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Management of Coronavirus Disease 2019 (COVID-19) Pneumonia

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Coronavirus Disease 2019 (COVID-19)

The Coronavirus disease 2019 (COVID-19) pandemic has caused a global crisis, along with unprecedented demands to the delivery of healthcare, large-scale adjustments in human behavior, and significant pressures on global economies. Since the first description of the disease in December 2019, with cases of unexplained respiratory infections throughout Wuhan in China's Hubei province, advances in understanding the disease and its management have been dramatic.

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 8 December 2019, the World Health Organization (WHO) published a report of a novel coronavirus associated with respiratory symptoms. By 11 March 2020, when the WHO declared a global COVID-19 pandemic, more than 118,000 cases and 4000 deaths from SARS-CoV2 had been reported in 114 countries. By the end of February 2021, there have been over 119.7 million reported cases and 2.65 million recorded deaths worldwide from COVID-19 (March 2021).

Whilst COVID-19 may cause multi-system pathology, this chapter will primarily focus on the management of COVID pneumonia.

SARS-CoV-2 Infection

SARS-CoV-2 is an enveloped positive-strand RNA virus within the *Coronaviridae* family. Coronaviruses infect humans, other mammals and birds. In humans they mainly result in respiratory or enteric disease, causing mild, seasonal respiratory infection presenting as a "common cold" (Corman et al., 2018). SARS-CoV-2 is the third documented coronavirus infection to transfer from an animal reservoir to humans in the past two decades. Severe acute respiratory syndrome coronavirus (SARS-CoV) (2002–04) and Middle-Eastern Respiratory Syndrome coronavirus (MERS-CoV) (2012 – 20) caused more than 10,000 cases globally with an associated significant mortality rate of 10% (SARS) and 37% (MERS) (Huang et al., 2020). The SARS-CoV-2 strain has proven to be even more infectious.

Coronaviruses are large, roughly spherical enveloped viruses with a nuclear capsid containing genetic material, housed in a lipid bilayer with multiple structural proteins on their surface. Membrane (M) and envelope (E) proteins are essential for maintaining the shape of the viral envelope, nucleocapsid (N) phosphoproteins enclose viral RNA; spike (S) proteins are club-shaped projections from the surface required for entry into host cells leading to infection and replication. The distribution of S-proteins creates the virus' characteristic ring-like appearance of a solar corona. The SARS-CoV-2 spike proteins have a high affinity for the angiotensin-converting enzyme 2 (ACE2) receptor on human cells (Lan et al., 2020). Once the virus has attached to the ACE2 receptor, protease enzymes, released by the cell, cleave and activate the spike protein. This allows viral entry into the cell by endocytosis or fusion of the viral envelope with the host cell's lipid membrane. Viral RNA is next translated by the host's ribosomes within the endoplasmic reticulum, and the viral proteins assembled to form progeny viruses. Once released by exocytosis, progeny viruses are able to infect other host cells and to be transmitted in the environment to infect other individuals.

The incubation period of COVID-19 following exposure to SARS-CoV-2 is typically 5–6 days but may be as long as 14 days. Human coronaviruses infect the respiratory epithelium and spread when viral particles are introduced into a new host's respiratory system by either droplets or aerosol spread via the upper respiratory tract, lungs (via inhalation) or eyes. Respiratory droplets are $\geq$5–10 μm in diameter, comprised of saliva or mucus of the respiratory tract generated during coughing, sneezing, talking or singing. The distance these droplets fall is affected by their size and environmental conditions such as ambient airflow or wind speed. Aerosols are particles less than 5 μm diameter generated from the respiratory tract and suspended in air, thus capable of traveling longer distances. Droplets and aerosols are generated during medical procedures (aerosol generating procedures [AGP]) including bronchoscopy, endotracheal intubation, non-invasive ventilation, high frequency oscillatory ventilation (HFOV), administration of high-flow nasal oxygen (HFNO), during airway suctioning, and sputum induction. Healthcare workers exposed to AGP may be at increased risk of infection, hence the recommendation for personal protective equipment (PPE) for all healthcare staff (Huang et al., 2020). However, there is little evidence directly linking exposure during AGPs and infection, most recommendations having originated from evidence from previous SARS outbreaks.

