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COVID-19 related organ dysfunction and management strategies on the intensive care unit

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Abstract: The Coronavirus Disease 2019 (COVID-19) pandemic has resulted in a significant surge of critically ill patients and an unprecedented demand on intensive care services. The rapidly evolving understanding of pathogenesis, limited disease specific evidence and demand-resource imbalances have posed significant challenges for intensive care clinicians. COVID-19 is a complex multisystem inflammatory vasculopathy with a significant mortality implication for those admitted to intensive care. Institutional strategic preparation and meticulous intensive care support are essential to maximising outcomes during the pandemic. The significant mortality variation observed between institutions and internationally, despite a single aetiology and uniform presentation, highlights the potential influence of management strategies on outcome. Given that optimal organ support and adjunctive therapies for COVID-19 have not yet been well defined by trial-based outcomes, strategies are predicated on existing literature and experiential learning. This review outlines the relevant pathophysiology and management strategies for critically ill patients with COVID-19, and shares some of the collective learning accumulated in a high volume Severe Respiratory Failure centre in London.

Keywords: SARS-CoV-2; COVID-19; Respiratory Failure; ARDS; Ventilation; MODS; ECMO

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Introduction

Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) is a novel enveloped RNA beta-coronavirus associated with the Coronavirus Disease 2019 (COVID-19) [1]. The viral genomic sequence and clinical significance was outlined by the World Health Organisation (WHO) on the 12th January, and has since been declared a global pandemic [2]. The first case in the United Kingdom (UK) was confirmed on the 31st January 2020, and there have been 312,654 confirmed cases and 43,730 deaths since [3].

Guy's and St. Thomas' NHS Foundation Trust (GSTT) is one of six Severe Respiratory Failure (SRF) centres in the UK, and offers a complete spectrum of advanced respiratory support including Extracorporeal Membrane Oxygenation (ECMO). By virtue of its central London location and SRF referral network covering a population of 18 million people, the critical care department has admitted 321 patients with COVID-19 to date, including 56 mobile ECMO retrievals. This has facilitated a rapid learning of disease behaviour and emerging phenotypes, and allowed tailored patient therapies to evolve accordingly. The authors have been encouraged by their 71.1% survival to critical care discharge [4], which compares favourably to large contemporaneous datasets in the UK and Italy [5,6]. This narrative review looks at the relevant pathophysiology and management strategies for critically ill COVID-19 patients, and shares some of the collective learning accrued in a quaternary SRF centre.

History and presentation

The majority of early SARS-CoV-2 infections were related to zoonotic exposure in Huanan Seafood Wholesale Market in Wuhan, China, however, human-to-human transmission has since been demonstrated in the initial outbreak [7]. Although respiratory tract related droplets likely account for the majority of new infections, there is increasing interest in the potential for fomite, aerosol and faeco-oral transmission [8]. These factors, combined with a large proportion of infectious patients with only mild or asymptomatic carriage [9], makes pertinent contact and travel history insensitive tools for stratifying the risk of COVID-19.

Beta-coronaviruses enter the body predominantly through the Angiotensin Converting Enzyme-2 (ACE2) receptors, and this is followed by intracellular translocation [10]. The abundance of ACE2 receptors within the lower respiratory tract explains the high incidence of cough (67.8%) amongst symptomatic cases at presentation [11]. COVID-19 may also be associated with pyrexia (43.8%), fatigue (38.1%), anosmia (19.4%), myalgia (14.9%), sore throat (13.9%), headache (13.6%) and diarrhoea (3.8%) [11,12]. Disease severity can be highly variable ranging from asymptomatic through to fulminant multi-organ failure. These variations may be related to the route of transmission, inoculation dose and host immunity status [13].

The median (IQR) incubation period, time from first symptoms to hospital admission and first symptoms to developing Acute Respiratory Distress Syndrome (ARDS) are 4 days (IQR, 2-7), 7 days (IQR, 4-8) and 8 days (IQR, 6-12) respectively [11,14]. To date, the 8,699 patients requiring critical care in the UK have been predominantly male (71.1%) with a

median age of 60 (IQR 51-67) years and an elevated body mass index (BMI) >25kg/m^2 (73.8%) [5]. Critically ill patients are also more likely to have a smoking history and underlying cardiovascular comorbidities [10,14].

Given the variability in host response during different stages of COVID-19, the authors have found it helpful to conceptualise three phases of illness following an incubation period (Figure 1). While these phases represent a *continuum* of disease, the varied behaviour observed in certain phases may lend themselves to time-sensitive tailored therapies:

1. **Phase one** (0-7 days after symptoms develop) - Rapid viral replication and innate immune response phase resulting in the symptomology outlined, lymphopenia, and elevated inflammatory biomarkers and cytokine levels [15]. In this early phase, focal peri-bronchovascular and subpleural ground glass opacities on computed tomography (CT) can precede respiratory symptoms [16].
2. **Phase two** (5-14 days after symptoms develop) - Organ dysfunction phase related to ongoing viral cytopathy and emerging adaptive immune response. Two divergent groups appear to develop with an acute respiratory failure necessitating early invasive ventilatory support and those with more indolent organ dysfunction [15].
3. **Phase three** (>10 days after symptoms develop) – This late deterioration despite invasive organ support is mediated by either:
    - Hyperinflammation: Dysregulated immune response appears to take the form of either a persistent systemic hyperinflammatory state, a more limited pulmonary hyperinflammation or rarely idiosyncratic hyperinflammatory

syndromes such as secondary Haemophagocytic Lymphohistiocytosis (sHLH) or Cytokine release syndrome (CRS) [17].

- Organ support complications: The severe pulmonary inflammation observed in COVID-19 appears to be exquisitely sensitive to the myriad of complications of critical illness and organ support; including patient-self-inflicted-lung-injury (P-SILI), ventilator-induced-lung-injury (VILI), extravascular lung water (EVLW) accumulation, nosocomial infections and multi-organ dysfunction syndrome (MODS) [18-20].

