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Evidence Based Management Guideline for the COVID-19 Pandemic - Review article

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Evidence-Based Management Guideline for the COVID-19 Pandemic

ABSTRACT:

COVID-19 has now been declared a pandemic. To date, COVID-19 has affected over 944,181 people worldwide, resulting in over 47,312 reported deaths. Numerous preventative strategies and non-pharmaceutical interventions have been employed to mitigate the spread of disease including careful infection control, the isolation of patients, and social distancing. Management is predominantly focused on the provision of supportive care, with oxygen therapy representing the major treatment intervention. Medical therapy involving corticosteroids and antivirals have also been encouraged as part of critical management schemes. However, there is at present no specific antiviral recommended for the treatment of COVID-19, and no vaccine is currently available. Despite the strategic implementation of these measures, the number of new reported cases continues to rise at a profoundly alarming rate. As new findings emerge, there is an urgent need for up-to-date management guidelines. In response to this call, we review what is currently known regarding the management of COVID-19, and offer an evidence-based review of current practice.

KEYWORDS: SARS-CoV-2, COVID-19, pandemic, management guidelines

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially named novel coronavirus or 2019-nCoV, is a single-stranded RNA virus which forms one of the seven *coronaviridae* - 229E, OC43, NL63, HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV))(1) - now known to infect humans. It is the virus responsible for causing coronavirus disease 2019 (COVID-19), a type of lower respiratory tract infection with the potential to cause severe and possibly fatal atypical novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) in humans (2–4).

1.1. Prevalence

Now labelled a pandemic (5), COVID-19 has affected over 944,181 people worldwide, with the majority of cases (n=215,608) seen in the USA alone, followed by Italy (n=110,820) and in third place Spain (n=104,118). There have been over 47,312 reported deaths and at least 194,647 recovered cases (6,7). Sohrabi et al. highlighted the extent of the outbreak with the World Health Organization (WHO) declaring the COVID-19 outbreak as a global emergency on 30th January 2020. (2)

1.2. Mode of evolution and transmission

To facilitate the characterisation of SARS-CoV-2, comparisons have been made with the better known structure of SARS-CoV. Both viruses share an amino acid sequence similarly of 76.5% (8) and utilise angiotensin-converting enzyme 2 (ACE2) receptors as a mode of entry into healthy cells. Variations between the receptor-binding domain of the two brought about by mutations (9), genetic recombination (10), and natural selection (9) enable SARS-CoV-2 to bind to the receptor more effectively (8). Furthermore, evidence of genetic recombination as a mechanism of viral evolution has sparked concerns regarding the misdiagnosis of infections by SARS-CoV-2, inaccurate tracking of transmission rates, adaptation of the virus to human immunity, as well as increasing severity of the infection with time (10).

A study looking into the first 425 confirmed cases of NCIP has provided evidence to support that the main method of viral transmission is human-to-human (3). To date, a confirmed case of NCIP is defined as at least one of the following obtained from lower respiratory tract to include pharyngeal swabs, sputum samples, and alveolar lavage or serological samples (1,11):

- Isolation of SARS-CoV-2
- ≥2 positive real time RT-PCR assays of SARS-CoV-2
- Genetic sequence matching of SARS-CoV-2

Recovery and clearance of the virus is thought to be achieved when ≥2 negative oral swabs are confirmed in an infected individual. Emerging evidence, however, has speculated the complete clearance of the virus in such cases as anal swabs and blood cultures may remain positive despite having negative oral swabs (12) and supports that the main modes of spread of the virus include respiratory droplets, bodily fluids, fecal-oral, direct contact, and transmission through environmental surfaces (13). Current evidence supports that there is no vertical transmission of the virus (14).

Alarmingly, despite extensive efforts by governments to contain the virus, a recent Chinese study has demonstrated that although 80.9% of sufferers had subclinical or mild symptoms of the disease they still possessed the potential to spread the virus further (15). Interestingly, they also possessed the same viral load to patients who

exhibited symptoms of the disease (16). As it stands, it has been estimated that an infected individual is likely to spread the disease to an average of 2.2 people (4).

1.3. Course of disease

Emerging evidence has been collated in an attempt to delineate the course of the disease. The World Health Organisation (WHO) estimates that the incubation time from infection to presentation of symptoms is 5.2 days, with a range of 1-14 days (17). Furthermore, the mean time from presentation of symptoms to seeking medical advice is 5.8 days, and to hospital admission is 12.5 days (4). The stages of the disease from onset of symptoms has been classified based on non-contrast enhanced chest computed tomography (CT) findings and can be divided into early (0-4 days), progressive (5-8 days), peak (9-13 days), and absorption stage (≥14 days) (18). Early stage disease consisted of subpleural ground glass opacities (GGO) located in the lower lung lobes. The progressive stage demonstrated bilateral distribution of the infective process and diffuse GGO. Presence of dense consolidation, crazy-paving pattern and residual parenchymal bands indicates transition into the peak stage. Finally, the absorption stage which may last more than 26 days, appears to demonstrate a better controlled disease process on CT, gradual resolution, and signs of recovery (18).