After infection of the upper airways the disease commonly causes fever, cough and malaise. Other symptoms commonly seen include headache, anosmia, sore throat, gastrointestinal symptoms, nasal congestion and dysgeusia.

Infected cells of the upper respiratory tract release inflammatory mediators, including C–X–C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and IFN-λ) which are sufficient in most cases to contain the spread of infection (Tang et al., 2005). Approximately one fifth of patients with upper respiratory tract infection progress to lower respiratory tract infection and develop severe symptoms. The virus enters type 2 pneumocytes via the ACE2 receptor and undergo replication as described. These cells release inflammatory mediators including interleukins (IL-1, IL-6, IL-8, IL-10 and IL-12), tumor necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α) (Chi et al., 2020). The inflammatory response attracts neutrophils, CD4 helper T cells and CD8 cytotoxic T cells which enter the lung parenchyma to destroy the virus. In so doing, they also cause widespread collateral damage to the lung tissue culminating in acute respiratory distress syndrome (ARDS) (Xu et al., 2020).

Multisystem complications of severe COVID-19 are common and include acute kidney and liver injury, arterial and venous thromboembolism, and central and peripheral nervous system complications. Cardiovascular complications of COVID-19 include myocarditis, dysrhythmias, heart failure, acute coronary syndrome and sudden death. In a meta-analysis of COVID-19 patients, cardiovascular symptoms or complications were seen in 14.1% of hospital patients and a case fatality rate of 9.6% (Sabatino et al., 2020).

Diagnosis of COVID-19

SARS-CoV-2 RNA is found in respiratory secretions, saliva, tears, feces, and semen of infected individuals. These not only provide many possible routes of infection but also means of testing for infection.

There are no pathognomonic symptoms to distinguish COVID-19 from other respiratory tract infections. Clinical suspicion of COVID-19 should therefore be considered in any individual with new-onset fever, persistent cough, dyspnea, smell or taste disturbance, myalgia, and gastrointestinal disturbance.

Nucleic acid amplification testing (NAAT) is the recommended modality for diagnosis of COVID-19. A sample is obtained, typically by swabbing the nasopharynx and/or oropharynx, and analyzed with a reverse-transcription polymerase chain reaction (RT-PCR) assay. Various assays are used worldwide, with different amplifying assays detecting different regions of the SARS-CoV-2 genome. NAATs are highly specific for the target RNA sequence and have high analytical sensitivity; their real-world sensitivity is limited by sampling technique. Antigen testing can be performed at the point of care and provides an alternative diagnostic method where NAAT is less easily available or convenient. These identify a specific viral antigen, for example the S-protein. Antigen tests have a lower sensitivity, however they can be reliably used to identify those with high viral loads who are most likely to spread the virus (Crozier et al., 2021). Antigen tests have been widely distributed amongst healthcare workers and other frontline staff with the purpose of frequent testing to identify cases early and allow early isolation to prevent nosocomial transmission.

Epidemiology of COVID-19

Assimilation of international, national and local data and patterns of disease has been vital to understanding, controlling and managing COVID-19. Published data has helped to stratify populations according to risk and highlight the disparity in health outcomes for patients with a positive COVID test. By February 2021, 400,000 cases had been admitted to hospital and over 118,000 had died within 28 days of a positive COVID-19 test.