Respiratory

Despite profound hypoxaemic respiratory failure being the dominating clinical feature of COVID-19, a unifying explanation of the pathophysiology remains contentious [21,22]. Beta-coronaviruses usually enter the body through the binding of surface spike glycoprotein via the variable receptor-binding-protein (mutated RaTG13) to the ACE2 receptors, and this is followed by intracellular translocation of virions through endocytosis or direct cell membrane fusion [10]. ACE2 receptors are expressed principally on type II pneumocytes but can also be found within the kidney, enterocytes and cardiac myocytes [10,13]. SARS-CoV-2 can elicit a pronounced inflammatory response through antigen presenting cells, and induction of cytokines and chemokines [10]. It remains uncertain what proportion of the pneumonitis and increased vascular permeability is driven by the viral cytopathy or dysregulated immune response.

The hypoxaemia seen in the early stages of COVID-19 has a different pathophysiology to that described in typical ARDS. Type-L phenotype presents with focal subpleural and peri-bronchovascular ground glass opacifications, limited atelectasis, low EVLW and low elastance, and the main mechanism seems to be ascribed to a dysregulation of pulmonary perfusion [22]. Recent histological data suggests an early isolated lymphocytic viral pneumonia in COVID-19 with later transition to an acute fibrinous and organising pneumonia (AFOP) [23]. Whilst the validity of such respiratory phenotypes in COVID-19 has been widely debated, it is important to remember that ARDS has never been a distinct diagnosis but rather a syndrome with a number of subphenotypes and different aetiologies [24]. This syndrome represents a final common pathway for a hugely heterogenous group of diseases that may require biologically targeted therapies in addition to lung protective ventilation (LPV).

These focal ground glass opacifications observed in early disease cannot fully explain the significant shunt fraction often observed. The aetiology of this early respiratory failure and disproportionate hypoxaemia is likely multifactorial:

- Pulmonary vasculopathy with loss of adaptive hypoxic pulmonary vasoconstriction and dysregulated pulmonary perfusion [21,22]. While the pivotal role ACE2 receptors play in SARS-CoV-2 transmission is well-defined, their expression within the pulmonary endothelium and role in dysregulated pulmonary perfusion is now becoming apparent [21]. The carboxypeptidase ACE2 counteracts the Renin-Angiotensin-Aldosterone-System through conversion of Angiotensin-I and II to

angiotensin-(1-9) and (1-7) respectively, these then promote localised vasodilation and attenuation of the immune response [25]. The initial downregulation of ACE2 results in Angiotensin-II accumulation with resulting chemotactic effects and accelerated lymphocyte recruitment [21,26]. The resulting pulmonary vascular inflammation results in an ACE1 'shedding' phenomenon where endothelial surface-bound ACE1 is released into the interstitium and ultimately results in sub-physiologic Angiotensin-II levels [26]. Low Angiotensin-II concentrations in this phase leads to vasodilation and worsened capillary leak.

- The high incidence pulmonary micro and macrovascular thrombosis offers insight into the high compliance, increased dead space, D-dimer elevation and right ventricular dysfunction frequently observed in COVID-19 and documented in post-mortem findings and histology [21,23,27-29].
- The neurotropic potential of SARS-CoV-2 with altered central control of breathing mediated by pontine pneumotaxic centre dysfunction which results in increased tidal volumes relative to respiratory rate. While low pulmonary elastance partially explains the deceptively effortless work of breathing [30], infiltration of SARS-CoV-2 into the cerebrospinal fluid and impaired brainstem autoregulation may also contribute [31,32].
- Increased basal metabolic rate resulting in higher tissue oxygen extraction, lower mixed venous oxygen content and increased venous admixture [33].
- Increased intrapulmonary shunt fraction with cardiac output elevation [34,35]. While high peripheral oxygen extraction partially explains the increased venous admixture observed in catabolic states, there may also be alterations in regional pulmonary

blood flow distinct from this related to increased cardiac output [33-35]. The contribution oxygen extraction and cardiac output play on arterial oxygen content can be visualised when the Fick equation is rearranged: $CaCO_2 = CvO_2 + VO_2/CO$.

- Iatrogenic component through excess positive end expiratory pressure (PEEP) application to compliant non-atelectatic alveoli resulting in over-distention, increased dead space ventilation and modification of shunt fraction due to redistribution of pulmonary perfusion [36].

Whilst many will recover from the Type-L pattern with supportive measures, a proportion of patients will progress through to the Type-H pattern. These two phenotypes do not represent discrete entities but a *continuum*, with a transition typically mediated by injurious organ support and hyperinflammatory states [22]. With the transition there are a number of associated changes in radiography and pulmonary mechanics outlined in Figure 2. The Type-H phenotype more closely resembles 'classical' ARDS on CT with high EVLW, atelectasis and increased non-aerated pulmonary units in the dependent areas which results in significantly smaller normally aerated lung volume, high elastance, and higher potential for lung recruitment [22]. This late phase three deterioration in pulmonary mechanics and oxygenation often coincides with referral for ECMO in our experience, typically 4-8 days after initiation of invasive ventilation. The early identification of other distinct CT patterns such as acute interstitial pneumonia (AIP) or cryptogenic organising pneumonias (COP) is essential to ensure tailored immunomodulation when indicated (Figure 3).

With the heterogenous disease behaviour observed, it follows that the intensive care support and therapies should be tailored accordingly (Figure 4). If significant hypoxaemia or work of breathing persists despite conventional oxygen therapy and a time-limited trial of awake prone position [37], the authors believe that intubation should not be delayed. A peripheral oxygen saturation (SpO_2) less than 92% on a non-rebreather mask (FiO_2 approximately 0.8) already represents a shunt fraction > 30%. In addition, the typical response to hypoxaemia when combined with high compliance is to generate excessively negative intrapleural pressures which result in substantial pulmonary strain [31]. If these large transpulmonary pressures are left unchecked, they can result in significant P-SILI [31,38,39]. Injurious spontaneous breathing has been shown to be associated with a deterioration in radiological appearances and diffuse alveolar damage at post-mortem [21,39]. Timely intubation and institution of LPV can overcome many of these problems.