2. Presentation:

2.1. Signs and Symptoms

Data from a report of 72,314 cases published by the Chinese Center for Disease Control and Prevention has revealed that the severity of clinical symptoms can vary between individuals (19). 81% of cases were described as mild (i.e. non-pneumonia and mild pneumonia). 14% of cases were severe (i.e. dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (i.e. respiratory failure, septic shock, and/or multiple organ dysfunction or failure) (20) (**Figure 1**). Other studies indicate that patients with multiple comorbidities are prone to severe infection and may also present with acute kidney injury (AKI) and features of ARDS.

Figure 1: Percentage of individuals from a Chinese study presenting with mild, severe, or critical symptoms of COVID-19 (20).

There are reports of both adult and paediatric patients being infected with COVID-19. Data pooled from three large case series indicate the following results (21,22); The majority of adult patients present with fever (92.8%; n=258), cough (69.8%; n=194), dyspnoea (34.5%; n=96), myalgia (27.7%; n=77), headache (7.2%; n=20), diarrhoea (6.1%; n=17), rhinorrhoea (4.0%), a sore throat (5.1%), and pharyngalgia (17.4%). In the paediatric population, symptoms may include fever, fatigue, cough, nasal congestion, runny nose, expectoration, diarrhoea, and headache. As the disease progresses, signs of dyspnoea, cyanosis, in addition to systemic toxic symptoms, including malaise or restlessness, poor feeding, bad appetite and reduced activity may also present. In the most severe situations, these younger patients may progress into respiratory failure unresponsive to conventional oxygen therapy, septic shock, metabolic acidosis, irreversible bleeding, and coagulation dysfunction (23).

2.2. Diagnosis and Differential Diagnosis

Clinical symptoms must be assessed to aid in the diagnosis of COVID-19. Both the WHO and United States Centers for Disease Control and Prevention (CDC) have issued guidance for key clinical and epidemiological findings suggestive of COVID-19 (24)(25). Extensive laboratory tests should be requested to confirm diagnosis of COVID-19. RT-PCR should be performed in isolated samples of throat swabs, sputum, stool, and blood samples.

Key laboratory results on admission include leucocytes below or above the normal range; neutrophils above the normal range; lymphocytes, haemoglobin and platelets below the normal range. Key liver findings may include elevated alanine aminotransferase, aspartate aminotransferase, C-reactive protein, creatine kinase, lactate dehydrogenase, blood urea nitrogen, and serum creatinine levels. Regarding the infection index, procalcitonin levels may be above the normal range (26).

Radiological findings may also aid the diagnosis of pneumonia in virally infected patients. Bilateral and multi lobe lung involvement were common in over 75% and 71% of adult patients, respectively (21,22). In paediatric patients, the following criteria for rapid respiratory rate should be followed for diagnosis of COVID-19 associated pneumonia: ≥60 times/min for less than 2 months old;≥50 times/min for 2–12 months

old, ≥40 times/min for 1–5 years old, ≥30 times/min for >5 years old (after ruling out the effects of fever and crying) (23).

Differential diagnosis can include other viral respiratory infections caused by SARS virus, influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus and metapneumovirus (23). These patients present with similar clinical presentations, except for normal or decreased leukocyte count in some patients. Patients may also present with pneumonia due to bacterial causes, which may be accompanied by high fever and moist rale cough (23). Mycoplasmal pneumonia is another common type of false presentation. Chest X-ray images for such patients may indicate reticular shadows and small patchy or large consolidations. Mycoplasma-specific IgM are helpful for this differential diagnosis. Epidemiological exposure and blood or sputum culture will be helpful for ensuring the correct diagnosis of COVID-19 (23).

2.3. High Risk Groups

Current reports suggest that all demographics of the global population could be susceptible to infection of COVID-19, however there are some groups that are at higher risk of severe disease (22,26,27). According to the CDC, older adults - further classified as over 65 years of age - are more at risk of severe disease than younger people. Furthermore, patients with serious chronic underlying medical conditions, namely cardiovascular disease, diabetes, cancer (especially of the lung), chronic obstructive pulmonary disease, and hypertension are at an increased risk of severe complications (28,29). There is currently no evidence to suggest that either sex is more at risk of severe disease, nor that children are more susceptible to infection (30). In one study of patients with confirmed COVID-19 infection, 85.9% (n=67) stabilised whereas 14.1% (n=11) continued to deteriorate despite treatment. Of the 14.1% who deteriorated, when compared to the stabilised group (median age 37; range=32-41), the patients were significantly older (median age of 66; range=51-70), had a history of smoking, and presented with a higher maximum body temperature on admission (31).

