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Coronavirus Disease 2019 (COVID-19): A look at the Pandemic from a UK Intensive Care Unit Epicenter

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ABSTRACT

Since the World Health Organisation (WHO) [1] reported the first case of viral pneumonias of unknown cause in Wuhan, the capital city of Hubei, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has rapidly spread. As of 13th March 2020, coronavirus disease 2019 COVID-19 was declared a global pandemic. It has caused worldwide disruption with many countries enforcing emergency lockdown. COVID-19 has spread rapidly over the globe and there are over 4.1 million confirmed cases and 280,000 deaths as of 11th May 2020 according to The Centre for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [2].

In the UK there has been variable compliance with the social distancing measures set out by Public Health England (PHE) [3]. We have now surpassed the containment phase: A strategy to prevent COVID-19 for as long as possible and are now firmly planted in the delay phase. As well as significant pressure on the NHS there has been disruption to businesses, housing, social care and education with the Deputy Chief Medical officer warning it could be up to 6 months before life in the UK return to normal.

The disruption to the NHS has caused a huge shift in organisation and allocation of staff and resources. Many doctors from other specialties have been re-deployed to critical care and hospitals are being re-structured to accommodate the large number of patients requiring both non-invasive ventilation (NIV) and invasive mechanical ventilation. The Nightingale Hospital has been opened in efforts to help ease the pressure of the large cohort of COVID-19 in an Intensive Care Unit (ICU). This article explores the most recent COVID-19 literature and our perspective from one of the major COVID-19 Intensive Care Units in the UK.

Keywords: COVID-19, SARS-CoV-2, NIV, CPAP, ARDS, Prone, HLH, Lymphopenia, Ferritin, LDH, CRP, CT, X-ray, Ultrasound, ACE-2, IL-6, NHS, PEEP, AKI

INTRODUCTION

SARS-CoV-2 belongs to a family of single stranded RNA viruses. There are four genera of coronaviruses however two are capable of infecting humans [4], SARS-CoV-2 is a betacoronavirus. In late December 2019, clusters of patients presented with pneumonia of unknown cause in Wuhan and were investigated by the Chinese Centre of Disease Control and Prevention. A novel coronavirus later named SARS-CoV-2 was linked to a seafood wholesale market in Wuhan, Hubei Province, China (European Centre for Disease Prevention and Control, 2020) [5].

There have also been previous Coronavirus outbreaks in the past namely that of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002-2003 and that of Middle East respiratory syndrome-related coronavirus (MERS-CoV) which began in 2012. The likely animal reservoir of Coronaviruses is bats. SARS-CoV infected more than 8000 people and killed 774 [6]. MERS-CoV likely spilled over from bats to dromedary camels at least 30 years ago [7].

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SARS-CoV-2 infection in humans

First cases of COVID-19 are thought to be linked to direct exposure from animals in Huanan Seafood Wholesale Market of Wuhan, the most frequent forms of transmission are human to human [8] airborne and fomite to face. Most coronaviruses infect the ciliated epithelium of the respiratory tract through the aminopeptidase N receptor or a sialic acid receptor. Once the virus has gained access into host cells via its spike glycoprotein, it is uncoated and ribonucleic acid (RNA) then attaches to host ribosomes for translation. Viral proteins and RNA are synthesized and transported to the Golgi apparatus where they are extruded from the host cell by exocytosis. Viral replication triggers an immune response causing the release of cytokines and chemokines and the symptoms of clinical disease [4].

SARS-CoV-2 is different to SARS-CoV, it uses the angiotensin converting enzyme 2 (ACE2) receptors for cell entry [9]. Type II pneumocytes of the lung are rich in ACE2 receptors, which is why the lung is the most susceptible target organ [10], however ACE2 receptors can also be found in the intestines, heart, kidney and endothelium. There is a theoretically associated risk of a higher susceptibility to infection due to up-regulation of ACE2 by drugs such as angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARB's). This notion was rapidly picked up and amplified in the media but currently there is no robust data proving a causal relationship between ACE2 activity and SARS-CoV-2 associated mortality. ACE-I and ARB therapy should be maintained or initiated in patients with heart failure, hypertension, or myocardial infarction according to current guidelines irrespective of SARS-CoV-2 [11].