The high shunt fraction with limited atelectasis and recruitability, combined with a protracted disease course and high transpulmonary pressures in spontaneous respiration, would question the role of prolonged non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP). The use of NIV in moderate-severe de novo hypoxaemic respiratory failure has also been consistently associated with high failure rates and increased mortality, particularly when associated with tidal volumes greater than 9mL/Kg if there is no reduction in the amplitude of the oesophageal swings [38,40]. In addition, any strategy involving wide-scale use of NIV should give consideration to the increased risk of aerosol-generation and SARS-CoV-2 transmission [41], and the potential impact on institutional oxygen supplies.

Following intubation, early LPV must be meticulously adhered to given the propensity for beta-coronavirus infections to behave like an inflammatory lung disease [42], which makes them extremely susceptible to VILI and biotrauma. Initially deep sedation and liberal use of neuromuscular blockade should be used to facilitate LPV, and to avoid dysynchrony and dramatic swings in transpulmonary pressures. In the event of progressive hypoxaemia, the use of strategies involving prone position, inhaled pulmonary vasodilators, higher mean airway pressures and ECMO should be tailored to disease behaviour (Figure 4). The authors adapt ventilation strategies based on an assessment of radiology and bedside pulmonary mechanics, including interrogation of quasi-static pressure-volume curves and recruitability-to-inflation ratios [43]. In the Type-L phenotype with low elastance and recruitability-to-inflation ratio less than 0.5, strategies involving high PEEP typically result in limited alveolar recruitment with over-distention, increased dead space ventilation and worsening venous admixture. To limit this unnecessary mechanical power application, the authors generally utilise a lower PEEP (5-10cmH_2O), inhaled pulmonary vasodilators and early prone position combined with standard tidal volume targets (6-8ml/kg). Type-H phenotypes with high elastance and recruitability-to-inflation ratio greater than 0.5, are more receptive to typical ARDS ventilation strategies including higher PEEP (10-15cmH_2O) and prone position while maintaining a plateau pressure less than 30cmH_2O and tidal volume of 6ml/kg [44]. When severe hypoxaemia is associated with persistent hyperthermia, a hypermetabolic state and hyperdynamic cardiac output, the authors use surface or endovascular cooling devices to limit oxygen consumption, improve mixed venous oxygenation and improve venous admixture [34]. In severe respiratory failure refractory to these conventional strategies, the authors have initiated mobile ECMO in 56 COVID-19 patients to date. Survival to critical care

discharge was achieved in 39 of the 51 (76.5%) patients; with five patients still currently being supported on ECMO.

Given the unusual pulmonary mechanics and propensity for exaggerated inflammatory response, the timing of spontaneous breathing and extubation can be challenging in COVID-19. The initial improvements often observed with invasive ventilation can be falsely reassuring resulting in premature deleterious spontaneous breathing and extubation attempts [45]. The authors believe that overreliance on pulmonary mechanics and oxygenation indices for assessing weaning readiness in isolation is flawed, and that other surrogates for disease resolution are needed. The authors regard an improving trajectory in radiological appearances and 'inflammatory panel' (temperature, C-reactive protein, ferritin, triglycerides and lactate dehydrogenase) as vital preconditions that should be assessed prior to undertaking any weaning attempts. Once spontaneous breathing is deemed appropriate, the use of P_{musc} Index (PMI) and P0.1 can be particularly helpful to limit injurious breathing patterns and ensure ongoing LPV [46]. With preconditions met and spontaneous breathing successfully initiated, a clear sensorium combined with an improved shunt fraction and tolerance of lower PEEP are particularly pertinent to extubation decisions. In patients with more extensive intensive care unit acquired weakness (ICU-AW) and greater risk of extubation failure, other traditional parameters for extubation readiness may also be helpful [45]. Prophylactic dexamethasone administration should be considered peri-extubation given the increased incidence of glottic oedema associated with prolonged periods of intubation and prone positioning [47].

Cardiovascular

The impact of SARS-CoV-2 on the cardiovascular system appears to be more sporadic with an elevated troponin occurring in 27.3% of hospitalised patients [48]. These patients have an increased in-hospital mortality compared to those with normal troponins (59.6% and 8.9%, *p<0.001*) [48]. While direct cardiovascular complications can be conveniently divided into categories (i.e. myopericarditis, ischaemic, and arrhythmias [49]), there is likely to be significant overlap between these groups.

There are few publications describing myocardial interstitial mononuclear inflammatory cells infiltrates and viral inclusions in COVID-19 [50,51]. Some of these changes are similar to those observed in classic viral myocarditis presenting with electrocardiogram (ECG) alterations, depressed systolic function, biomarker leak and cardiogenic shock [52]. The proportion of myocardial necrosis related to direct viral cytopathy versus later molecular mimicry and dysregulated immune response varies amongst viruses [52]. Whilst there have been a few reported cases of fulminant myocarditis presenting with low cardiac output states, dramatic elevations of troponin and N-terminal pro–brain natriuretic peptide (NT-proBNP) [51,53,54], the vast majority of patients admitted with cardiac injuries present with only a mild biomarker leak, absent ECG changes and preserved systolic function [55]. In addition, the authors have observed four COVID-19 myopericarditis cases with precipitous cardiovascular collapse and pericardial tamponade necessitating emergent pericardiocentesis.

The ischaemic cardiac injury observed in COVID-19 likely represents a range of disease pathogenesis including inflammatory myocarditis. Myocardial infarctions mediated by either atherosclerotic plaque rupture and coronary thrombus, or type II pattern related to flow-demand imbalance, are often observed in acute respiratory illnesses [56]. The linear correlation between troponin and C-reactive protein (CRP) does, however, pose the interesting question whether the majority of cardiac injuries are merely the consequence of an exaggerated immune response, and surrogate of disease severity and organ dysfunction rather than a distinct entity [48].

The culmination of these mechanisms contributes to the 17.3% of patients with elevated troponin experiencing ventricular fibrillation or ventricular tachycardia during hospitalisation [48]. In 136 COVID-19 patients with witnessed in-hospital cardiac arrests (IHCA) the initial rhythm was shockable, asystole and pulseless electrical activity in 5.9%, 89.7% and 4.4% respectively [57]. Accounting for the higher proportion of primary respiratory events, there was still a disproportionate rate of asystole compared to non-COVID-19 IHCA data [57]. The authors have witnessed a number of sudden non-shockable cardiac arrests in previously fit and well young COVID-19 patients without preceding respiratory embarrassment, significant echocardiographic or ECG findings, and only mild troponin release. Published cardiovascular pathogenesis in COVID-19 cannot fully explain such unpredictable disease behaviours. A number of these patients have presented with symptoms compatible with meningoencephalitis, a recognised complication of COVID-19 [32,58], and the authors hypothesise such precipitous cardiovascular collapse could be

partly mediated by neuro-cardiac axis dysfunction as a result of vasomotor centre injury in the rostral ventrolateral medulla as seen in other viral induced rhombencephalitis [59].