Occupational risks have also been identified by various authorities. During the preliminary stages of the COVID-19 outbreak, employees of seafood and wet animal wholesale markets in Wuhan were most at risk of contracting the virus in addition to any customers who had visited these markets (32). This was closely followed by the subsequent epidemic which posed a high risk to healthcare workers who regularly came into contact with patients with suspected COVID-19. As a result, healthcare workers with pre-existing risks such as an increased age or chronic respiratory disease are

advised to ask colleagues who are not in high risk groups to care for patients with potential COVID-19 where possible (29).

2.4. Complications

Various mild and severe clinical syndromes have been associated with the SARS-CoV-2 infection. Mild uncomplicated illnesses include non-specific symptoms including fever, cough, sore throat, nasal congestion, headache, and muscle pain. Elderly and immunosuppressed individuals may present with atypical findings. Mild and severe pneumonia have also been associated with COVID-19. In adults, the latter is characterised by fever or suspected respiratory infection plus one of either respiratory rate >30 breaths/min, severe respiratory distress, or SpO2 <90% on room air. In children, severe pneumonia is indicated by cough or difficulty in breathing plus at least one of either central cyanosis or SpO2 <90%, severe respiratory distress (e.g. grunting, very severe chest indrawing), signs of pneumonia with a general danger sign (e.g. inability to breastfeed or drink, unconsciousness, or convulsions). ARDS presents with new or worsening respiratory symptoms within one week of known clinical insult, and chest imaging reveals bilateral lung opacities. Sepsis and septic shock are further complications of COVID-19. Notably, long-term complications amongst SARS-CoV-2 survivors are not yet available. The mortality rate for cases globally remains between 1-2%.

3. Management:

3.1. Prevention

Although spread via an airborne route, air disinfection of communities is currently not known to be effective in halting further viral transmission and spread. Human-to-human transmission should be limited in order to prevent transmission amplification events. The use of personal protective equipment should be carefully considered since resources are currently in short supply. Surgical masks in particular are utilised widely within the general population, but have not been clinically proven to reduce or prevent the acquisition of COVID-19. Within the hospital setting, however, high-filtration masks including N95, goggles, and gowns should be worn by healthcare professionals working in direct contact (within 1-2 metres) of infected patients (33). If an infected individual has been identified, rapid isolation and the administration of optimised care should be provided. Suspected patients should also be given a medical mask and placed in an isolation room if available. Wherever possible, the use of adequately ventilated single rooms when performing aerosol-generating procedures should be employed. All patients should be instructed to cover their nose and mouth during coughing or sneezing with tissue. Hand hygiene after contact with respiratory secretions should be enforced. If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs, and thermometers) for suspected cases, and avoid contaminating environmental surfaces (e.g. door handles).

In mid-January of 2020, Chinese authorities implemented an array of unprecedented containment strategies, including restriction of human movement, Hubei province lockdown, and the suspension of flights and trains. These time-critical measures have contributed grossly to the decline in reported cases, and the WHO have since congratulated China on a “unique and unprecedented public health response that reversed escalating cases”. (34) Moreover, between 16th and 30th January 2020 the number of people infected by an individual host dropped to an estimated 1.05, (35) and data from other cities having implemented lockdown measures reported approximately 37% fewer cases in comparison to cities without. (36) Notably, the implementation of control measures a week earlier could have prevented approximately 67% of all Chinese cases according to a model simulation from the University of Southampton, UK. (37)

Non-pharmaceutical interventions (NPIs) have been addressed in an attempt to suppress and/or mitigate the disease, with suppression defined as a reduction in the Reproduction Number (R_0) - the average number of individuals one infected person can

infect - to less than 1, and mitigation defined as a reduction of the effects of the pandemic on health, ultimately reducing mortality and morbidity.

