REVIEW ARTICLE

COVID-19, SIXTEEN MONTHS INTO THE PANDEMIC: A NARRATIVE REVIEW

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COVID-19, the disease caused by the newly-discovered SARS-CoV-2 virus, has quickly spread from China throughout the world since January 2020. Its potential severity, despite in a minority of cases, has paralysed healthcare systems struggling for adequate resources, as well as entire nations often forced to adopt radical measures, such as lockdowns and surveillance, to contain the disease and restrict its spread. Initially presenting as a respiratory infectious disease, it can not only progress to an acute respiratory distress syndrome, but also have multisystemic consequences. There are many proving theories as regards to the pathophysiology and there are currently no proven definitive treatments. Due to its high transmissibility and the risk of infecting healthcare workers, hospitals also had to rethink their organisation. We have completed a literature review of the sixteen months of the pandemic, with attention to pathophysiology, key epidemiological concepts, hospital organisation, critical care considerations, and finally current and prospective treatments.

Keywords: COVID-19, Pandemic, SARS-CoV-2

Citation: Saumtally H, Cassidy S, Lal S, Khan E. COVID-19, sixteen months into the pandemic: A narrative review. J Ayub Med Coll Abbottabad 2021;33(4):673–84.

INTRODUCTION

The second severe acute respiratory syndrome coronavirus (SARS-CoV-2), previously known as the 2019 novel coronavirus (2019-nCoV), has rapidly spread throughout the world from Wuhan in the Hubei province in China since December 2019. On the 11th March 2020, the WHO called it a global pandemic.[1] The epicentre of the pandemic has since shifted from Asia to Europe, and eventually to the United States.

As of April 2021, there have been more than 150 million reported cases of the COVID-19, throughout the world, and more than 3.15M deaths.[2] This international health crisis has mobilised scientists and governments alike in order to better understand the pathophysiology of the disease, to find an efficient treatment along with containing the spread of the disease. Dealing with a new multi-systemic disease while observing strict protective measures are some of the challenges faced by physicians worldwide. Due to its rapid spread, this has had impacts both on a clinical and from an organisational standpoint.[3] Much like the disease itself, the literature around COVID-19 is growing exponentially by the day, via international collaborations through internet and social media as well as multi-centre trials. In some instances, there has been up to 4000 new papers a week[4], others estimate this number doubles every two weeks.[5] A synthesis of available information is therefore essential to monitor the progresses made since the beginning of the pandemic. This review will look at the symptomatology of the disease, discussing the proposed pathophysiology, how it has impacted hospitals and the critical care approach to COVID-19.

Virus structure and origin

The seventh reported human coronavirus, SARS-CoV-2, was first isolated in Wuhan, China at the Wuhan Institute of Virology from bronchoalveolar lavage fluid from infected patients.[6] Six of the seven patients were sellers or deliverymen from a local wet market in Wuhan, the likely source of the outbreak. The previous large scale severe coronavirus outbreaks were due to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2003 and 2012 respectively.[6] Like other coronaviruses, SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus, subclassified as a betacoronavirus.[7] The origin of the virus is the subject of much discussion. Conspiracy theories have been running aplenty on the Internet but there is strong genetic evidence that it is not the product of genetic manipulation.[7] The human virus shares 96% of its genetic code with the bat coronavirus RaTG13 and also similarities in the spike protein's receptor binding domain (RBD) from coronaviruses isolated in Malayan pangolins[7].In humans, the RBD binds preferably to the human metallopeptidase angiotensin-converting enzyme 2 (ACE2), much like the original SARS-CoV. The ACE2 enzyme is relatively widely distributed throughout the body, mainly in the pulmonary alveolar epithelial cells, enterocytes of the small intestine as well as on vascular endothelial and smooth muscle cells.[8] This is of relevance when

considering the myriad of symptoms that patients experience but has yet to be fully proven. The Global Initiative on Sharing All Influenza Data (GISAID) has been tracking the genome sequences from virus strains around the world. This extensive database has enabled the capacity of testing for viral RNA.

First presentation

The first case was reported on the 31st December 2019[9], however retrospective analyses claims that the first case may have been detected as early as the 17th November 2019[9]. The disease manifested itself in a pneumonia-like pattern (cough, fever, shortness of breath), with radiological signs of pneumonia, a low or normal white-cell count or low lymphocyte count, and no clinical improvement after 3–5 days of a standard antimicrobial regimen.[10] Out of the first 425 patients with confirmed COVID-19 in Wuhan, 56% were male, the median age was 59 years, with a mean incubation period of 5.2 days, comparable to SARS.[10] It was estimated then that the basic reproductive number (R_0), the number of secondary cases generated by a primary source, was 2.2. Children seemed to be spared, showing no or mild symptoms. This study, published at the end of January 2020, was already recommending aggressive testing in the outpatient setting, both to limit local spread and treat the disease as early as possible as the majority of patients would not present until day 5 of the disease.[10]