The influence of cardiorespiratory interactions observed in critical illness must also be considered in COVID-19. Clinicians should remain vigilant for the development of acute cor pulmonale given the high incidence of thrombotic pulmonary complications combined with frequent hypoxaemia, hypercarbia and elevated intrapulmonary pressures [28,60]. Early therapies to optimise pulmonary vascular resistance and right ventricular function are key to avoiding ventricular uncoupling and worsening MODS [61]. Early bedside echocardiographic assessment in patients with high acute cor pulmonale scores or escalating vasoactive drug requirements is essential to facilitate timely resuscitation [60]. Therapies for acute right ventricular dysfunction in the context of pulmonary hypertension should be multifaceted [61,62]:

- Treatment of specific aetiologies.
- Optimise intravascular volume and venous capacitance.
- Optimise inotropy with a preference for phosphodiesterase III inhibitors or levosimendan.
- Minimise right ventricular afterload through ventilatory manipulation to optimise functional residual capacity, limit intrathoracic pressures and achieve normocarbia/normoxia.
- Prone position to improve right ventricular pressure overload.

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- Reduction in pulmonary vascular resistance through inhaled or systemic pulmonary vasodilators, and a preference for vasopressin over catecholaminergic agents if a systemic vasopressor is required.
- Temporary percutaneous and extracorporeal life support (ECLS).

Given the overwhelming volume of admissions and low incidence of cardiovascular derangement observed in COVID-19, a standardised approach to general haemodynamic support is suitable for the majority of patients [63].

In the later phase of the COVID-19 pandemic, a number of patients (predominantly children and adolescents) have presented with a prior respiratory illness followed many weeks later by gastro-intestinal symptoms, fever and acute heart failure [64]. Ten young patients have been referred to our ECMO service with similar symptomatology, severe left ventricular systolic dysfunction, and a high CRP and ferritin. These patients have all responded to a combination of intravenous immunoglobulin (IVIG), methyprednisolone and inopressors. Depending on the mode and severity of the cardiovascular decline, a strategy including ECLS may also be appropriate [65,66]. While a proportion of these cases may represent a classical viral myocarditis, there is growing interest in the possibility of a distinct vasculitic process such as Kawasaki disease shock syndrome [67,68]. If this presentation is combined with SARS-CoV-2 IgM and/or IgG positivity and any mucocutaneous features (strawberry tongue, conjunctivitis and palmar or plantar erythema), consideration should also be given to high dose aspirin and a follow-up CT coronary angiogram to exclude coronary aneurysms.

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Neurology

Neurological symptoms occur in up to 36.4% of patients presenting with COVID-19, and these are more prevalent in those with severe disease [69]. These complications appear to be mediated by either an anoxic injury or SARS-CoV-2 neurotropism through haematogenous and retrograde neuronal infiltration [31,32,58,69]. The pathogenesis of the anoxic injury could be global oxygen delivery issues or more territorial related to cardioembolic disease and primary in-situ thrombosis [32,70]. The neurological consequences of these can include meningoencephalitis, HLH, and cerebrovascular infarcts and bleeds [32,58,69,71,72]. The authors have sadly seen three catastrophic multi-territory strokes in patients with severe COVID-19; both patients were under the age of 35, with no cardiovascular risk factors or echocardiogram abnormalities detected.

For the majority of neurological emergencies in COVID-19 the treatment will be supportive. Maintaining homeostasis with a particular focus on gas exchange and blood pressure optimisation is essential to limiting secondary brain injury. In patients presenting with strokes, the complex decision making around the timing of anticoagulation, and the role of mechanical thrombectomy and surgery are best addressed in high volume centres [73].

COVID-19 can present significant sedation challenges given the need for deep planes of anaesthesia in hypermetabolic patients. Despite the use of 2% propofol and a strict upper dose limit of 5mg/kg/hr, the authors have observed high rates of hypertriglyceridaemia. This elevation likely reflects exaggerated macrophage activation rather than evolving propofol

related infusion syndrome (PRIS) [74,75]. However, given the high prevalence of risk factors for PRIS in COVID-19 it would seem prudent to utilise adjunctive sedatives such as alpha-2 agonists, benzodiazepines or ketamine early to limit the lipid load when hypertriglyceridaemia develops. Reducing lipid intake and modulating the underlying disease process are the primary therapeutic strategies for hypertriglyceridemia in critical illness. In patients requiring ECMO support with hypertriglyceridaemia, the authors initiate fenofibrate given the increased risk of mechanical failure of extracorporeal circuits [76] and potential novel protective effect in acute lung injury through restoration of free fatty acid oxidation [77]. Volatile anaesthesia use in intensive care has a growing evidence base [78], and where the depth of sedation is difficult to attain without significant side effects, they have been delivered locally with the AnaConDa® system to good effect.

Renal

Acute kidney injury (AKI) has emerged as a serious complication in critically ill patients with COVID-19. The prevalence is variable with an incidence of less than 5% in some initial reports from China, to greater than 20% in more contemporary UK datasets [5,11]. This variation may be explained by differences in clinical practice but there also appears to be socioeconomic and genetic components. ACE2 receptor expression in renal podocytes and proximal tubule cells is more pronounced in Occidental subjects than in Asians, suggesting that the risk of COVID-19 associated AKI may differ between different ethnic groups [79].

The aetiology of COVID-19 related AKI is multifactorial and includes hemodynamic disturbance, inflammation, cytokine release, endothelial dysfunction, alteration of the microcirculation, nephrotoxic exposure, and the impact of invasive mechanical ventilation.