NPIs comprise of strict social isolation and distancing measures and include:

1. Case isolation at home:
   Symptomatic cases to remain at home for 7 days which is expected to reduce the number of contacts outside the household by 75% during this timeframe. (38) All forms of social contact must be avoided by symptomatic individuals. (39)

2. Voluntary home quarantine:
   If a symptomatic case is identified in the household, the entire household must remain at home for 14 days. This is thought to decrease contacts outside of the household by 75% and household contact to increase two-fold. (38)

3. Social distancing for those above 70 years old:
   Individuals over 70 years of age are to practice **social distancing** i.e. must maintain a 2 meter distance from other individuals when possible and to avoid gatherings or congregations. (40) This measure is targeted to reduce contacts by 50% in the workplace an decrease other contacts by 75%, while inadvertently increasing household contacts by 25%. (38)

4. Social distancing for the entire population:
   All individuals are to practice social distancing as described above, this way reducing all household contacts by 75% and workplace contacts by 25%. School contact rates remain the same and household contacts increase by 25%. (38) Non-essential use of public transport must be avoided and, if possible, arrangements to work from home should be made. (39) Individuals should use remote technology to keep in touch with friends and family, as all large and small gatherings must be avoided. Telephone and online services should be used to contact healthcare professionals and other essential services. (39)

5. Closure of schools and universities:
   All schools to remain closed and only 25% of universities to remain open, in essence increasing household contact for families of students by 50% and community contacts by 25% during the time of closure. (38)

The overall effects of these measures are illustrated in **Figure 2**.

Figure 2: The power of social distancing. Attribution: Robert A.J. Signer, Ph.D, Assistant Professor of Medicine, University of California San Diego and Gary Warshaw, Art Director @SignerLab @GaryWarshaw.

Additionally, strict handwashing habits and respiratory hygiene must be followed by individuals to curb the spread of the respiratory viruses, including COVID-19. (39)

Ferguson et al. predict that without control measures, the deaths in the UK and US will reach 510,000 and 2.2 million respectively due to the coronavirus alone with 81% of the UK and US populations becoming infected (Reproduction Number (R_0) = 2.4). The number of Intensive Care Unit (ICU) beds required is expected to reach 30 times the available number in both countries. With an aim to reach $R_0 \leq 1$, the study recommends a combination of social distancing and case isolation in combination with household quarantine or school and University closures for a duration of 5 months, with maximum effects felt if all four interventions plus complete lockdown (i.e. individuals prevented from going to work) are implemented. Such measures are predicted to result in a decrease in the number of critical beds required by two-thirds, a figure which equates to 8 times the number of available ICU beds at present. With the above measures, they also estimate that the number of deaths will decrease by one-half - 250,000 and 1.1-1.2 million deaths in the UK and US respectively.

Of note, Ferguson et al. warn that lifting the measures in the absence of a vaccine is likely to lead to a second peak of infection due to the absence of or insufficient herd immunity, with cases reaching the predicted figures in the no-intervention scenario mentioned above. In order to minimise this effect, social distancing policies must be in place until a vaccine is made readily available- a timeframe of at least 18 months. As a response to this predicted, prolonged period of social distancing, the study examined an ‘adaptive triggering’ strategy with ‘on’ and ‘off’ thresholds (**Figure 3**). ‘On’ triggers are to include the implementation of social distancing and closures of schools and Universities. Case isolation and household quarantine are to be implemented throughout the on/off periods. It is proposed that an ‘on’ trigger be set as 100 cases requiring ICU admission per week to keep below the UK’s ICU bed capacity (reached when 200 ICU cases are admitted per week). An ‘off’ trigger to be set as 50 ICU cases per week. (38).

Figure 3: Graph by Ferguson et al. illustrating the ‘adaptive triggering’ strategies in the UK with use of 100 cases admitted to ICU as an ‘on’ trigger and 50 ICU admissions as an ‘off’ trigger. (41)

Public health education must be based on validated scientific evidence in order to adequately inform the public of the current situation as well as to reduce anxiety levels and distress. Misinformation may inadvertently spread panic amongst the general population. As such, epidemiological findings should be reported promptly to ensure accurate assessment and interpretation.

Although there is currently no known effective treatment for COVID-19, reports of the use of oseltamivir, lopinavir/ritonavir, and antibiotics have been reported despite the WHO making no recommendation for the use of antiviral drugs, antibiotics, or glucocorticoids (22). Care should therefore be taken to not administer medication with unknown efficacy to patients of critically-ill status. Consequently, efforts to prevent and control COVID-19 require an evidence-based and likely multifactorial approach. Fundamentally, successful prevention requires an in-depth understanding of the clinical severity of COVID-19, extent of transmission and infection, and the efficacy of treatment options in order to accelerate the development of diagnostics and therapeutic modalities.

3.2. Supportive Management

Supportive management received by a patient is dependent upon the observed severity of disease, feasibility of quarantine, and possible need for hospitalisation.

For asymptomatic neonates and young children with suspected COVID-19 infection, monitoring and supportive care in a quarantined ward are essential. Vital observations including heart rate, respiration rate, SpO2 should be closely monitored. Neonatal feeding should be considered if the mother is COVID-19 positive. For symptomatic neonates, medical management and intervention are necessary (42).