Symptomatology

The most common symptoms of COVID-19 are recent onset of a new continuous cough and/or high temperature. The inpatient definition includes anyone requiring admission to hospital having either clinical and/or radiological evidence of pneumonia **(Figure 1)**, acute respiratory distress (ARDS) syndrome or an influenza like illness (fever ≥37.8°C and at least one of the following respiratory symptoms, which must be of acute onset: persistent cough (with or without sputum), hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing, sneezing) [12].

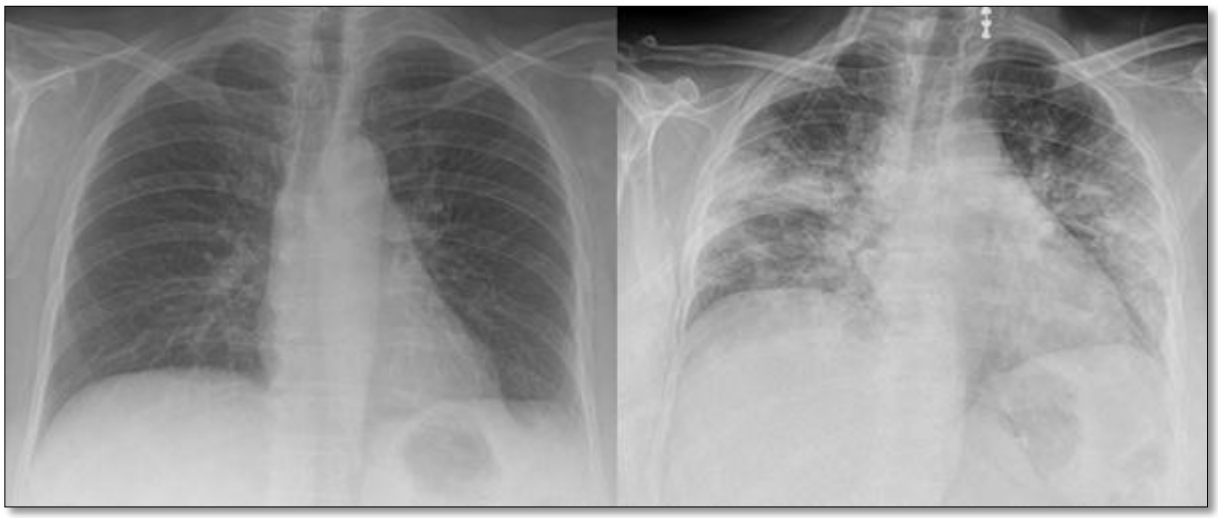

Figure 1. The chest x-ray on the left shows clear lung fields, with long-standing blunting of the left costophrenic angle. The chest x-ray on the right was done a week later due to worsening shortness of breath. There is extensive bilateral and lower zone air space opacification in keeping with COVID-19. The diagnosis was confirmed with a RT-PCR for COVID-19.

The estimated median incubation period of COVID-19 was 5.1 days (CI, 4.5 to 5.8 days) and nearly all infected persons will have symptoms within 12 days of infection [13]. COVID-19 can cause a spectrum of disease varying from being asymptomatic, having constitutional symptoms or severe, requiring mechanical ventilation. Common clinical features are indistinguishable from other respiratory infection. In a study of 1994 patients, the main clinical symptoms of COVID-19 patients were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), dyspnoea (21.9%). Minor symptoms include headache or dizziness: (12.1%) diarrhoea (4.8%), nausea, and vomiting (3.9%) [14].

When COVID-19 is suspected, the differential diagnosis is to be excluded. For example, those infections caused by bacteria, atypical organisms, fungi and other viral pathogens, as well as non-infectious causes, for example a pulmonary embolism. This should be elucidated by the history and clinical examination of the patient as well as analysis of

laboratory results and imaging. Elderly patients and patients with comorbidities are at increased risk. A meta-analysis by [15] of 46,248 infected patients showed the most prevalent risks factor were hypertension (17±7, 95% CI 14-22%) and diabetes (8±6, 95% CI 6-11%), followed by cardiovascular diseases (5±4, 95% CI 4-7%) and respiratory system disease (2±0, 95% CI 1-3%).