[80-82]. Although these factors are similar to AKI in non-COVID-19 settings, it appears there are additional factors specific to SARS-CoV-2:

- The SARS-CoV-2 virus uses ACE2 as a cell entry receptor. Following entry into the tubular epithelium and podocytes, the virus may exert direct cytopathic effects in the kidney [83]. The deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T-lymphocytes, complement C5b-9 or antibodies) may cause additional damage [83,84].
- ACE2 is pivotal in the conversion of Angiotensin-II to the vasodilatory and anti-inflammatory peptide angiotensin-(1–7). With ACE2 downregulation there is an initial increase in local Angiotensin-II concentration associated with vasoconstriction, endothelial activation and cytokinaemia [85]. With evolving pulmonary vascular inflammation and ACE-1 'shedding' there is an eventual drop in Angiotensin-II concentration to sub-physiologic levels [86]. This results in vasodilation, worsened capillary leak, alteration of glomerular autoregulation and reduction of glomerular filtration.
- Renovascular microthrombi. Post-mortem studies have shown segmental fibrin thrombi and erythrocyte aggregates obstructing peritubular capillaries and impacting intrarenal microcirculation [83].
- Rhabdomyolysis. Some reports of renal histology demonstrated pigmented tubular casts containing high levels of creatine phosphokinase [83].
- Collapsing glomerulopathy, an aggressive variant of focal segmental glomerulosclerosis with high rates of podocyte injury and depletion, has also been reported in renal biopsies [87].

Presently, there is no specific treatment for COVID-19 associated with AKI, although several potential therapies targeting different aspects of the pathophysiology are being explored [88-90]. Intravascular volume, microvascular flow and perfusion pressure should be optimised and if renal replacement therapy (RRT) is required, there is no evidence that a particular timing, mode or dose is superior but adjustments may need to be made in case of reduced RRT capacity [91,92]. Given the frequent thrombotic loss of extracorporeal circuits in COVID-19 [93], the authors have a low threshold for initiating systemic anticoagulation alongside regional citrate if problems are encountered.

COVID-19 related AKI is associated with an increased risk of mortality especially if RRT is required [5,94]. The long-term impact on kidney function, risk of chronic dialysis, cardiovascular morbidity and mortality remain unknown at this stage.

Haematology

There is escalating concern over thrombotic complications in COVID-19 related to the intricate interplay between cytopathic-ACE2 related endotheliopathy, hypoxic pulmonary vasoconstriction, and the cytokine storm with procoagulant-anticoagulant dysequilibrium. Initially, it was reported that 71.4% of COVID-19 deaths fulfilled the International Society on Thrombosis and Haemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC) [95]. However, a French case series of 150 patients has since revealed no cases of DIC as defined by the same score [93], and there have been no reported cases of the classical

hyperfibrinolytic consumptive process with bleeding propensity [96]. There has been renewed interest in D-Dimer concentrations given the significant elevation noted in patients admitted to intensive care and non-survivors [14,95]. It remains unclear what proportion of these D-Dimer elevations are related to thrombosis formation and fibrin turnover or merely intense pulmonary inflammation. A number of procoagulants have also been reported to be increased in COVID-19 including Fibrinogen, Factor VIII, Von Willebrand factor activity and antigen, and interestingly lupus anticoagulant and anticardiolipin antibodies [93,97]. While the incidence of prolonged Direct Russell Viper Venom Time (dRVVT) does seem particularly high, caution must be exercised when interpreting a single set of tests in the context of critical illness with acute viral infections, particularly given the lack of reporting of anti-β2-glycoprotein-1 titres. Furthermore, during significant inflammation there is frequent impairment of endogenous anticoagulant pathways such as Activated Protein C, Antithrombin III and Tissue factor pathway inhibitor [98].

There is a growing body of evidence suggesting a significant micro and macrovascular thrombus burden in COVID-19 [21,23,27-29,93,99,100], and this incidence exceeds those observed in matched non-COVID-19 severe ARDS patients [21,93]. In addition to standard cross-sectional imaging, the authors feel there is an emerging role for Dual Energy Computed Tomography (DECT) to better delineate the presence of subtle perfusion defects and microvascular thrombosis [101]. The underlying mechanism as alluded to, is not fully understood but appears primarily immunothrombotic in nature culminating in high fibrinogen levels with hypercoagulability, endothelial injury, and hypoxic pulmonary vasoconstriction with stasis. Tang et al suggested anticoagulation treatment may reduce

mortality in COVID-19 patients with 'sepsis induced coagulopathy' or elevated D-Dimers but the dose of anticoagulation utilised constituted venous thromboprophylaxis [102]. Enhanced thromboprophylaxis may reduce Fibrinogen and D-Dimer concentrations along with improving hypercoagulable viscoelastic parameters [103], however, given the small sample size and retrospective nature of this work, it remains unclear whether this was causation or association. Upstream immunotherapy, particularly interleukin-6 (IL-6) modulation given its correlation with fibrinogen levels [103], could also have an important role in limiting immunothrombosis.

While there appears to be consensus on anticoagulation in confirmed thrombosis and thromboprophylaxis in all other critically ill COVID-19 patients, the role for enhanced thromboprophylaxis remains uncertain. Given a pressing clinical need and previous precedent in other high risk populations [104], an interim solution may be to titrate thromboprophylaxis according to AntiXa levels or an empiric increase in patients stratified to be high risk of thrombosis and low risk of bleeding [105]. Whilst the use of antiplatelet agents in pulmonary microvascular thrombosis related to ARDS has some biological plausibility, more evidence is required before widespread adoption [106]. Figure 5 represents one potential pragmatic solution to anticoagulation management while further prospective trials are awaited.