For adults with mild infection - typically characterised by an uncomplicated illness with absence of a severe acute respiratory infection (SARI) - management at home is deemed appropriate and a patient may be isolated in an outpatient setting. Key aspects of delivered care involve monitoring for any clinical deterioration that may require hospitalisation as well as preventing the transmission to other people in the household (43,44).

For patients with severe disease (**Figure 6**), the WHO defines early supportive therapy and monitoring as follows:

Intravenous Fluid Administration

- Use conservative fluid management in patients with SARI with no evidence of shock.
    - Treat carefully with IV fluids as aggressive resuscitation can impact oxygenation where mechanical ventilation availability is limited.

Oxygen Therapy

- Provide supplemental oxygen therapy immediately if patients present with SARI, hypoxaemia or shock.
    - Give oxygen therapy at 5L/min to reach target SpO2 of at least 90% in non-pregnant adults (over 92% in pregnant patients).
    - Children with severe breathing difficulties should have a target SpO2 of over 94%.

- Closely monitor patients with SARI in case of rapid respiratory failure or sepsis and intervene immediately.
    - This is of utmost importance for patients with COVID-19.
    - Patients with increased work of breathing or hypoxemia despite oxygen therapy may be developing hypoxemic respiratory failure seen in ARDS. Clinicians should consider mechanical ventilation at this point. (25)

- Appreciate a patient's comorbidities to enable management to be tailored and prognosis realised. Communicate this early with both the patient and relatives. (25)

Corticosteroids

- Routinely administer corticosteroids in the treatment of viral pneumonia unless in a clinical trial or if steroids are indicated for another condition.
    - Their use in studies on influenza have been found to exacerbate the infection and increase mortality rates (25).

3.3. Management of critical COVID-19

Admission to ICU

With 5% of all COVID-19 cases becoming seriously or critically unwell and 20-30% (45) of hospitalised patients requiring intensive care support, it is imperative that up-to-date guidelines are in place to aid management. Patients with failing standard oxygen

therapy are likely to require advanced oxygen therapy or ventilatory support. (25) With hospital admissions overwhelming healthcare systems worldwide, the National Institute of Health and Care Excellence (NICE) has published an algorithm to ensure appropriate ICU admissions (**Figure 5**). Factors taken into consideration when making such decisions are age over sixty-five, frailty - assessed via the Clinical Frailty Scale (CFS) - and comorbidities. Special considerations should be made in patients with long-term disabilities, learning disabilities and autism. In such cases an individual assessment of frailty must be performed. (46)

Figure 5: NICE algorithm for appropriate critical care referrals (46)

NICE encourages intensivists to start critical care therapy with clear targets or outcomes from the start. It recommends frequent reviews with simultaneous assessment of response to treatment. Critical care treatment should be withdrawn when the outcomes set at initiation of treatment are not reached and the patient fails to improve. Decisions must be communicated with the patient when possible and their family, carers and/or independent mental capacity advocate, if appropriate. (47)

Non-invasive ventilation (NIV)

Initial reports did not favour the use of NIV in COVID-19, over fears of large tidal volumes and high transpulmonary pressures causing further lung damage. (25) NIV methods - continuous positive airway pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP)- were also not recommended as they are aerosol-generating medical procedures and therefore increase the risk of spread of COVID-19. (48) There is now emerging evidence to support CPAP use during the pandemic. (49) Reports from Italy and China claim that many patients benefited from receiving non-invasive mechanical ventilation. Specifically in Italy, 50% of patients who received CPAP did not require invasive ventilation. (50–52) The WHO recommends that patients receiving CPAP should be supervised by experienced clinicians who are able to perform endotracheal intubation if the patient fails to improve or rapidly deteriorates. (25) **Table 1** offers an escalation plan in cases where NIV is being trialled.

Teams from University College London (UCL) and University College London Hospital (UCLH) have collaborated with Mercedes Formula One. Using reverse engineering methods, the teams have adapted the existing CPAP model making it better suited for mass production. This will make the machines readily available for COVID-19 patients. (51)

National Health Service (NHS) England has specified that CPAP should be used for hypoxaemic respiratory failure and BiPAP for hypercapnic states in cases of acute on chronic respiratory failure. Indications include (53):

- As a ceiling of care option
- In an attempt to avoid intubation
- In an attempt to aid extubation

Table 1: Treatment and escalation plan issued by NHS England for adult COVID-19 patients. (53)

Endotracheal Intubation

If endotracheal intubation is deemed appropriate, the WHO recommends endotracheal intubation to be performed by an experienced clinician using protective equipment.