Laboratory features

Initial testing for suspected cases is with a nasopharyngeal swab (National Centre for Immunizations and Respiratory Disease, 2020) [16] and it is recommended to obtain samples from the lower respiratory tract where possible. The basis of testing is nucleic acid amplification tests (NAAT), real time-polymerase chain reaction (RT-PCR). In a series of 51 patients with chest CT and RT-PCR assay performed within 3 days, the sensitivity of CT for COVID-19 infection was 98% compared to RT-PCR sensitivity of 71% (p<.001) [17]. Reasons for lowered sensitivity of RT-PCR may include immature NAAT technology, low viral load and improper clinical sampling.

Lymphocytopenia is a common feature of COVID-19. In a study by of 1099 patients with laboratory-confirmed COVID-19, 83.2% of patients had lymphocytopenia and thrombocytopenia was less common (36.2%) [18]. D-dimer, ferritin, interlukin-6 (IL-6), lactate dehydrogenase (LDH) and high-sensitivity cardiac troponin I were significantly more elevated in non-survivors than survivors [19] these markers may have a role in predicting patients who will have severe disease and a significant predictor of mortality.

CRP levels of all patients were increased in COVID-19, but in the severe group they are higher than in the non-severe group (P < 0.01) [20]. Predictors of fatality from a recent retrospective, multicentre study by Ruan [21] of 150 confirmed COVID-19 cases in Wuhan, included elevated ferritin (mean 1297·6 ng/ml in non-survivor's vs 614·0 ng/ml in survivors; p:<0.001) and elevated IL-6 (p<0.0001) showing mortality may be driven by a hyperinflammatory process as seen in hemophagocytic lymphohistiocytosis (HLH). Tocilizumab is licenced for cytokine release syndrome. It is a monoclonal antibody which binds soluble IL-6, thus hindering its pro-inflammatory effect and has been approved for use in a clinical trial in China for patients with severe pneumonia and elevated IL-6 levels.

AKI can accompany multi-organ failure. It has been hypothesized that the pathophysiology is linked to SARS-CoV-2 binding to the ACE2 in the kidneys and causing damage. In-hospital death in the patients with elevated baseline serum creatinine was 33.7%, which was significantly higher than in those with normal baseline serum creatinine 13.2% [22]. This shows that AKI may be more prevalent in patients who already have underlying renal impairment and predict increased mortality.

Radiographic features

Computed tomography (CT) would be the preferred imaging modality **(Figure 2)**. The first report of patients with COVID-19 described bilateral lung changes on initial chest CT in 40 of 41 patients, with a consolidative pattern seen in ICU patients and a predominantly ground-glass pattern in patients who were not in the ICU [22]. The appearances on chest x-ray for COVID-19 are opacities **(Figure 3)** which are bilateral and predominantly peripheral and lower zone. Chest x-rays, unlike CT, do not require the transfer of a potentially hypoxemic and hemodynamically unstable patient and limits exposure of SARS-CoV-2 to others, images can also be generated and viewed rapidly.

Ultrasonography (US) is of value in COVID-19, it is non-invasive, low cost and uses non-ionising radiation. Furthermore, it allows rapid de-sterilization decreasing infection risk compared CT. However, a drawback is the skill of the operator to obtain images and interpret them. Findings on US vary in accordance with the stage of disease; there can be varying degrees in interstitial or alveolar consolidation which can be correlated to disease severity. Characteristic findings include thickened pleura, B-lines and varying patterns of consolidation. A-line are found in convalesce and pleural effusions are uncommon [23].

Management

Any clinician seeing suspected or confirmed COVID-19 patients must ensure they adequately protect themselves with personal protective equipment (PPE) as per national guidelines. PHE's criteria for admission has been described earlier however clinical judgment is also vital, with early review of deteriorating patients by critical care physicians to guide appropriate management.

Concurrent bacterial pneumonia is treated empirically and also covers for atypical organisms and influenza until investigative tests are reported. Management is largely supportive. Presentation with severe respiratory failure necessitates admission to ICU for mechanical ventilation. Multiple organ dysfunction syndrome (MODS) and multi-organ failure (MOF) may require other organ support such as renal replacement therapy (RRT) and cardiovascular support with inotropes and vasopressors.

Current management guidelines for COVID-19 have been published by the European Society of Intensive Care Medicine [24]. In adults with peripheral oxygen saturation <90% it is recommended to start supplemental oxygen, for patients with acute hypoxemic respiratory failure on oxygen, saturations are recommended to be maintained no higher than 96%.