Disproportion representation of COVID-19 patients and poorer outcomes affected by age, gender, ethnicity, and socioeconomic status have been reported. Data from a prospective observational cohort study of more than 20,000 hospitalized patients with COVID-19 in the United Kingdom showed a median age of 73 years (IQR 58-82), the majority of whom were male (60%) (Docherty et al., 2020). Age demonstrates the greatest disparity in mortality, with patients over 80 years being 70 times more than likely to die than patients under 40 years. Modeling by PHE to estimate excess all-cause mortality in the population for the

period 20 March to 7 May 2020, calculated 46,000 excess deaths in the United Kingdom when compared to corresponding dates between 2015 and 2019. Most excess deaths have occurred in those aged 75 and older, 45% of whom are aged 85 years and over.

The Intensive Care National Audit and Research Centre (ICNARC) reports 71% of COVID-19 admissions to critical care are male. Men of working age are more than twice as likely to die as age-matched females (Public Health England). It is unclear what drives this difference between males and females, however hypotheses include how healthcare is accessed, and physiological difference between the sexes.

Socioeconomic status is an independent risk in COVID-19 (Patel et al., 2020). Local authorities in the United Kingdom with the highest rates of diagnosis and mortality are mostly urban. COVID-19 mortality in London was three times higher than the South West of England, which saw the lowest number of deaths nationally. This inequality is significantly greater than all-cause mortality rates in previous years. People living in deprived areas have higher diagnosis and mortality rates compared to the least deprived areas. Infection and mortality amongst Black and Asian ethnic groups was higher than those seen in White ethnic groups. After accounting for the effect of sex, age, region and deprivation, people of Bangladeshi origin had approximately twice the risk of death compared to White British individuals. People of Chinese, Indian, Pakistani, other Asian, Black Caribbean and other Black ethnicity had between 10% and 50% greater risk of death than White British. These data did not account for the effect of comorbidities or occupation which have significant impact on the risk of contracting COVID-19 and the risk of death.

People with underlying health conditions including diabetes mellitus, chronic lung disease, obesity and cardiovascular disease are at higher risk of poor outcomes from COVID-19 than those without. A significant relationship between being overweight and COVID-19 has been reported; meta-analysis of over 400,000 patients has identified those with a body mass index (BMI) >25 kg/m^2 are more likely to require advanced respiratory support (odds ratio (OR) 6.98, CI 5.37–9.07), to be critically ill (OR 2.03, CI 1.75–2.36) and to die (OR 3.68, CI 1.54–8.83) (Hussain et al., 2020). ICNARC data up to September 2020 showed that 11.5% of patients in ITU with COVID-19 had a BMI of ≥ 40, compared to 2.9% of the general population.

Implications of COVID-19 on Healthcare Provision

The COVID-19 pandemic has placed enormous strain on health services worldwide, with rapid changes in the priorities in delivering care. The UK National Health Service (NHS) implemented multiple interventions for the provision of healthcare to COVID-19 patients, which included creating additional bed capacity in hospitals, redeployment of staff including to high-demand areas such as critical care, emergency departments and acute medical wards, and interruption to elective services. Medical and nursing students in the final stages of their training, as well as recently retired staff, were deployed to front-line roles. Procurement of equipment necessary for managing this disease included sourcing PPE, ventilators and anesthetic machines in the anticipation of patient numbers vastly overwhelming the NHS capacity. Operating theaters and beds in private were opened to NHS patients, increasing the national capacity for care of COVID-19 patients. NHS England established seven temporary hospitals across the country as part of the requirement to increase capacity. These "Nightingale Hospitals" were initially envisaged to provide additional critical care beds but have also been used for step-down and rehabilitation of COVID-19 patients. Manufacturing of the necessary equipment was increased, with companies not used to producing medical products volunteering to convert their production lines in order to help with the demand.

Despite creating de novo critical care areas and conversion of existing wards and clinical areas within hospitals, the availability of suitably trained critical care staff limited critical care capacity. Staffing standards of these areas dictate that there is one trained intensive care nurse for each critically ill patient (Williams et al., 2006). NHS England and NHS Improvement with Health Education England updated these guidelines for staffing during the pandemic after consultation with the UK Critical Care Nursing Alliance (UKCCNA), agreeing that two critically ill patients can be cared for by one specially trained intensive care nurse, supported by another registered healthcare professional (1:2). In the authors' experience however, nursing ratios of between 1:4 to 1:5 were required during the peak of the pandemic.