Prevalence and clusters

Due to the lack of herd immunity, spread has been extremely rapid. This has overwhelmed hospitals in some areas and led to serious economic consequences. As such, epidemic and transmission dynamics are major aspects that needs to be considered. Some of the central concepts that have helped in determining public health policies are identifying clusters, computing the net or effective reproduction number, R_t (i.e., the mean number of new cases generated by a primary source at a given time) and predicting prevalence.[11–13] Identification of clusters has been a priority in the management of spread in countries such as Singapore[12] and South Korea[14]. Building on experience from the previous SARS pandemic, methods have included not only self-isolation of symptomatic individuals, but also containment of these local clusters. Methods to identify clusters and implement containment measures include travel history, contact tracing, reports of other clusters from news and official sources, viral genomic and phylogenetic sequence analysis, or enhanced surveillance through regular video calls and sometimes tracking devices.[12,15] Prevalence has varied with time and geographical location. What started in one country in January 2020 had spread to more than 200 countries by the end of May 2020. Monitoring and predicting the prevalence is central for the implementation of public health policies to limit the spread of the virus; this could include prioritising essential over non-essential services, social distancing or resource allocation. Several statistical tools exist[13] but the models are difficult to implement as epidemics depend on a lot of factors and therefore can be quite random. Automatic Regressive Integrated Moving Average (ARIMA) is a model that has been implemented to monitor spread during previous outbreaks and has shown to be reliable for predicting prevalence in Italy, Spain and France. It should be noted however that data acquisition can be limited due to countries testing capacities, surveillance and tracing.

Sign, symptoms and severity

A proportion of COVID-19 positive patients will be asymptomatic. Reports on the rate of asymptomatic patients are however unreliable.[16] Reports vary largely, with figures quoted from 5–80%.[16] In a large cohort study of 72,314 cases in China, 81% of infected patients experienced mild disease, 14% experienced severe disease requiring hospitalisation[17], and the remaining 5% became critically ill. The definition of mild and moderate is still blurred across the literature, as a review of 18 studies show.[18] However, markers of severe disease seem to be consistent, such as P_aO_2/F_iO_2 less than 300 mmHg, S_pO_2 less than 93%, more than 50% of lung infiltrates and chest radiograph and a respiratory rate greater than 30 breaths per minute despite oxygen therapy. These often match the criteria for acute respiratory distress syndrome (ARDS) and may warrant tracheal intubation and intensive care admission.[19] Flu-like and respiratory symptoms are the hallmark of the disease. Fever remains the most common initial symptom, reported in up to 80% of cases in China and 45.4% in Europe. Additionally, cough (63,2% of cases), dyspnoea (31–40% of cases) and fatigue (40–70% of cases) are common features. Anosmia was reported as a symptom in March 2020, and has been found to be a strong predictor of COVID-19 infection.[20] The median age of patients is between 34 and 59 years with severe cases usually involving patients above 60 years of age.[21] Headache, rhinorrhoea, gastrointestinal symptoms such as nausea, vomiting, are less common (less than 10%). Chest pain has been reported in 5–40% of cases. More rarely, skin rash and conjunctivitis have been observed (1% in Europe, and less than 5% in China). Risk factors for severe disease or presentation requiring a need for hospitalisation seem to be consistent between findings in the US, Italy and China.[22] Most of the patient's requiring

hospitalisation are male, elderly, obese, hypertensive and diabetic patients. Pre-existing conditions including the ones previously stated as well as ischaemic heart disease, chronic renal failure, or cancer are also associated with higher mortality.[23] As per the Centre for Disease Prevention and Control (CDC), the median time to dyspnoea, ARDS and ICU admission are respectively 5–8, 8–12 and 10–12 days. Survivors typically stay in hospitals between 10–13 days.[24]

Diagnosis and testing

A key component in the management of COVID-19 is high throughput testing this has been attributed to a substantial contact tracing programme which allows isolation. Testing can be of two sorts: molecular and antibody-based. Molecular testing involves nasopharyngeal swabs, bronchoalveolar lavage (BAL) or sputum samples while antibody testing requires a serum sample.[25] In the absence of a gold standard test, molecular testing in laboratory, namely real time reverse transcriptase polymerase chain reaction (rRT-PCR) assay, remains the best method available.[25] Early in the pandemic, the time from testing to a result could be three to six hours, increasing if there were heavy demands on a single lab.[26] Sensitivities of rRT-PCR tests have been reported as between 71–98%, with specificity of approximately 95%. The specificity can be influenced by the sample type (93% for BAL samples, 72% for sputum, 63% for nasopharyngeal swabs, and 32% for throat swabs), which gene target is used, viral load kinetics, disease prevalence in the population and timing since inoculation. Sensitivity is a crucial parameter not only in the clinical setting but also in the community, as it could help in identifying asymptomatic cases and help reopen economies in the context of mass testing.[27] Clinicians should bear in mind the pre-test probability of the disease when interpreting results, and therefore should treat patients with symptoms suggestive of COVID-19 as positive until repeated testing is available or other causes has been identified. Antibody tests measure levels of IgG and IgM and are suggested to indicate prior infection, and thus potential immunity however further research is required before this can be assumed.[28] These are rapid tests, yielding results within 10–30 minutes. Sensitivities are quoted between 87% and 93.9%, and specificities of 100% (for samples taken 14 days after onset of symptoms).[29] This is good for determining asymptomatic cases. However, they will not diagnose a current infection or give an indication of the ability to transmit the virus to other people. New direct SARS-CoV-2 antigen detection kits are also under development[30] and would help detect presence of the virus[30].