Techniques such as non-invasive ventilation (NIV) are being used variably throughout the world. NIV in particular continuous positive airway pressure (CPAP) recruits more alveoli thus increasing surface area for ventilation.

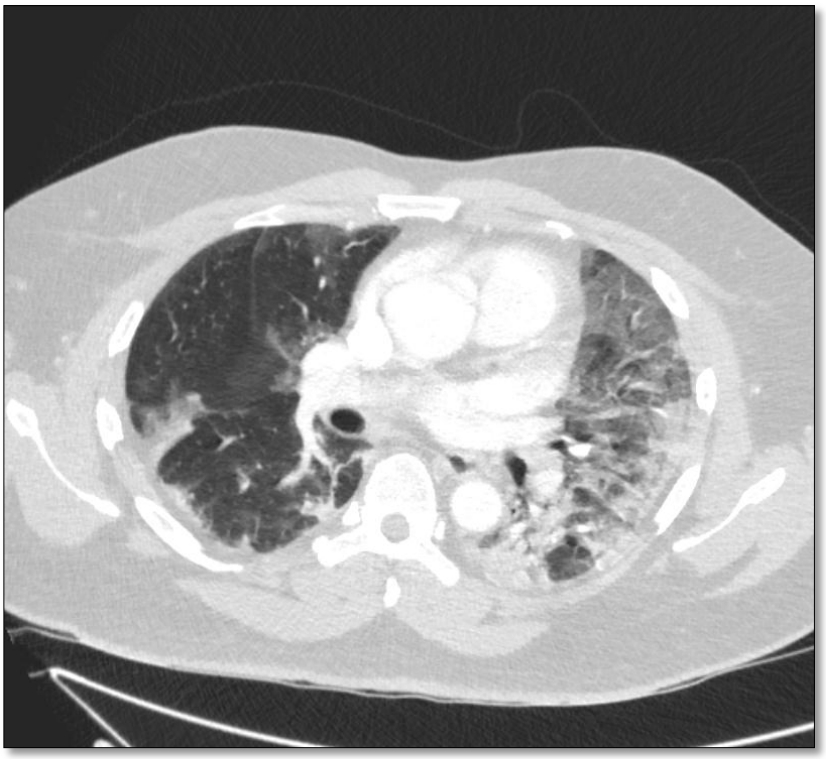

Figure 2. CTPA (CT-Pulmonary Angiogram) shows dense left sided consolidation with crazy paving sign and sub-pleural ground glass opacification.

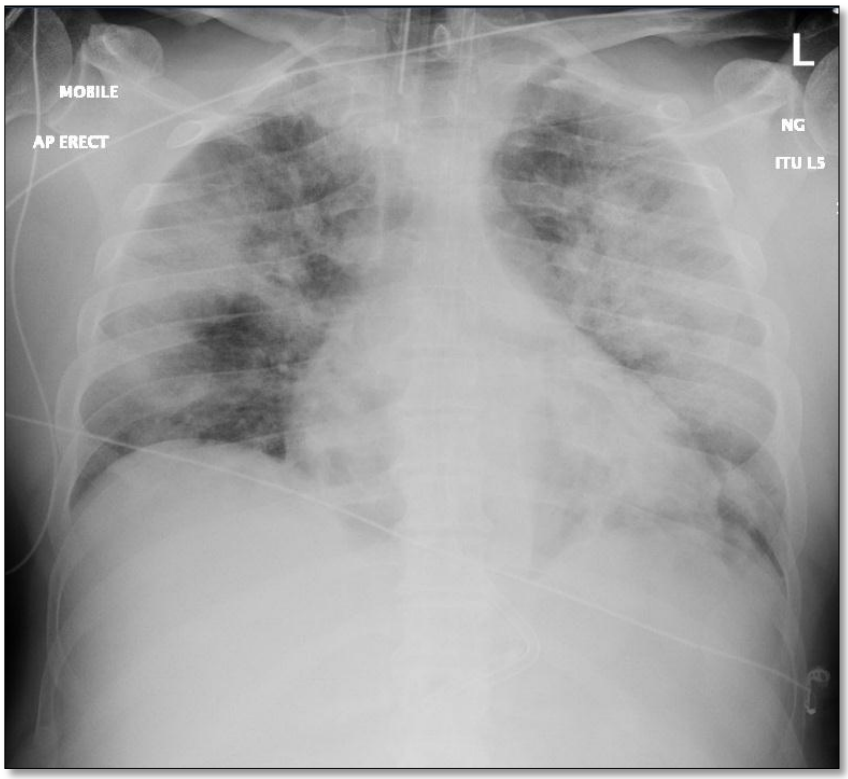

Figure 3. This chest x-ray shows significant bilateral patchy airspace opacities within both lower, mid and upper zones with a more peripheral preponderance on the right. This was consistent with a severe COVID-19 infection.