- Preoxygenate the patient with 100% Fi02 for 5 minutes using a face mask, bag-valve mask, High-flow nasal oxygen (HFNO) or Non-invasive ventilation (NIV) prior to attempting intubation.(25)

Invasive Mechanical Ventilation

Summation of evidence from a recent review by King's College Hospital NHS Trust as well as guidelines issued by the WHO conclude that severe cases requiring mechanical ventilation may benefit from the following principles:

1) Usage of low tidal volumes (4-8 ml/kg predicted body weight (PBW)) and target plateau pressure <30 cmH20 (<28 cmH20 in children):

    a) Adults: Initial tidal volume 6ml/kg PBW (may be increased to 8ml/kg PBW if initial tidal volume not tolerated)

    b) Children: Target tidal volume 3-6 ml/kg PBW (may be increased to 5-8 ml/kg PBW in cases with well preserved respiratory compliance). (25)

2) As a general rule, titration of positive end-expiratory pressure (PEEP) should be guided by the Fraction of Inspired Oxygen (Fi02) required to achieve a desired

arterial oxygen saturation (Sp02). The settings presented in **Table 2** have been derived from the ARDSnet trial and can be used to achieve an Sp02 >90%. (25,54)

Table 2: Settings for Positive End-Expiratory Pressure (PEEP), based on the required Fraction of Inspired Oxygen (FiO2) derived from the ARDSnet trial. (54)

3) Early airway pressure release ventilation should be considered in certain patients. (55)

4) Consideration of early prone ventilation in patients where there is no improvement observed after twelve hours of ventilator optimisation (i.e. PaO2/FiO2<150). Prone ventilation should last 12-16 hours a day. (25,55)

5) Permissive hypercapnia may be considered if haemodynamically satisfactory parameters are maintained as opposed to forms of ventilation which may cause further lung damage. (25,55)

Figure 6: Illustration by *Bouadma et al*. demonstrating the progression of severe COVID-19 cases requiring ICU admission. (56)

Extracorporeal membrane oxygenation (ECMO)

Cases of COVID-19 with refractory hypoxemia despite lung protective ventilation should receive ECMO if an extracorporeal life support (ECLS) service is available. (25)

Fluid resuscitation and vasopressors

In **adults**, fluid resuscitation should be administered as 250-500ml crystalloid fluid boluses over 15-30 min followed by assessment for fluid overload after each bolus. Vasopressors can be used if septic shock (**Table 3**) persists despite fluid resuscitation to maintain a mean arterial pressure (MAP) ≥ 65 mmHg. In patients over 65, a MAP of 60-65 mmHg is acceptable, a recent study suggests. (25,57). In adults, norepinephrine

is the drug of choice, which can be supplemented by epinephrine or vasopressin to maintain MAP targets.

In **children**, fluid resuscitation should be administered as 10-20 mL/kg crystalloid fluid boluses over 30-60 min followed by assessment for fluid overload after each bolus. Vasopressors may be used if signs of septic shock (**Table 3**) and/or fluid overload are observed or if there is an inability to maintain age-appropriate blood pressure parameters. In children, epinephrine is the drug of choice, with norepinephrine supplementation if septic shock persists. (25)

Table 3: Parameters for recognition of septic shock in adults and children (58)

3.4. Medical Management

The CDC echoes the WHO's comments regarding the use of corticosteroids and further explains that their use can prolong replication of the virus when used in similar viruses to COVID-19 such as MERS-CoV. (59) When patients present with SARI, the WHO advises to administer empiric antimicrobials that can treat any likely causative agent within 1 hour of assessment with confirmed sepsis. This treatment should be based on clinical diagnosis - whether community or hospital acquired pneumonia - and treated according to local guidelines. (25) Conversely, Wang et al. have suggested that the inappropriate use of broad-spectrum antibiotics should be avoided unless there is evidence of secondary bacterial infection. (42)

More recently, pioneering laboratory tests have suggested that there may be drugs already used for other viruses that could be applicable to COVID-19. Remdesivir - a broad spectrum antiviral agent - is an adenosine analogue capable of interrupting the nascent viral RNA chains to cause premature chain termination, and has previously been tested for treatment of the Ebola virus. When remdesivir is injected into Vero E6 cells infected with COVID-19, the antiviral effectively inhibits the virus. When tested in human cell lines (Huh-7 cells) the virus is effectively inhibited. (60) This supports the CDC's statement that remdesivir has *in vitro* activity against COVID-19. (61) Further studies are needed to confirm Remdesivir's use against COVID-19, however the National Institute of Allergy and Infectious Diseases is currently conducting a double-blind randomised controlled trial on the use of remdesivir in patients with COVID-19 infection, with results pending. (62)

