-19 currently exist. Drugs currently approved for other indications as well as investigational drugs are being studied in clinical trials 17 FDA approved drugs that may be used off-label Chloroquine or Hydroxychloroquine—blocks viral entry into the endosome; in vitro data suggests some utility but data from RCTs is lacking Investigational agents available in the U.S. Avoid prophylactic use Remdesivir—anti-viral nucleotide analogue Other drugs Lopinavir/ritonavir—anti-viral protease inhibitors; recent negative RCT19

RECOVERY Trial (Randomised Evaluation of COVID-19 Therapy)

Clinical trials using Convalescent Plasma for COVID-19 in the United Kingdom Blood and Transplantations services (There are 2 clinical trials managing the provision of COVID-19 CP

1. REMAP-CAP – this clinical trial is looking at treatments including CP for patients with COVID-19 infection who have been admitted to the intensive care unit (ICU).
2. RECOVERY– this clinical trial is comparing treatments including CP for patients with COVID-19 infection who have been admitted to hospital.)

Serology assays for SARS CoV 2 (COVID 19) Uses and limitations

The last few days/weeks we have been receiving increasing requests from HCW for a serology test for SARS CoV 2 (COVID 19). Many of the HCW, who are working in the front line, understandably would like to have a reassurance that they were/are not asymptomatic. Additionally, HCW would like to return to work earlier, if they have had detectable IgG against COVID 19.
The serology test looks for the presence of antibodies, which are specific proteins made in response to infections. IgG antibodies can be found in the blood and other antibodies (IgA) can be found in other tissues. This suggests that presence of IgG antibodies may indicate that a person had an immune response to SARS-CoV-2. Serological tests results are important in detecting infections with few or no symptoms.
However, the problems facing introduction of such tests are many. Serology tests are less than ideal tools for diagnosing people who are unwell. The seroconversion typically occurs only after the first week of infection and as such should not be used as the sole basis to diagnose COVID-19. RT-PCR remains the gold standard and ideal test for diagnosing infections with COVID 19, early in the infection. Therefore, HCW should not delay testing for staff swabbing for PCR if symptomatic and not post-pone testing with serology when it becomes available.
There have been numerous commercial manufacturers that check for SARS CoV 2 IgG; however, to date they are all pending validation, and none of these have been approved. To my knowledge, very

importantly, none of these are currently designed to test individuals who want to know if they have been previously infected with COVID-19.
Serological tests in the future (coming weeks/months) may play a role in the fight against COVID-19 by helping HCW to identify individuals who have overcome an infection in the past and have developed an immune response. In the future, results of such tests, plus correlation with other clinical data may potentially be used to help determine, that such individuals are no longer susceptible to infection and can return to work.
Until then, we would have to wait to hear from reputed scientific bodies for introduction of such tests.

Prognosis:

Based on initial experience in China and now on the other countries 80% of patients have mild symptoms, 15% moderate, and 5% severe (requiring mechanical ventilation). Most patients deteriorate gradually with a median of 9 days from symptom onset to ICU admission. Pregnant women and children appear to have a better prognosis. The following factors have been associated with worse outcomes:

- Increasing age
- Comorbidities including diabetes, cardiovascular disease (including hypertension), and chronic lung disease
- Higher admission sequential organ failure assessment (SOFA) score
- Laboratory abnormalities: elevated D-dimer, ferritin, and troponin

Control Strategies:

The following strategies are recommended to slow the rate of SARS-CoV-2 spread:

- Contact tracing
- Travel restrictions
- Social /Physical distancing
- Quarantine of suspected cases and exposed individuals

Transmission:

Human-to-human transmission is now well established for COVID-19, with an R_0 (the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population) currently estimated by the WHO as 1.4–2.5. For comparison, seasonal flu has a reported median R_0 of 1.28 (IQR 1.19–1.37), while measles has an R_0 usually reported as 12–18. However, an R_0 must be calculated from imperfect data and in different populations, and estimates are influenced by local variations in susceptibility, efficiency of case detection and infection control responses. Thus, the reported COVID-19 R_0 may change as further information becomes available.

Most human coronaviruses are transmitted mainly by the respiratory route or via contact with infected secretions. Samples from seven patients (six of whom were seafood peddlers or deliverers at the wholesale market) with severe pneumonia in ITU early in the current outbreak were found to be positive for SARS-CoV-2 in six bronchoalveolar lavage fluid samples and five oral swabs by quantitative PCR and conventional PCR, supportive of a respiratory transmission route. Virus has also been detected in patient stool samples. Fomite spread via contaminated surfaces is also probable,

based on SARS-CoV. Nosocomial spread is also a significant concern. The mean incubation period is brief, reported as 5.2 days, with the 95th percentile of the distribution at 12.5 days (95% confidence interval 9.2–18). One case documented an incubation period of just 3 days. However, it is not completely clear yet when a patient becomes infectious within this time frame. Asymptomatic carriage of virus has been documented; in a 10-year-old boy who also showed lung infiltrates on CT. Asymptomatic transmission of the virus was reported in a cluster of co-workers in Bavaria; however subsequent information refuted this, with the index patient confirming that they already had mild symptoms (myalgia, fatigue and use of an antipyretic analgesic) at the time of transmission. The relative contribution of asymptomatic carriage or transmission (if such can be confirmed) to the overall disease burden remains unclear.

Conclusions:

COVID-19 is a deadly and highly infectious RNA virus, the case fatalities varies worldwide, it is now apparent in western world that ethnic populations are at the highest risk of dying due to COVID-19 and its related complications leading to multi-organ failures. The scientists and clinicians worldwide are working round the clock to develop the best management strategy and rapid discovery of a safe and effective vaccine. Common sense and isolations strategy advocated by WHO and leading authorities seems to be working at least flattening the mortality curves. It is not very clear why some patients are more susceptible for early respiratory complications and sad outcomes then others who can just have mild symptoms and or no symptoms at all. Hope ongoing research will elucidate this within a short period of times.

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