Despite higher exposure to COVID-19, U.K. healthcare workers did not have a higher rate of COVID-19 related deaths when compared to those of the same age and sex in the general population up to April 2020 (U.K. Office for National Statistics (ONS)). In the same period, mortality was higher for men and women working in caring personal services including nursing auxiliaries, home careers and dental nurses, with a relative increase of 1.8 times compared to mortality between 2014 and 2018. The greatest increase in death was amongst security guards with a 2.6-fold increase.

Management of COVID-19 Pneumonia

Treatment of COVID pneumonia should be guided by disease severity (**Table 1**) and risk of deterioration, considering patient's comorbidities, home environment, and social support. For most patients, those with mild disease (symptomatic without pneumonia or hypoxia, or asymptomatic/pre-symptomatic with a positive SARS-CoV-2 PCR test), emergency intervention or hospitalization may not be required. Self-management at home may be appropriate, with advice on maintaining hydration, the use of simple analgesics and antipyretics, and when to seek medical help. Guidance from the WHO states that patients and any household members should remain in isolation at home for a minimum of 10 days following symptom onset (or following a positive COVID-19 test if asymptomatic), plus at least three additional days without fever and respiratory symptoms (in symptomatic patients).

Table 1 Severity grading of COVID-19.

Mild disease		*Symptomatic, without evidence of viral pneumonia or hypoxia*
Moderate disease	Pneumonia	Clinical signs of pneumonia (fever, cough, dyspnea, tachypnea) with no signs of severe pneumonia, and $SpO_2 \geq 90\%$ on room air
Severe disease	Severe pneumonia	Clinical signs of pneumonia (fever, cough, dyspnea, tachypnea) plus one of the following; respiratory rate >30/min, severe respiratory distress; or $SpO_2 < 90\%$ on room air
Critical disease	Acute Respiratory distress syndrome (ARDS)	*Onset* within 1 week of clinical insult (i.e., pneumonia) or new or worsening respiratory symptoms. *Chest imaging* bilateral opacities not fully explained by volume overload, lobar/lung collapse or nodules. *Origin of pulmonary infiltrates*: respiratory failure not fully explained by cardiac failure or fluid overload. *Impaired oxygenation*: with PEEP or CPAP 5 cmH_2O *Mild ARDS*: 200 mmHg $< PaO_2/FiO_2 < 300$ mmHg *Moderate ARDS*: 100 mmHg $< PaO_2/FiO_2 < 200$ mmHg *Severe ARDS*: $PaO_2/FiO_2 < 100$ mmHg

Adapted from World Health Organization.

Patients with severe COVID pneumonia or those with significant risks should be admitted to hospital for monitoring and treatment. Risk stratification at hospital presentation should be undertaken to help guide admission and clinical management. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) derived and validated a pragmatic risk score to predict mortality in patients hospitalized with COVID-19 (Knight et al., 2020; Gupta et al., 2021).

Severe disease, as defined by the WHO, are those having clinical signs of pneumonia with at least one of: (i) a respiratory rate >30 breaths per minute, (ii) severe respiratory distress, or (iii) oxygen saturations (SpO_2) $<90\%$ whilst breathing room air. Supplemental oxygen should be administered to patients with respiratory failure, with U.K. guidance from NHS England recommending a target of maintaining SpO_2 92–96% (88–92% in patients with know or at risk of hypercapnic respiratory failure). The Intensive Care Society (ICS) recommends all patients receiving $FiO_2 > 0.28$ attempt prone positioning. This recommendation is extrapolated from ARDS patients receiving invasive mechanical ventilation. The rationale of prone positioning in ARDS is to reduce ventilation/perfusion mismatching, hypoxemia and shunting (Koeckerling et al., 2020). This strategy has been trialed in awake, non-invasively ventilated patients, with a "self-prone" strategy demonstrating a delay or reduction in the need for intensive care admission (Ng et al., 2020).