Viral Load

The viral load is the quantity of a specific virus detected in a test sample obtained from a patient. As mentioned, detection of SARS-CoV-2 is by rRT-PCR. Various clinical samples can be analysed, and viral load in these samples differs. Most commonly nasopharyngeal swabs are used because of their acceptability to patients and not necessarily because they yield the highest viral load. The highest viral load is present in sputum and upper airway secretions[31]. Live virus has also been detected in faeces and blood[31]. Viral load is highest during the early phase of the disease, decreasing as illness progresses.[32,33] The duration of shedding can be prolonged and virus has been detected at day 20 of illness and longer in some patients. A persistently high viral load has been seen in critically unwell patients.[33,34] It is unknown if prolonged shedding represents potential infectivity. Age has been associated with an increased viral load similarly to SARS-CoV.[32,33] Importantly, a high viral load at presentation can influence treatment. This may represent an increased risk of drug resistance, potentially requiring combination therapies of any therapeutic agents developed.[33,34]

Hospitalisation / Admission

Due to lack of evidence, the Oxford COVID-19 Evidence Service Team concluded that there is currently no reliable clinical model to predict outcomes or guide decisions towards hospitalisation for mild and moderate cases.[35] In cases of mild symptoms and no significant co-morbidities, patients can be discharged home and asked to self-isolate for 14 days while observing strict social distancing measures. As per the Centres for Disease Control (CDC), hospital admission is clearly needed for the support of severe COVID-19: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalisation, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy.

Hospital preparation and intensive care capacity

The World Health Organisation (WHO) provides recommendations and suggestions for preparation of hospitals and intensive care units based on the experiences of different countries.[36] In creating extra capacity, the 4S theory can be applied.[36,37] This consists of space, staff, supplies and systems. Creation of space includes hospital beds and other facilities that can be modified to provide extra capacity. For COVID-19 disease, negative pressure

areas for aerosol generating procedures are required.[36] Capacity can be increased by postponement of non-urgent procedures, appointments and activities and expediting the discharge of patients with non-acute medical issues, this all requires financial investment and organisation.[36] In COVID-19 capacity has been increased by use of operating theatres as ICUs and the use of private hospitals in public systems.[36] Secondly, adequate staffing is essential for surge capacity.[36] Additional medical and nursing staff in addition to other healthcare workers, modification of hiring procedures to aid rapid recruitment and early graduation and entry into the workforce of nursing and medical students may be considered.[36] Recruitment of retired professionals and mobilisation of military health care professionals are other strategies.[36] Postponement of holiday leave, study leave and altering maximum work-time directives temporarily increase the available workforce.[36] Cross-skilling of staff may be required. With all of this comes an increase in stress among healthcare workers and so mental health protection is important. Rest days, alternative living arrangements and counselling should be available to all staff. The third S refers to supply of essential equipment and materials. Procurement teams should secure supply chains that can become vulnerable in a pandemic. This can may involve national centralisation of purchase and/or the repurpose of non-healthcare facilities to produce equipment. Finally, system responses include creation of policies and procedures to allow appropriate and sustainable surge capacity. This involves decision making, communication, supply chain management. Some examples include intubation guidelines and designated intubation teams, proning teams and pre-made intubation packs[38].These increase the availability of skilled staff that are in short supply e.g., intensivists, to maximise their time engaging in more skilled work.[38] Every part of any the above preparation strategy requires strong management, teamwork and constant communication and assessment of the situation to be successful, particularly in a rapidly evolving pandemic like SARS-CoV-2.

Personal Protective Equipment

Personal protective equipment (PPE) is essential to reduce transmission to healthcare workers which would result in morbidity, mortality and increased pressure on healthcare systems. It also reduces transmission from healthcare workers to family and asymptomatic transmission to patients.[39] Figures from China show more than 3300 healthcare workers had been infected with COVID-19 as of early March and in Italy 20% of healthcare workers had tested positive.[39] There are many reports of deaths of healthcare workers.[40] Procedures generating aerosols include tracheal intubation and manual ventilation prior to this, non-invasive ventilation (NIV), tracheostomy, cardiopulmonary resuscitation and bronchoscopy.[41] Basic preventative measures to reduce transmission include frequent hand hygiene (training in technique is essential), avoidance of touching eyes, nose and mouth and sneezing and coughing into elbow/tissue. If symptomatic a surgical mask should be worn.[41] The appropriate PPE should be used in the correct situations and staff should be trained to apply and remove PPE safely and a two-person buddy system when doing this is recommended.[41,42]

A&E management

Accident and Emergency (A&E) units have had to rethink patient management including triage, training of staff in PPE donning, identifying susceptible patients, limiting exposure of staff to the patient, prompt testing, engaging with microbiology and ICU early in the care for susceptible patients.[43] A safe distance of 2 meters should be respected during triage until a facemask has been applied to the patient.[44] The minimum number of essential staff should be in the room with the patient, while observing correct PPE precautions and hand hygiene. Stable patients should be placed in a private room with closed door, while critically ill patients or those requiring an aerosol generating procedures should be treated in a negative pressure isolation room and with aerosol precautions worn by staff.[44] When leaving the treatment room, the patient should wear a facemask, a clean hospital gown and adhere to hand and respiratory hygiene guidelines.[44]

Discharge criteria

Discharge criteria vary from country to country. The European Centre for Disease Prevention and Control (ECDC) have based their guidelines on the duration of virus shedding in the bodily fluids of asymptomatic patients. This is developed with consideration of different accuracies of tests to in detect a resolved infection, the difference between persistent viral RNA and infectious virus and by comparing guidelines from the US, China, Singapore and Italy.[45] Recommendations are described in Table 1. Patients ideally should fulfil all of the mentioned criteria but ultimately the decision to discharge is made by the clinician and based on their clinical judgement. These apply for times where the healthcare system is not under extreme pressure and guidelines may change over time.