Immunology

There is an increasing appreciation of the critical impact the host immune response has on illness severity and outcomes in COVID-19 [107,108]. Initial rapid SARS-CoV-2 replication results in activation of lymphocytes (natural killer, T-helper and T-cytotoxic cells), release of a range of cytokines and chemokines, and in severe cases lymphocyte exhaustion and peripheral lymphopenia. In COVID-19 Interleukin-1α/1ra/2/7/10/17, Interferon-γ, inducible interferon protein-10, granulocyte colony-stimulating-factor, monocyte chemoattractant peptide-3 levels are strongly associated with viral load and lung injury scores [109]. Synergistic innate and adaptive immunity is an essential host response to ensure viral clearance. In a small proportion of patients this host response is either protracted or disproportionate with exaggerated monocyte activation and IL-6 production [15,17]. Maladaptive macrophage activation can result in hyperinflammatory syndromes such as sHLH characterised by a persistent pyrexia, hyperferrintaemia, similar cytokine profiles and organ dysfunction [17]. The authors routinely screen all COVID-19 patients admitted to critical care for sHLH utilising the Hscore [110] but in our experience only a small proportion of patients have scores greater than 169. High levels of IL-6 associated with decreased lymphocyte subsets, pyrexia and organ dysfunction are critical components of CRS. While there has been much interest in COVID-19 related CRS and ‘cytokine storms’ [111], the IL-6 levels and inopressor requirements in the majority of patients rarely approaches those previously outlined in the CRS literature [26]. The authors feel while a generalised hyperinflammatory state is relatively common in COVID-19, only a small proportion of patients have true sHLH or CRS.

The authors consider a maladaptive hyperinflammatory state in the context of persistent organ dysfunction associated with ongoing pyrexia and inflammation (raised CRP, hyperferritinaemia and hypertriglyceridaemia) in the absence of demonstrable infection. The role of immunomodulation in maladaptive immune responses in COVID-19 remains controversial with a paucity of high quality evidence. The WHO recommended against the use of corticosteroids but this was largely based on concerns over increased viral shedding observed in Middle Eastern Respiratory Syndrome (MERS) [112] and an inconclusive systematic review in SARS-CoV-1 [113]. One of the largest studies of corticosteroids in SARS-CoV-1 has since been published demonstrating both safety and a decreased risk of death in severe disease (hazard ratio 0.53; 95% confidence interval 0.35-0.82) [114]. Prolonged use of corticosteroids in ARDS has also been previously associated with decreased mortality and healthcare utilisation [115,116]. The authors believe this data, combined with the high incidence of AFOP [23] and preliminary evidence of improved outcomes in COVID-19 [117], justified the judicious use of corticosteroids in patients with hyperinflammatory disease behaviour. The dose of methylprednisolone utilised locally is 1mg/kg/day in early disease or 2mg/kg/day if initiated late in patients with persistent severe respiratory failure. After five days at this dose, the methylprednisolone is then weaned over three weeks. Reassuringly, this approach is supported by recent initial reports from the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial which suggested early low-dose dexamethasone can improve survival in COVID-19 patients, with a number needed to treat of 8.5 in those requiring invasive mechanical ventilation [118]. When deciding on the timing of immunomodulation, integration of proactive surveillance for intercurrent infections with procalcitonin, microbiological cultures, cytomegalovirus viral load and fungal serology is

essential. The use of high dose corticosteroids, IVIG, anakinra (IL-1 receptor antagonist) or tocilizumab (IL-6 receptor antagonist) are reserved locally for patients with more overt features of sHLH or CRS.

The use of vitamin C in severe ARDS may attenuate cytokine surges, and limit activated neutrophil accumulation and extracellular trap formation [119]. These mechanisms may improve alveolar fluid clearance and limit endothelial injury. In the CITRIS-ALI trial, although the use of vitamin C in ARDS was not associated with an improvement in any of the primary outcomes, there was a significant reduction in 28-day mortality [119]. Given the perceived benefits and favourable safety profile, we tend to administer Pabrinex® to COVID-19 patients with organ dysfunction, particularly in the context of increased thiamine losses with diuresis or RRT [120].

Whilst the use of antivirals to limit replication, cytopathic injury and immune response would seem intuitive, initial randomised control trials of Remdesivir and Kaletra proved disappointing [121,122]. However, the recent Adaptive COVID-19 Treatment Trial showed Remdesivir was associated with a reduced time to recovery and non-significant reduction in mortality [123]. The reduction in median recovery time from 15 to 11 days is a particularly meaningful endpoint in the resource limited backdrop of a pandemic. The impact on outcome was greatest in patients in the initial phases of illness on oxygen therapy alone rather than those requiring ventilation or ECMO [123].

The ongoing and wider use of other novel therapies such as macrolides, Hydroxychloroquine, Interferon-β-1a, Anakinra, Tocilizumab, Sarilumab or convalescent plasma should be limited to prospective clinical trials such as the Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community Acquired Pneumonia (REMAP-CAP) [124].

Conclusion

COVID-19 is a complex multisystem inflammatory and microvascular disease conferring a significant mortality. A greater understanding of pathogenesis, combined with evidence-based organ support and tailored therapies where appropriate, will optimise outcomes in the later stages of the pandemic.

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Figure 1. Three phases of Coronavirus Disease 2019 (COVID-19). ARDS - Acute Respiratory Distress syndrome, AKI - Acute Kidney Injury, MODS - Multi-Organ Dysfunction Syndrome, GGO - Ground glass opacities, AIP - Acute Interstitial pneumonitis, COP - Cryptogenic Organising Pneumonia, iNO - Inhaled Nitric oxide, PEEP - Positive End Expiratory Pressure, APRV - Airway Pressure Release ventilation.