Bacterial co-infection (at presentation) and secondary infection (after presentation) is relatively low in patients with COVID-19 pneumonia. Meta-analysis data reported rates of 3.5% (95%CI 0.4–6.7%) and 14.3% (95%CI 9.6–18.9%) respectively, with higher rates in patients requiring critical care support (8.1% (95%CI 2.3-13.8%) (Langford et al., 2020). Despite this, three-quarters (74.6% (95%CI 68.3–80.0%)) of hospitalized patients with COVID-19 receive antibiotics, with higher rates of prescribing with increasing age (Langford et al., 2021). Procalcitonin is a protein biomarker for the presence and severity of bacterial infection which may have a role in guiding appropriate use of antibiotic therapy. At present, the evidence for procalcitonin as a clinical tool is lacking though it may reduce unnecessary antibiotic use (Peters et al., 2021). The U.K.'s National Institute for Health and Care Excellence (NICE) provides national evidence-based guidance and advice for use within the NHS and other public health services. NICE's guidance on the use of antibiotics in COVID-19 infection recommends that antibiotics should be administered if there is clinical suspicion of bacterial infection, however not to start antibiotics if the clinical features are typical for COVID-19.

High rates of arterial and venous thromboembolisms have been reported in hospitalized patients with COVID-19, especially in critically ill patients. Viral-mediated endothelial inflammation, prothrombotic abnormalities leading to hypercoagulability, and thrombotic microangiopathy are central to this pathophysiology. Meta-analysis data reports an overall incidence of 17.0% (95% CI, 13.4–20.9) of venous thromboembolism (VTE), and 7.1% (95%CI, 5.3–9.1) for pulmonary embolism (Jimenez et al., 2020). It is therefore essential that thromboprophylaxis is considered for all hospitalized patients with COVID-19, in the absence of contraindications. Expert consensus and evidence-based guidelines have produced recommendations for prevention of VTE in critically and non-critically ill COVID-19 patient.

Children appear to have lower susceptibility to COVID-19 compared with adults, with an odds ratio of 0.56 of being an infected (Viner et al., 2021). Between January and July 2020, children represented 0.9% of COVID-19 hospital admissions in the United Kingdom with a median age of 4.6 years. Risk factors for requiring critical care support in these cases were age under 1 month, age 10–14 years, and black race (Swann et al., 2020). A Multisystem Inflammatory Syndrome in Children (MIS-C) in groups of children and adolescents has been described. These children present acutely with multisystem organ dysfunction (rash, fever, gastrointestinal symptoms, conjunctivitis and peripheral oedema) leading to multi-organ failure and shock, typically 3–4 weeks after SARS-CoV-2 infection. The majority of these cases were serologically positive for COVID-19, some of which were asymptomatic. A review of cases has shown 71% required critical care admission, 60% requiring vasopressor support and/or fluid resuscitation. MIS-C cases in this review had a mortality of 1.7%, comparable to adults with severe COVID-19 aged between 55 and 64 years.