According to WHO, recent publications suggest that NIV systems with good interface fitting do not create widespread dispersion of exhaled air and therefore should be associated with low risk of airborne transmission. Helmet interfaces have been used in Italy, but this has not been supported by evidence. There is also a role for proning patients on NIV to delay or possibly avoid intubation.

In patients who are mechanically ventilated lung protective strategies such as using low tidal volumes are recommended (4-8 mL/kg of predicted body weight) and plateau pressures (Pplat) of <30 cm H_2O to decrease ventilator-induced acute lung injury (VILI). There is a weak recommendation for using higher positive-end expiratory pressure (PEEP) to sustain alveolar recruitment over lower PEEP's. There is no current definition of the optimal PEEP, however this is likely to vary based on the lung compliance, stage of disease and patient factors.

Neuromuscular blockers can be used when proning or when there is ventilator asynchrony or high inspiratory pressures in ARDS. This may be given as intermittent boluses or a continuous infusion. Patients with COVID-19 tend to present febrile and tachypnoeic and are likely be hypovolemic. Hypovolemia may cause AKI, oliguria, poor pulmonary perfusion and increased dead space. There are no RCT's directly comparing a liberal and conservative fluid strategies however hypovolemia should be avoided and euvolemia should try to be achieved.

Two phenotypes have been described known as L (low) and H (high) in COVID-19, which are useful in guiding management. The L phenotype describes lungs with low elastance, low ventilation to perfusion (V/Q) mismatch, low lung weight and low lung recruitability. On the other hand, the H phenotype describes lungs with high elastance, higher recruitability, more right to left shunting and increased recruitability [25]. Patients with the L phenotype have consolidated alveoli with high compliance, they are less likely to benefit from recruitment strategies and increasing PEEP can compress the pulmonary vasculature exacerbating VQ mismatch. The H phenotype is similar to pulmonary oedema in ARDS and responds to higher PEEP's and proning. Distinguishing these phenotypes may be useful in guiding therapeutic approach and likely are part of continuum where there is progression from L to H.

CONCLUSION

The RECOVERY trial conducted by Oxford University over the UK is currently evaluating HIV drugs Lopinavir/Ritonavir, Dexamethasone, Azithromycin and Hydroxychloroquine in the treatment of COVID-19. Anti-viral Remdesivir is also being investigated in clinical trials and has gained emergency approval for use in the USA by the Food and Drugs Administration (FDA). A recent paper from France by Gautret [26] has shown that hydroxychloroquine (HCQ) and azithromycin were effective in clearing viral nasopharyngeal carriage of SARS-CoV-2 however it was non-randomised, the outcome is based on viral load not clinical outcomes, the sample size is small and there is limited long-term outcome follow-up. At present there is not enough evidence to support pharmacotherapy in COVID-19, larger robust RCT's are still needed elucidate management of patients with COVID-19.

The crisis of COVID-19 is relentlessly taking lives. According to data from the UK by PHE as of the 11th May 2020 there have been over 200,000 laboratory confirmed cases and over 30,000 deaths, with London carrying the greatest case burden. Actual case numbers are much higher as we are not testing all of those with symptoms and all of those in care homes. There was a steep upward trend and we have experienced a surge of patients requiring ICU beds. As an effort to ease the pressure on NHS hospitals the procurement of the NHS Nightingale Hospital at the ExCel centre in London is expected to be able to hold 4000 patients with staff being deployed from different trusts and the military.

At present practice is changing rapidly based on new evidence and experience among physicians looking after COVID-19 patients. Although ICUs are instrumental in supporting organs of patients affected by COVID-19 the most important principal to retard transmission and keep cases down is social distancing. It is absolutely imperative for the whole population to strictly adhere to social distancing guidance in order reduce transmission or SARS-CoV-2 and flatten the COVID-19 curve.

Conflict of Interests

No coniflcts of interest.

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