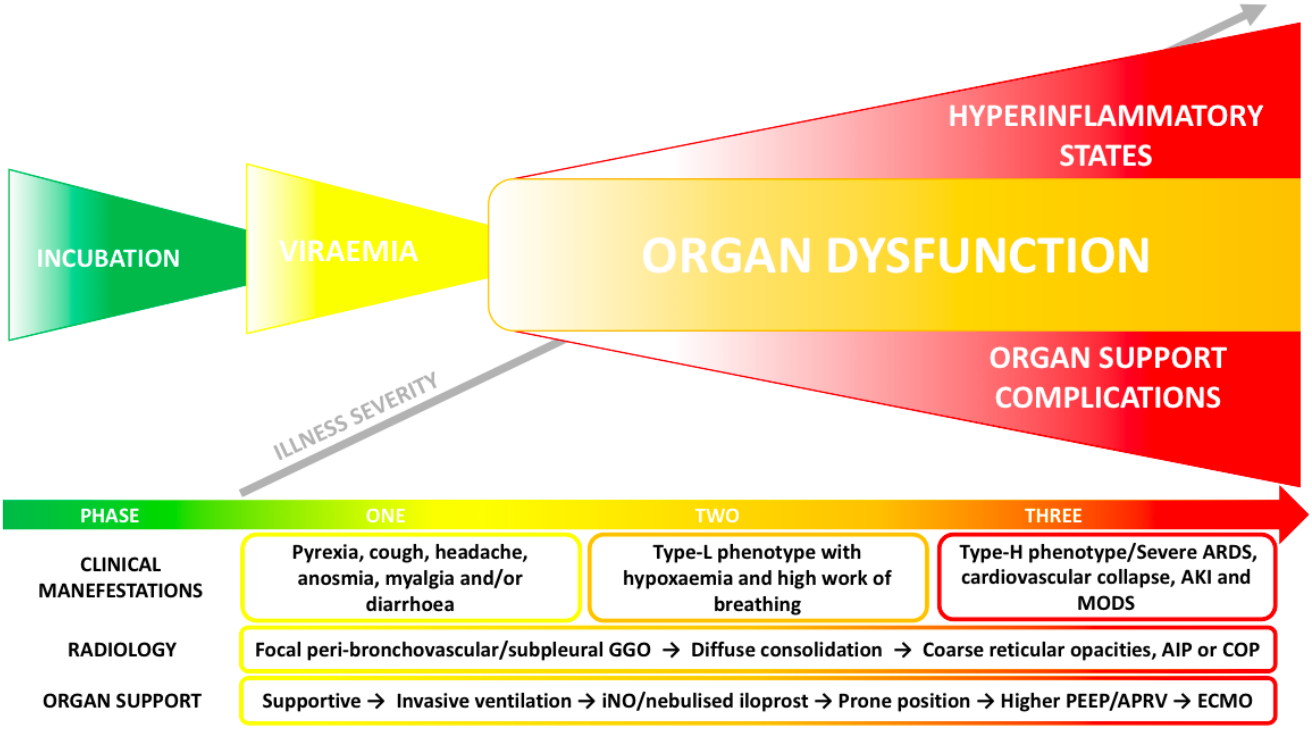


Figure 2. Comparison of two typical Coronavirus Disease 2019 (COVID-19) patients with the Type-L and Type-H phenotypes contrasting chest radiographs, computed tomography, quasi-static pressure-volume loop, gas exchange and pulmonary mechanics (PaO_2/FiO_2, Cstat - static lung compliance, C20/Cstat Ratio of static compliance in the last 20% of inspiration to total compliance, LIP - lower inflection point and R/I ratio - recruitment-to-inflation ratio).

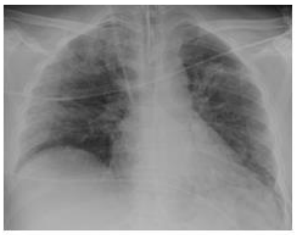
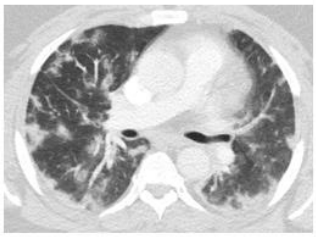
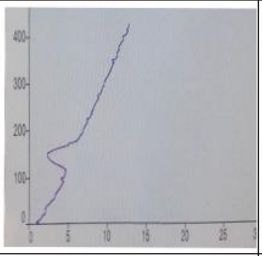
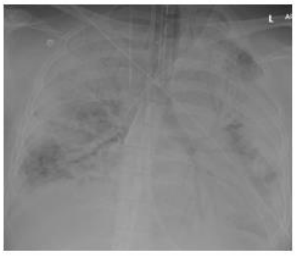
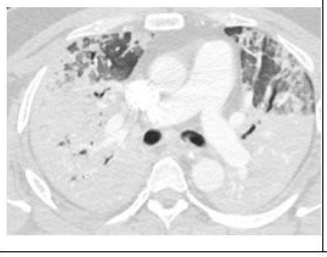
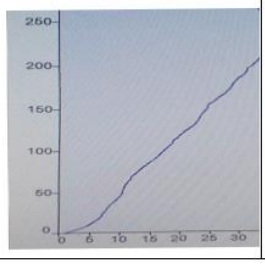
Phenotype	Chest radiograph	Computed Tomography	Low flow PV curve (x-axis cmH_2O, y-axis ml)	Gas exchange and pulmonary mechanics
TYPE-L				• PF ratio = 11.8 kPa • Cstat = 37.9 ml/cmH_2O • C20/Cstat = 1.06 • LIP = 2 cmH_2O • R/I ratio = 0.02
TYPE-H				• PF ratio = 8.6 kPa • Cstat = 10.4 ml/cmH_2O • C20/Cstat = 0.82 • LIP = 11 cmH_2O • R/I ratio = 0.72

Figure 3. Admission computed tomography (CT) of three Coronavirus Disease 2019 (COVID-19) patients requiring retrieval to the severe respiratory failure unit at Guy's and St. Thomas' NHS Foundation Trust following extracorporeal membrane oxygenation implantation at the referring centre. **A-** 44-year-old male referred after five days of invasive ventilation. CT shows classical ARDS pattern with diffuse ground glass opacities and dorsal consolidation/atelectasis. Required standard intensive care therapies and no immunomodulation. **B-** 52-year-old male with CT demonstrating more extensive parenchymal distortion/fibrosis and traction bronchiectasis typical of acute interstitial pneumonitis (AIP) or Hamman-Rich syndrome after seven days of invasive ventilation and preceding non-invasive ventilation. Pulsed methylprednisolone (500mg for three days) utilised followed by tapering course. **C-** 32-year-old male admitted with severe respiratory failure, vasoplegia (Norepinephrine 1.7mcg/kg/min) and normal biventricular function related to cytokine release syndrome (CRS). Ferritin of 12,000ng/ml and CT appearances of cryptogenic organising pneumonia (COP) appearance with occasional reverse halos noted (Atoll sign). Immunomodulation in the form of intravenous immunoglobulin, methylprednisolone 1mg/kg twice daily and anakinra.