Specific Therapies Treating COVID-19 Pneumonia

Attenuating the innate immune response to viral infection, the precipitant for multi-organ failure, and interrupting viral replication are key principles for disease modifying therapies for COVID-19. Several landmark studies, launched at the beginning of the pandemic, sought to identify potential therapeutics that could alter the disease course and reduce mortality and morbidity. Most notably, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Study ambitiously investigated a range of anti-inflammatory, immunomodulatory and antiviral treatments. In one treatment arm, patients were randomized to receive either standard care alone, or standard care plus oral dexamethasone for 10 days. The primary outcome of this trial was all-cause mortality within 28 days of randomization. Secondary outcomes included time until discharge from hospital, and number of patients who were not receiving invasive ventilation at time of randomization who subsequently received invasive ventilation. The hazard ratio from Cox regression was used to estimate the mortality rate ratio for the primary outcome. Administration of dexamethasone 6 mg once daily for up to 10 days (compared to usual care) reduced 28-day all-cause mortality in patients receiving either invasive mechanical ventilation (29.3% vs. 41.4%) or oxygen alone (23.3% vs. 26.2%); no treatment benefit was reported in patients not receiving supplementary oxygen (Horby et al., 2021). Corticosteroids are now recommended for all patients with severe or critical COVID-19 pneumonia by the NICE, using either dexamethasone (6 mg once daily) or hydrocortisone (50 mg eight-hourly) be administered for 7–10 days. There is no evidence to suggest that either dexamethasone or hydrocortisone is superior. Caution should be used to monitor for adverse effects including hyperglycemia, secondary bacterial or fungal infection, psychiatric effects and reactivation of latent infection.

Viral inhibition and disruption to SARS-CoV-2 replication aims to shorten the infective period and complications from COVID pneumonia. Repurposed antiviral drugs with in vitro evidence supportive of a potential clinical benefit were trialed in several large international studied. Lopinavir, a protease inhibitor, is used combined with ritonavir in the management of human immunodeficiency viral (HIV) infection. Despite in vitro and observational results, trials of lopinavir-ritonavir failed to report a significant reduction in death, progression to invasive mechanical ventilation or duration of hospital stay (Cao et al., 2020; Horby et al., 2020a,b). Remdesivir is an adenosine nucleotide prodrug and metabolized intracellularly into the active substrate remdesivir triphosphate. In its active form, it is capable of inhibiting viral replication by binding to viral RNA-dependent RNA polymerase. It had previously demonstrated in vitro activity against SARS-CoV and MERS-CoV (Sheahan et al., 2020; Agostini et al., 2018), and recent in vitro data supports its activity against SARS-CoV-2 (Wang et al., 2020a). No study has yet demonstrated a significant clinical benefit and no meaningful impact on survival (Wang et al., 2020b; Spinner et al., 2020). There is similarly no evidence to supporting remdesivir showing benefit in patients requiring ventilatory support, non-invasive ventilation, mechanical ventilation or extra-corporeal membrane oxygenation (ECMO). Nonetheless, clinical trial data has shown that intravenous remdesivir administered for 10 days statistically reduced time to recovery of adult patients hospitalized with COVID-19 who were receiving supplemental oxygen compared to placebo (10 days (95%CI 9–11 vs. 15 (95%CI 13–18))) (Beigel et al., 2020). Following this, Remdesivir became the first treatment of COVID-19 pneumonia to be approved by the U.K. Medicines and Healthcare products Regulatory Agency (MHRA), with expert panel guidance concluding a weak recommendation for the use of remdesivir in severe COVID-19 (Rochwerg et al., 2020).