Another familiar drug that may be viable for COVID-19 is chloroquine; it is traditionally used as an antimalarial as well as against autoimmune diseases. The mechanism of

action of chloroquine increases the endosomal pH above that required for virus and cell fusion whilst also interrupting the glycosylation of cellular receptors in similar viruses such as SARS-CoV. When chloroquine is introduced to Vero E6 cells infected with COVID-19, it appears to treat the infection at both entry and post-entry stages of infection. Chloroquine may also enhance immune modulation of cells, potentially increasing efficacy of the drug *in vivo*. In general, chloroquine is cheap and safe to use, and is widely distributed to all organ systems including the lungs when taken orally (**Figure 7**) (63).

Figure 7: A graph to show the antiviral activities of test drugs against COVID-19 in vitro (63).

Oncological drugs are another class with growing interest. Some oncology drugs - whilst laboratory results are promising - cannot be tolerated by humans due to the required dose being significantly higher than the established therapeutic dose for other diseases. Conversely, anti-inflammatory drugs have been suggested due to the significant effect of inflammatory responses on lung damage and resulting mortality. **Table 4** details three anti-inflammatory agents trialed on COVID-19. Their underlying mechanism of action involves inhibition of JAK-STAT signalling thus decreasing the extent of elevation of cytokines seen in patients with COVID-19 (64).

Table 4: Properties of three anti-viral and anti-inflammatory drugs (64).

3.5. Operative Management

The first double lung transplant was successfully performed on a patient in China with irreversible bilateral lung damage secondary to COVID-19 on 29th February 2020. The 59 year old male was infected with SARS-CoV-2 on 26th January 2020, and although repeated tests confirmed the resolution and absence of ongoing infection, prolonged endotracheal intubation, ventilation, and ECMO therapy were nevertheless required. The team at Wuxi People's Hospital, led by cardiothoracic surgeon Dr Chen Jinguy, performed the five hour operation. The operation was performed successfully with the

patient requiring postoperative observation and medical therapy to avoid infection or rejection (65).

3.6. Measuring response

Due to the limited treatment options available, the ability to measure a response to treatment is challenging. When patients are tested for initial infection, a positive result is based on nucleic acid detection for SARS-CoV-2 infection. When assessing patients with deteriorating conditions, it has been noted that CRP is significantly raised and albumin is low (31). While no clear guidelines exist on the evaluation of response to supportive treatment, a study by Cascella et al. has suggested that laboratory evaluation of samples from patients should demonstrate viral clearance prior to discharging from observation in the form of two negative respiratory tract specimens taken at least 24 hours apart (66,67).

4. Outcomes

There is currently an estimate of 702,222 active cases worldwide, of which 95% (n=670,532) display mild symptoms of the COVID-19 and 5% (n=31,690) of currently infected patients are seriously (requiring oxygen therapy) or critically unwell (requiring mechanical ventilation). Of the closed cases (n=241,959), 82% (n=194,647) of infected individuals have recovered from the disease or have been successfully discharged from hospital. 18% (n=47,312) of these cases have died of the illness or related complications (7). As it stands, the 46th WHO situation report estimates the Crude Mortality Ratio of COVID-19 to be between 3-4% based on current data (68). Median time for recovery from the onset of symptoms is approximately 2 weeks in mild cases and 3-6 weeks in severely or critically unwell individuals (34) .

5. Conclusion

With over 76,836 new cases confirmed on 1st April 2020 alone (69), there are fears that these findings could indicate exponential spread of the disease. Implementation and adherence to tighter restrictions of social distancing to suppress and mitigate the spread of COVID-19 will prove to be crucial in the months to come. Up-to-date, evidence-based guidelines for acute management of COVID-19 are imperative to guide clinicians through the rapidly evolving pandemic. As new evidence emerges, it is imperative that current and potential treatment options are frequently re-evaluated in order to offer the best possible care under such unprecedented circumstances.

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Category	Clinical status	Suggested action
Green	RR ≥ 20bpm with SpO_2≤94%	Administer O_2<40% by face mask. If SpO_2 rises to >94%, observe and monitor
Yellow	RR ≥ 20bpm with SpO_2≤94% on FiO_2 ≥40%	Start 15L/min O_2 via non-rebreathe mask *Senior clinical review to consider:* If orientated and able to tolerate well-fitted non-vented face mask, trial CPAP 10cmH_2O with FiO_2 0.6 If further escalation appropriate, consider increasing CPAP 12-15 cmH_2O + 60-100% oxygen if needed If not, IMV if in accordance with TEP
Red	RR ≥ 20bpm with SpO_2≤94% on 15L/min O_2 via non-rebreathe mask and/or patient unable to tolerate CPAP mask, obtunded/ disorientated, rising FiO_2 needs, significant clinical decline	Urgent critical care review and prepare for intubation if in accordance with TEP