Table-1: Discharge criteria as per the European Centre for Disease Prevention and Control[45]

Clinical Features	No fever for > 3 days, improved respiratory symptoms, pulmonary imaging showing absorption of inflammation, no hospital care needed for other pathology, clinician assessment
Laboratory evidence of SARS-CoV-2 clearance in respiratory samples	2 to 4 negative rRT-PCR tests for respiratory tract samples (nasopharynx and throat swabs with sampling interval ≥ 24 hours). Testing at a minimum of 7 days after the first positive rRT-PCR test is recommended for patients that clinically improve earlier.
Serology	The appearance of specific IgG when an appropriate serological test is available

Management

The management of COVID-19 disease is largely supportive. Those displaying moderate to severe disease should be admitted to hospital for treatment and monitoring. Supplementary oxygen with nasal cannula or a Venturi mask can be commenced aiming to keep SpO2 between 90–96%. In severe cases, when there is an increasing oxygen requirements and respiratory distress intubation should be considered. Fluid management is important. Patients are often hypovolemic on presentation due to poor oral intake and insensible losses from fevers which may have been ongoing for several days. When this is corrected, the goal should be to avoid hypervolemia. This can be achieved with vasopressors (noradrenaline is the vasopressor of choice) to maintain mean arterial pressures (MAP). A MAP target of 60–65 mmHg is recommended.[19] Careful monitoring of volume status is required with replacement of insensible losses from tachypnoea and fever. Prophylactic venous thromboembolism prophylaxis is important as these patients appear to be at an increased risk of thrombotic events.[46]

Intubation and Mechanical Ventilation

Despite the use of algorithms, an example of which is shown in Figure-1, deciding when to intubate in respiratory distress secondary to SARS CoV-2 can be difficult. In ARDS, early mechanical ventilation is the standard approach, based on evidence of worse outcomes in late intubation compared to never intubate and early intubated.[47] In addition, patients who are intubated following failure of NIV have been shown to have a worse prognosis in ARDS.[48] Patients using NIV generate very high tidal volumes, this in itself has been shown to predict the need for intubation and ventilation.[49] These high tidal volumes are suggested to cause a patient-induced lung injury due to a high respiratory drive with high minute ventilation.[49] This can be deleterious for patients and this forms the basis for the early intubation, sedation, lung protective ventilation and sometimes paralysis in the management of ARDS.[49] NIV in the form of continuous positive pressure ventilation (CPAP) and high flow nasal cannula (HFNC) is useful in the management of mild to moderate ARDS and type 1 respiratory failure secondary to pulmonary oedema. In the setting of a highly infectious disease such as COVID-19 there are transmission implications for the use of NIV. HFNC and CPAP are considered aerosol generating and thus full aerosol PPE is required with viral filters on the ventilation circuits and it should take place in a in a negative pressure room. At minimum a single room is required. A tight-fitting mask is essential to reduce air leak. Ideally a CPAP helmet should be used but availability is resource dependant. There is likely a group of patients that will benefit from NIV however it is important that tracheal intubation is not delayed.[50] Risk factors for failure of NIV include higher disease severity score, respiratory failure secondary to ARDS or pneumonia, older age and failure to improve after 1 hour of treatment.[50] Close monitoring is essential and failure rates of NIV are 30% in SARS and 13–77% in H1N1 influenza.[51] Case series have shown that patients with non-COVID-19 related ARDS benefit from prone positioning while awake and using supplemental oxygen via HFNC or CPAP. It is unknown if this prevents intubation and should not be attempted in rapidly deteriorating patients.

In Spain early intubation of patients with new hypoxemic respiratory failure secondary to SARS-CoV-2 has been recommended due to the risk of failure with NIV.[51] This does not apply in patients with P_aO2/F_iO2 >100 mmHg and the absence of multiorgan failure.[51] However in these lower risk patients, if there is no improvement in one hour tracheal intubation should be strongly considered.[51] If a documented ceiling of care applies, NIV may be used.[51] Chinese data showed a failure rate of 41% with HFNC in those in respiratory distress secondary to SARS-CoV-2. These patients were administered NIV as rescue treatment and 29% were subsequently intubated. Those requiring intubation had lower P_aO2/F_iO2 with 64% having a P_aO2/F_iO2 of <200 mmHg. Patients with P_aO2/F_iO2 >200 mmHg were successfully managed with HFNC, in these patients the respiratory rate decreased after 1–2 hours of treatment.[52] NIV is being used in a number of centres and evidence suggests it has an important role but emphasis should be on patient selection with close monitoring for signs of

deterioration or a lack of improvement and timely intubation if required.[52–54]