Treatment efficacy of remdesivir is however augmented when given in combination with the Janus kinase (JAK) 1 and 2 inhibitor baricitinib. Baricitinib, licensed for rheumatoid arthritis, disrupts intracellular signaling pathways, and has been shown to have antiviral effects by impairing endocytosis of SARS-CoV-2 (Cantini et al., 2020). A double-blinded randomized controlled trial compared remdesivir (up to 10 days of treatment) with up to 14-days of baricitinib, or placebo. Patients receiving baricitinib recovered a median of 1 day faster than the placebo group (7 vs. 8 days, rate ratio for recovery 1.16 (95% CI 1.01–1.32)), and by a median of 8 days faster in patients receiving non-invasive ventilation (NIV) or high-flow oxygen therapy (10 days in the combination group vs. 18 days in the control group (rate ratio for recovery, 1.51; 95% CI, 1.10–2.08)). More importantly, the odds of progression to needing oxygen therapy were 17.4% less (95% CI 2.1–31.6) in the baricitinib treatment arm, and progression to mechanical ventilation or death were lower in the baricitinib treatment arm than placebo group (31% (hazard ratio 0.69, 95% CI 0.5–0.95)) (Kalil et al., 2021). At the time of writing, baricitinib has not been incorporated into a UK national treatment guideline for the management of severe COVID-19.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine released in response to infection and stimulates inflammatory pathways as part of the acute phase response. Specific monoclonal antibody treatment against the IL-6 receptor, namely tocilizumab and sarilumab, are licensed for the treatment of conditions including severe, active rheumatoid arthritis and CAR-T cell-induced cytokine release syndrome (Gordon et al., 2021). It was hypothesized that these agents may improve outcomes by dampening the COVID-hyperinflammatory syndrome. The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia study group (REMAP-CAP) demonstrated favorable outcomes when IL-6 receptor antagonists were administered within 24 h of intensive care admission with severe COVID-19 pneumonia. Median organ support-free days after administration of tocilizumab was 10 days (IQR −1 to 16), sarilumab, 11 days (IQR 0 to 16) compared to a control group (0 days (IQR −1 to 15)); improved hospital mortality for the same groups was reported (tocilizumab 28%, sarilumab 22.2% compared to control 35.8%). The RECOVERY Collaborative Group analyzed data from over 4000 patients, showing a decreased mortality in patients receiving tocilizumab (29%) compared to those receiving standard care (33%). There was also an increase in the number of patients discharged home alive at 28 days (rate ratio 1.23 (95% CI 1.12–1.34) $P < .0001$), and reduced likelihood of requiring invasive ventilation, or death (risk ratio 0.85 (95% CI 0.78–0.93) $P = .0005$) (Recoverycollaborativegroup, 2021).

In other treatment arms, the RECOVERY trial reported no significant improvement in 28-day mortality in hospitalized COVID-19 patients who received hydroxychloroquine, or any benefit from azithromycin compared to standard care, thus these are not recommended in the management of COVID-19 (Horby et al., 2020a,b; Recoverycollaborativegroup, 2021).

It has been hypothesized that convalescent plasma obtained from patients who have recovered from COVID-19 might provide passive immunity to infected patients due to transferral of antibodies specific against SARS-CoV-2 (Casadevall and Pirofski, 2020). Several randomized controlled trials have compared the outcomes of cohorts receiving convalescent plasma versus those receiving standard care, showing no significant differences in mortality or disease progression.

Critical Care Management of COVID Pneumonia

Pneumonia may lead to acute hypoxemic respiratory failure, with intensive care unit (ICU) admissions typically occurring in patients at approximately 7–12 days after the onset of symptoms (Phua et al., 2020). Acute respiratory distress syndrome (ARDS) was seen in 60–70% patients admitted to ICU. Data from China and Italy report 5–9% of patients admitted to hospital are admitted to a critical care environment for organ support (Tyrrell et al., 2021). It is important that patient's preferences for their care should be ascertained after discussion of the risks, benefits and likely outcomes of treatments options available. A meta-analysis published in early 2021 reported a mortality of 35.5% (95%CI 31.3–39.9) for patients admitted to intensive care (data up to 30 September 2020), a reduction when compared to a similar analysis in early 2020 when treatments and understanding of the disease were in their infancy (Armstrong et al., 2021).

NHS England recommends CPAP as first-line ventilatory support for hypoxemia in the setting of COVID-19, with NIV reserved for patients with acute on chronic hypercapnic ventilatory failure. Patient tolerance of ventilatory support is a limiting factor which may be improved with low dose benzodiazepines or opioids. In the absence of appreciable improvement using a non-invasive ventilation strategy, early intubation and mechanical ventilation should be considered.