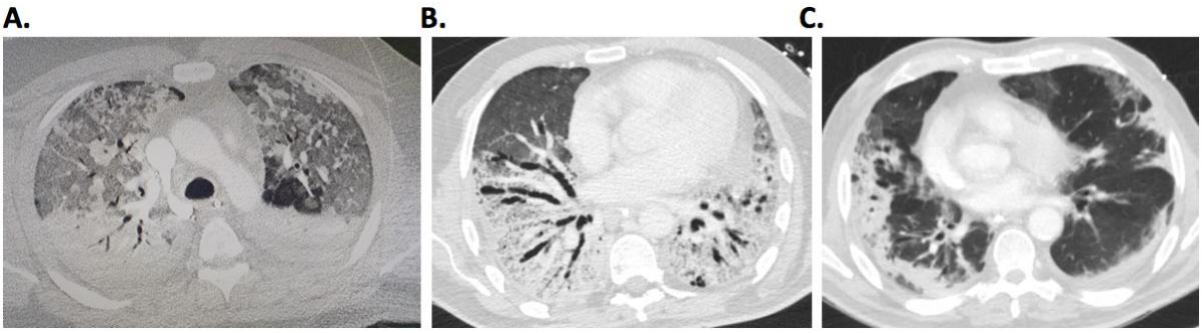


Figure 4. Guy's and St. Thomas' NHS Foundation Trust suggested management of respiratory failure in Coronavirus Disease 2019 (COVID-19). RR - Respiratory rate, NRBM - Non-Rebreather Mask, CRT - Critical Care Response Team, MERIT - Mobile Emergency Response Intubation Team, HCID - High Consequence Infectious Disease, HDU - High Dependency Unit, ED - Emergency Department, MV - Minute ventilation, PEEP - Positive End Expiratory Pressure, Vt - Tidal Volume, PBW - Predicted Body Weight, RM - Recruitment Manoeuvre and ECMO - Extracorporeal Membrane Oxygenation.

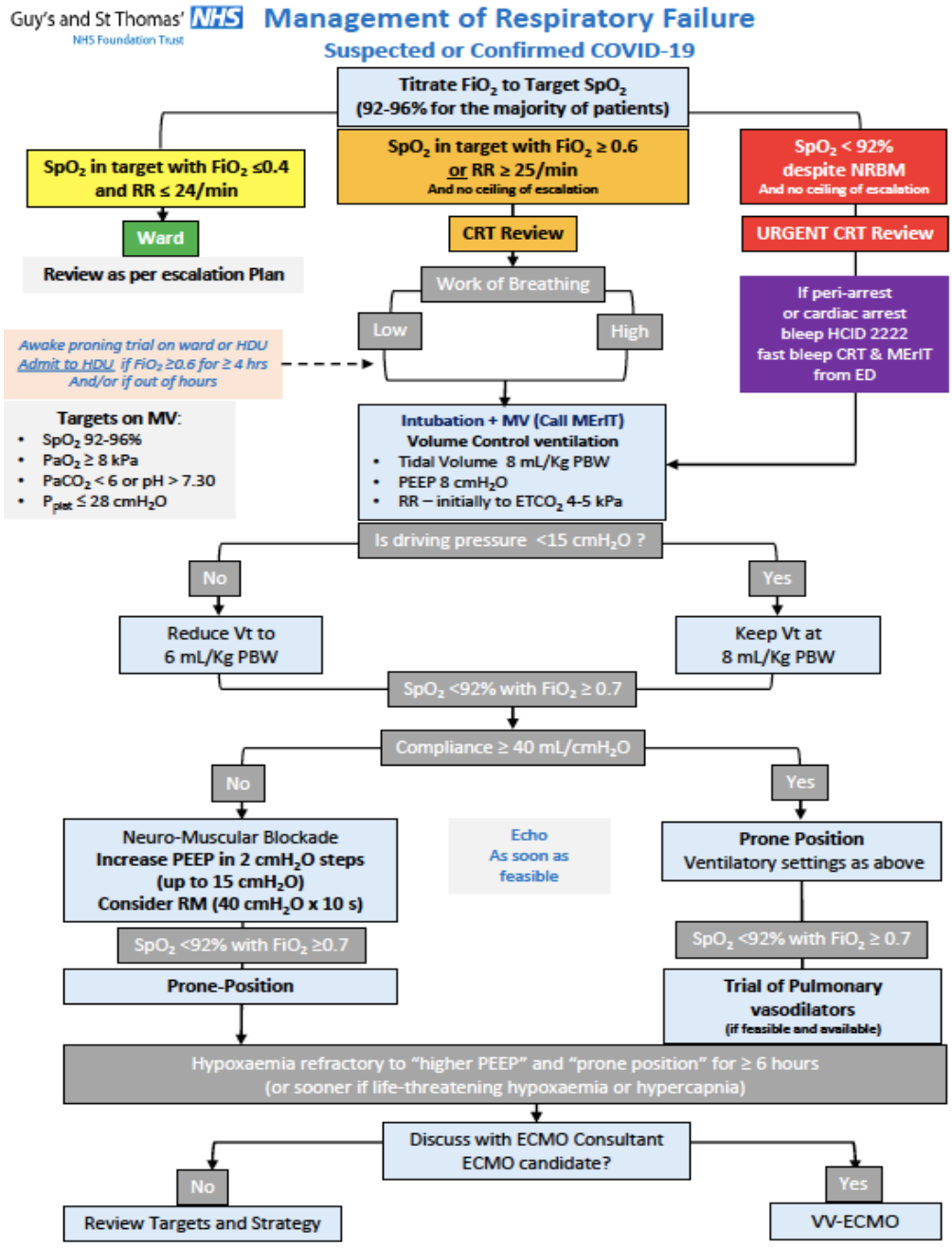


Figure 5. Anticoagulation strategy in Coronavirus Disease 2019 (COVID-19). CTPA - Computed Tomography Pulmonary Angiogram, UFH - Unfractionated Heparin, DECT - Dual Energy Computed Tomography, NT-proBNP - N terminal pro Brain Natriuretic Peptide, LMWH – Low Molecular Weight Heparin, VTE - Venous Thromboembolism, eGFR - Estimated Glomerular Filtration Rate.