When a patient has been intubated for COVID-19 respiratory failure, mechanical ventilation recommendations reflect the ARDSnet guidelines. The emphasis is on lung protective ventilation with tidal volumes of 6 ml/kg (4–8 ml/kg) ideal body weight. Target plateau pressure should be <30cmH_2O with a higher PEEP while monitoring for barotrauma.[55] Periods of prone ventilation (16 hours per day) have been shown to improve gas exchange and reduce mortality in ARDS unrelated to COVID-19 and can be used in refractory hypoxaemia (P_aO2/F_iO2 of <150 mm Hg and $F_iO_2$of 0.6 despite appropriate PEEP). Neuromuscular blockade boluses and infusions to facilitate lung protective ventilation are also recommended. The concept of COVID-19 respiratory disease existing as two different phenotypes has emerged and challenged the recommendation to treat all patients in the same way. In ARDS, the respiratory compliance tends to be decreased. There are studies showing that in COVID-19 there is preserved compliance in some patients suggesting heterogeneity between patients[56], two phenotypes of patients have been described; type L and type H. Type L patients have low elastance (high compliance), a low ventilation to perfusion ratio and low lung weight and recruitability[56]. These patients differ in presentation to ARDS. Type H patients have a more typical ARDS presentation with high elastance, decreased compliance, high right to left shunt with high lung weight and recruitability. It is proposed that type L occurs at the start beginning of the illness followed by either recovery or deterioration with and transition from type L to type H. This transition may be related to depth of negative intrathoracic pressure driven by an increased tidal volume secondary to hypoxia. Combined with increased lung permeability from inflammation and interstitial oedema. Treatment based on this model depends on the phenotype and for an L-type patient would include increasing $F_iO_2$and consideration of HFNC or NIV. If these patients go on to require mechanical ventilation, then a higher tidal volume than that used for lung protective ventilation could be considered with tidal volumes of 8–9 ml/kg, PEEP 8-10cmH2O and avoidance of proning unless as a rescue measure.[56] Early intubation may prevent transition from type L to type H. Type H management can be considered as similar to that of ARDS. CT scan may help to differentiate these two subgroups.[56] This approach needs further study and randomised controlled trials would be essential prior to this approach superseding the standard management of ARDS as favoured by other groups.[57]

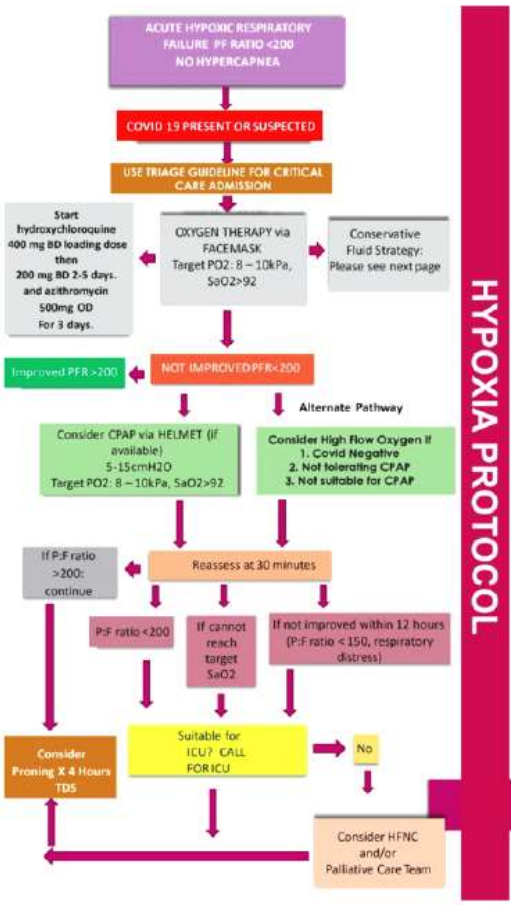

Figure-1: Hypoxia management protocol (Adapted from Our Lady of Lourdes Hospital guidelines, Drogheda, Ireland)

Intubation considerations

Intubation of patients infected with SARS-CoV-2 represents significant infection risk to healthcare workers, in particular the person responsible for managing the airway. Airway management is a potentially aerosol generating procedure. Data from Wuhan suggests that transmission from aerosols may be associated with more severe illness. This relates to patients being intubated and ventilated as a result of respiratory failure due to COVID-19 and also those with mild disease presenting for emergency surgery. There should be local guidelines in place for intubation of a SARS-CoV-2 positive or suspected patients. A consensus statement from the Difficult Airway Society, Association of Anaesthetists in Great Britain and Ireland, Royal College of Anaesthetists Faculty of Intensive Care Medicine and Intensive Care Society describes recommended precautions.[58] Preparation should ensure appropriate PPE providing aerosol protection. Training in safe donning and doffing should be provided to all staff, ideally with a two-person buddy system. Visual aids an example of which can be seen in