Mechanically ventilated patients with ARDS should receive "lung-protective" ventilation, with low tidal volume and low inspiratory pressure. Positive end expiratory pressure (PEEP) prevents alveolar collapse, minimizes trauma associated with atelectasis and improves oxygenation. The U.K.'s Faculty of Intensive Care Medicine suggest the use of high PEEP in moderate to severe ARDS; defined as a PaO_2/FiO_2 ratio $\leq$27 kPa. Ventilatory mechanics in COVID-19 patients are heterogenous and therefore PEEP should be managed on an individual basis after consideration of oxygenation and lung compliance. Prone positioning for at least 12 h in patients with moderate to severe ARDS in addition to lung protective invasive ventilation has shown improved survival, however this strategy is labor intensive and requires attention to detail to prevent injury during turning, misplacement of endotracheal tube, vascular access and pressure effects to the skin and eyes (Mittermaier et al., 2020). To facilitate low inspiratory pressure mechanical ventilation intermittent bolus dosing of neuromuscular blocking drugs can be used. If plateau pressures remain persistently high then a continuous infusion may be considered.

Extracorporeal Membrane Oxygenation (ECMO) is a commissioned therapy for potentially reversible severe respiratory failure which has not responded to conventional management. In the U.K., the national multi-center ECMO network was created after the H1N1 influenza pandemic in 2009. Total ECMO capacity at the five U.K. centers was increased to 100 beds in response to COVID-19 demands, who have received a significant increase in the number of referrals during this pandemic. In April 2020, a total of 898 ECMO referrals were made; in comparison, in April 2019 the services received 82 referrals. As of May 2020, a total of 216 patients had received ECMO for respiratory failure secondary to COVID-19. Mean survival rate of ECMO for acute respiratory failure refractory to conventional measures in adults over the 6 years before the COVID-19 pandemic was 74%, identical to the survival rate for patients receiving ECMO for COVID-19 (Camporota et al., 2021).

Recovery From Severe COVID-19

Anticipation and recognition of substantial multisystem and psychological morbidity following COVID-19 infection is key in the recovery pathway. Survivors of severe COVID pneumonia may have persisting symptoms, with breathlessness reported in approximately a third of patients 2 months after hospital discharge (D'cruz et al., 2021), the etiology being multifactorial. A spectrum of abnormalities has been reported in three-quarters of patients imaged 6 weeks after hospital discharge, with a predominance of organizing pneumonia although persisting widespread fibrosis has been observed (Myall et al., 2021). Functional disability resulting from physical deconditioning and critical illness myopathy, and dysfunctional breathing patterns are similarly contributory to persisting breathlessness in the recovery period. Adverse mental health outcomes are important to recognize, with significant levels of anxiety (22%), depression (18%) and post-traumatic stress (25%) reported in one study at follow-up (D'cruz et al., 2021). A holistic multidisciplinary approach to reviewing patients recovering from severe COVID pneumonia is advocated by the authors, to identify and treat ongoing pathology, and support patients in physical, vocational and mental health rehabilitation (D'cruz et al., 2020).

The Future Landscape of COVID-19

As the U.K. emerges from a second "wave" of the COVID-19 pandemic, it is important to recognize the advances in patient management and the attenuation of the morbidity and mortality made over the past 12 months. Clinical trials continue to evaluate efficacy of novel immunomodulatory therapies to add to a treatment armory. Alongside this, and in parallel to continuing physical interventions to interrupt and control viral spread, vaccination against SARS-CoV-2 is key to reducing mortality and morbidity rates in patients with COVID-19. COVID-19 vaccine trials and real-world data have demonstrated prevention of disease, reduced viral transmission, with early and unpublished data indicating prevention of infection (Voysey et al., 2021). Obstacles to a recovery from the COVID-19 pandemic remain, including the emergence of novel SARS-CoV-2 mutants with variances in infectivity, pathogenicity and efficacy from existing COVID vaccines, along with inequity of inoculation worldwide.

In just over 1 year, extraordinary progress has been made in understanding COVID-19 disease. Expeditiously established clinical trials have led to effective treatments. Similarly, vaccination programs based on new vaccines and novel technologies have been created with unprecedented speed and with early indications of success. However, it is important to recognize and manage the persisting morbidity for surviving patients from COVID-19.

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