Figure-2. reinforcing preparation for intubation is encouraged. The virus can remain be present on surfaces for many hours, thus safe decontamination of surfaces and equipment is important and there should be avoidance of unnecessary contact with surfaces. Tracheal intubation should take place in a single negative pressure room with a minimum of 12 air exchanges per hour.[58] The number of people in the room should be minimised with roles assigned and cognitive aids. In addition to an intubator, an assistant and a person to administer drugs and watch monitors, there should be a runner outside the room. Simulation of scenarios is recommended. Intubation of critically unwell patients can be a time of instability and the 1st pass success can be less than 80%. The intubator should be the clinician with the most experience as increased attempts represent increased exposure. High risk groups may wish to avoid intubation, in particular immunosuppressed and pregnant healthcare workers. All airway equipment should be in the room. The airway device the intubator is most familiar with should be used. For most experienced anaesthetists this will be a video laryngoscope. Single use devices are recommended when they are of equal quality to reusable and available. Reusable items require decontamination after use. The primary plan should be discussed with a rescue plan verbalised.

Rapid sequence induction is the preferred method with three to five minutes of preoxygenation with a closed circuit and a heat and moisture exchanger (HME) filter between the catheter mount and the circuit. Drugs recommended are propofol or ketamine (if haemodynamically unstable), rocuronium (1.2 mg/kg) or suxamethonium (1.5 mg/kg) with vasopressors for blousing if necessary. Bag mask seal should be achieved with a two handed VE grip using an oropharyngeal airway if necessary and two people. Gentle CPAP can be considered if indicated and if a good bag mask seal but with caution as this can generate aerosols. An alternative to bag mask ventilation is a second generation supraglottic airway. A tracheal tube (ETT) with a subglottic suction port should be used (internal diameter of 7–8 mm in females and 8–9 mm in males).[58] A bougie or stylet may be helpful if carefully removed to avoid contamination of team members. Cuff inflation to 20–30 cmH20 is required prior to ventilation.[58] Confirmation of placement should be with waveform capnography and bilateral chest rise; auscultation is not recommended. Depth of the ETT should be recorded, nasogastric tube and any invasive lines should be placed at this time. If the patient is not confirmed as SARS-CoV-2 positive then a deep tracheal sample should be obtained for testing. Difficult Airway Society (DAS) guidelines apply for difficult airway with scalpel-bougie-tube being the preferred option for front of neck access over a cannula technique. Post intubation monitoring of the cuff pressure is important and if high airway pressures are present aim for a cuff pressure 5 cmH_20 above the peak inspiratory pressure.[59] Dry circuits are advised in this guideline, which involves using a HME filter for humidification. However, based on UK experience wet circuits can be considered to reduce the cast formation and plugging that can affecting the dry circuits. Dry circuits with HME filter scan result in increased dead space and thus a resulting increase in $P_aCO_2$when compared to a wet circuit. These need to be checked regularly to ensure water does not accumulate in the circuit and they need to be changed every 24 hours.[60] In patients with a high secretion burden, wet circuits are more favourable as they reduce drying out of secretions and so reduce mucous plugging and alteration of mucociliary escalator.[60]

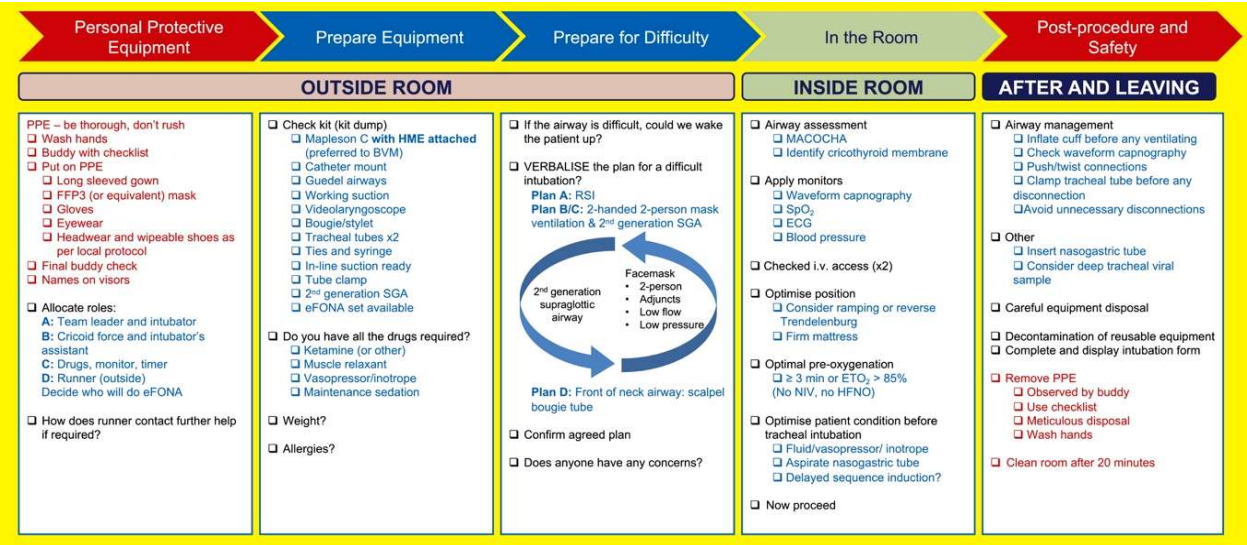

Figure-2: Emergency tracheal intubation checklist[58]

Multi organ failure

A meta-analysis of 31 articles based on the Chinese experience including almost 46000 patients has shown an ICU admission rate of 29.3% in patients with COVID-19. Organ failure is common in this group with respiratory failure being most common, unsurprisingly as COVID-19 most commonly affects the respiratory system. Of ICU patients, 99% required respiratory support and 88% of these required intubations and ventilation.[61] Acute cardiac injury occurred in 14.1%, acute renal injury in 7.1% and 8.5% developed multi organ failure.[61,62] Myocardial dysfunction is relatively common and the recommendation is for judicious fluids, measurement of BNP and troponin, echocardiographic assessment and early vasopressors and inotropes in patients presenting with COVID-19.[63] Acute cardiac injury has been observed in 14.1–44% with heart failure in 24%.[64] This can manifest as a raised high sensitivity troponin and patients with pre-existing cardiovascular disease are at an increased risk. Raised troponin is present in 7–17% of those hospitalised and 22–31% of those admitted to critical care.[65] Renal involvement is common and ranges from proteinuria to an acute kidney injury which can require renal replacement therapy (RRT).[66] It is considered a prognostic factor and up to 40% of patients have a proteinuria on presentation and 20% of ICU patients require renal replacement therapy.[67–70] Early recognition is important and treatment is supportive. Lung protective ventilation reduces haemodynamic effects of ventilation. Careful fluid balance is recommended, and this should be based on fluid responsiveness. With regard to RRT, citrate RRT is advised due to the hypercoagulable state that may be present in the COVID-19 patient. There is evidence of an increased number of thrombotic complications events among critically unwell patients with COVID-19. It has been reported that 25–31% of ICU patients develop thrombotic complications. Post mortem examinations of lungs from patients who died from COVID-19 complications have showed widespread microthrombi and angiogenesis.[71] Vigilance for complications is essential, especially where patients are intubated and so do not to present with typical symptomology. Early diagnostic imaging is useful. Microvascular complications have been also reported with inflammatory cells found in the endothelium of vessels in the heart, small bowel, lung, kidneys or liver consistent with endotheliitis.[72] This leads to vasoconstriction leading to organ ischaemia, tissue oedema and favours pro-coagulant state. Immune thrombocytopaenic purpura (ITP) has also been reported.[73]

Laboratory markers may have a role in prognostication. Patients studied with severe and fatal illness have increased incidence of leucocytosis, lymphopenia and thrombocytopenia. Patients who died also had higher procalcitonin levels compared to those who survived. Those with severe and fatal disease also had increased levels of liver enzymes, renal indices and coagulation measures in addition to higher troponin.[74] Based on other coronaviruses, SARS-CoV-2 is likely to have neurotropic features, supported by the neurological complications that have been observed in infected patients.[75] These include anosmia and also systemic symptoms such as headache and fatigue. Less commonly, encephalitis, Guillain-Barré and acute haemorrhagic necrotizing encephalopathy have been observed.[75] The cause for multi-organ involvement has not been fully determined yet. It is believed that the course to ARDS, and possibly to multi organ failure, is precipitated by an uncontrolled production of inflammatory cells, or cytokine storm. Elevated titres of pro-inflammatory cytokines and chemokines were observed in the first series from China in January 2020 with significantly higher levels of CXCL10, CCL2 and TNFα in ICU patients.[76] Associated biochemical findings are thrombocytopenia, hyperferritinaemia as well as persistent hyperpyrexia. This cytokine and clinical profile are also the hallmark of secondary haemophagocytic lymphohistiocytosis (sHLH) and may affect other systems in the body.[77]

Table-2: summary of COVID-19 involvement by system

Systems affected	Manifestation
Respiratory	Pneumonia, ARDS (Type H & L)[56,61]
Cardiovascular	Myocarditis, myocardial injury, acute myocardial infarction, acute heart failure, cardiomyopathy, dysrhythmias, endotheliitis[65]
Renal	Proteinuria, acute kidney injury, renal failure[66,67]
Gastrointestinal	Nausea, vomiting, diarrhoea, anorexia
Neurological	Anosmia, seizures, conjunctivitis, encephalitis, Guillain-Barré[75]
Haematological	Venous thromboembolism, arterial thrombosis, coagulopathy[46,49]

Mortality

Crude mortality figures for COVID-19 vary between 2–4%.[78] It is difficult to fully assess mortality as there are likely a much larger number of patients who have been infected but because of mild symptoms did not present for testing or qualify for testing by local

guidelines.[78] Mortality figures may also be much higher if the mortality rate is calculated by using the number of patients with confirmed infection 14 days earlier given the delay in symptoms. If this 14-day delay estimate is used then the mortality has been estimated to be from 5.7–20% in Wuhan.[79] In Chinese patients admitted to hospital, there have been mortality rates of 1.1% and up to 32.5% in severe cases.[80] ICU mortality rates are higher and have been reported from 16–78%.[80]

Pharmacological treatment

Patients with mild forms of COVID-19 usually improve with supportive care at home. As for the moderate and severe forms of the disease, a review article in JAMA from the 13th April 2020 states clearly "no proven effective therapies for this virus currently exist". This article lists potential therapeutic agents as "repurposed agents", "investigational agents" and "adjunctive therapies".[81] Among the few therapies that initially gained traction, the combination of anti-retroviral Lopinavir/Ritonavir was proposed as a potential treatment due to its benefits during the SARS outbreak in 2003, but results in cases of COVID-19 were not as positive and its use diminished[82]. Hydroxychloroquine has been heavily reported in the media and has generated polarised opinions in countries such as the USA, Brazil and France, despite a lack of scientifically proven benefits.[83] A recent multinational registry analysis from 671 hospitals across 6 continents (totalling more than 96,000 patients) published in the Lancet in May 2020 failed to show any benefit for the drug, when used with and without a macrolide antibiotic. This showed a potential higher mortality and risk of cardiac complications. However, data discrepancies were noted by scientists all over the world. On the 4th June 2020, the Lancet retracted this study.[84] In June 2020, a double blind randomised controlled trial (RCT) published in the NEJM showed no benefit of hydroxychloroquine in the management of COVID-19 when administered post-exposure.[85] Some hydroxychloroquine trials around the worlds have been halted, such as the British study Recovery, but the WHO's Solidarity and Australasia's Ascot trials were resumed early June 2020. Another investigational agent, Remdesivir, a pro-drug converting to a C-adenosine nucleoside triphosphate analogue, showed promise in the early stages of the pandemic. The New England Journal of Medicine published results at the end of May 2020 showing a shorter recovery time and a decrease in mortality when compared to placebo.[86] As for adjunctive agents, corticosteroids are currently used, not without controversy, in the management of refractory shock. However, no benefit or improved survival was observed during the SARS and MERS outbreaks and there was a potential delay in viral clearance with corticosteroids. A study mentioned in a JAMA article also suggests that bacterial infections are more responsive to steroids than viral infections. Currently, only one retrospective study, undertaken in China, has showed reduced mortality in ARDS patients given methylprednisolone however the authors potential bias and residual confounding factors. For the management of the cytokine storm, an IL-6 inhibitor, Tocilizumab, has been showing success through small series and is part of Chinese management guidelines but RCTs are ongoing. Other immunomodulatory agents under investigation include Sarilumab, Bevacizumab, Fingolimod, Eculizumab. In addition to these systemic pharmacotherapies, inhaled pulmonary vasodilators have been used to improve gas exchange in refractory hypoxemia and may be considered. However, evidence for these agents have been in non-COVID-19 ARDS and have not been shown to reduce mortality. Even though these trials are investigating benefits of individual drugs, there are also some multi-centre RCTs comparing combinations of these potential treatments, such as DisCoVeRy (ClinicalTrials.gov Identifier: NCT04315948), comparing Remdesivir, Lopinavir/Ritonavir, Interferon Beta-1A, Hydroxychloroquine and standard of care. Other supportive therapies include Extracorporeal Membrane Oxygenation (ECMO). This may be of benefit in refractory respiratory failure but the cytokine storm may cause clotting of the circuit. As for targeting endothelitis, it is proposed that Angiotensin Converting Enzyme Inhibitors (ACEi) or statins could have a role, although this has yet to be demonstrated in clinical trial. The CDC, the American Heart Association, the Heart Failure Society of America and the American College of Cardiology do not recommend discontinuation of ACEi and angiotensin receptor blockers in those patients prescribed these agents for another indication.

Convalescent Plasma Therapy

Convalescent plasma therapy (CPT), that is therapeutic use of plasma from patients who have had COVID-19 and recovered, has been used for the treatment of Ebola, MERS and influenza A H1N1.[87–89] There are currently no RCTs showing efficacy of convalescent plasma. A systematic review of five studies in mostly critically ill patients has showed a significantly reduced viral load and increased neutralising antibody over time following CPT.[87] However this is based on small treatment numbers and significant variability relating to dosing and duration of CPT and the use of other antimicrobial

agents.[87] Importantly, there was zero mortality and no adverse events reported in those receiving CPT in this analysis. However, a Cochrane review documents one case of severe anaphylaxis following CPT. There are 22 ongoing RCTs investigating CPT. Until evidence is generated from this research, there can be no certainty regarding the efficacy of convalescent plasma in the treatment of COVID-19.

Vaccine

Vaccines are a most effect tool in preventing the spread of COVID-19. Vaccines are the main measure expected to play a crucial role in contributing to control the pandemic.

There are many different vaccines available now with various efficacy and side effects.

In the first phases of vaccination campaigns, vaccinate those who are most at risk. In the meantime, all measures for controlling the spread of this virus – physical distancing, appropriate hand hygiene, respiratory etiquette, and the use of face masks where required – remain of key importance.

CONCLUSION

The wave of the COVID-19 pandemic is still on at different stages in different countries, and yet no definitive treatment has been found, along with the pathophysiology which yet need to be fully understood. COVID-19 has manifested as an insidious respiratory disease that can progress to multi-systemic involvement. The fear of a next wave in countries that are beginning to recover from the initial surge in cases is also present. The speed of research therefore cannot slow down if we are to understand the different aspects of the disease and the best ways to manage them until a vaccine or an efficient treatment is found.

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Submitted: May 1, 2021	*Revised: May 14, 2021*	*Accepted: May 28, 2021*

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