Abbreviations: RR = respiratory rate; SpO_2 = oxygen saturation; CPAP = continuous positive airways pressure; FiO_2 = fraction of inspired oxygen, IMV = invasive mechanical ventilation, TEP = treatment escalation plan

FiO_2	PEEP
0.3	5
0.4	5–8
0.5	8–10
0.6	10
0.7	10–14
0.8	14
0.9	14–18
1.0	18–24

SEPTIC SHOCK	
ADULTS	CHILDREN
• Suspected or confirmed infection • AND Vasopressor requirement* • AND Lactate ≥ 2 mmol/L • Absence of hypovolemia	• Hypotension** • OR ≥ 2 of the following: ○ Altered mental state ○ Tachycardia or Bradycardia*** ○ Prolonged capillary refill time ○ Feeble pulses ○ Tachypnea ○ Mottled or cold skin/petechial rash/purpuric rash ○ Raised lactate ○ Oliguria ○ Hyperthermia or hypothermia

* Vasopressor requirement to maintain a mean arterial pressure (MAP) ≥ 65mmHg

**Systolic Blood Pressure <5th percentile or >2 SD below normal for age

***In infants Heart Rate(HR) <90 bpm or > 160 bpm and children HR <70 bpm >150 bpm

	Baricitinib	Ruxolitinib	Fedratinib
Daily dose, mg	2–10	25	400
Affinity and efficacy: K_d or IC_{50}, nM*			
AAK1†			
Cell free	17	100	32
Cell	34	700	960
GAK†			
Cell free	136	120	1
Cell	272	840	30
BIKE†			
Cell free	40	210	32
Cell	80	1470	960
JAK1			
Cell free	6	3	20
Cell	12	20	600
JAK2			
Cell free	6	3	3
Cell	11	21	100
JAK3			
Cell free	>400	2	79
Cell	>800	14	2370
TYK2			
Cell free	53	1	20
Cell	106	7	600
Pharmacokinetics			
Plasma protein binding	50%	97%	95%
C_{max} (unbound), nM	103‡	117	170
Safety: tolerated dose	≤10 mg/day	≤20 mg twice daily	≤400 mg/day

Category	Clinical status	Suggested action
Green	RR ε 20bpm with SpO_2δ94%	Administer O_2<40% by face mask. If SpO_2 rises to >94%, observe and monitor
Yellow	RR ε 20bpm with SpO_2δ94% on FiO_2 ε40%	Start 15L/min via non-rebreathe mask *Senior clinical review to consider:* If orientated and able to tolerate well-fitted non-vented face mask, trial CPAP 10cmH_2O with FiO_2 0.6 If further escalation appropriate, consider increasing CPAP 12-15 cmH_2O + 60-100% oxygen if needed If not, IMV if in accordance with TEP
Red	RR ε 20bpm with SpO_2δ94% on 15L/min O_2 via non-breathe mask and/or patient unable to tolerate CPAP mask, obtunded, disorientated, rising FiO_2 needs, significant clinical decline	Urgent critical care review and prepare for intubation if in accordance with TEP

Abbreviations: RR = respiratory rate; SpO_2 = oxygen saturation; CPAP = continuous positive airway pressure; FiO_2 = fraction of inspired oxygen, IMV = invasive mechanical ventilation, TEP = treatment escalation plan

Table 1: Treatment and escalation plan issued by NHS England for adult COVID-19 patients. (53)

FiO_2	PEEP
0.3	5
0.4	5-8
0.5	8-10
0.6	10
0.7	10-14
0.8	14
0.9	14-18
1.0	18-24

Table 2: Settings for Positive End-Expiratory Pressure (PEEP), based on the required Fraction of Inspired Oxygen (FiO2) derived from the ARDSnet trial. (54)

SEPTIC SHOCK	
ADULTS	CHILDREN
• Suspected or confirmed infection • AND Vasopressor requirement* • AND Lactate ≥ 2 mmol/L • Absence of hypovolemia	• Hypotension** • OR ≥ 2 of the following: ○ Altered mental state ○ Tachycardia or Bradycardia*** ○ Prolonged capillary refill time ○ Feeble pulses ○ Tachypnea ○ Mottled or cold skin/petechial rash/purpuric rash ○ Raised lactate ○ Oliguria ○ Hyperthermia or hypothermia

* Vasopressor requirement to maintain a mean arterial pressure (MAP) ≥ 65mmHg

**Systolic Blood Pressure <5th percentile or >2 SD below normal for age

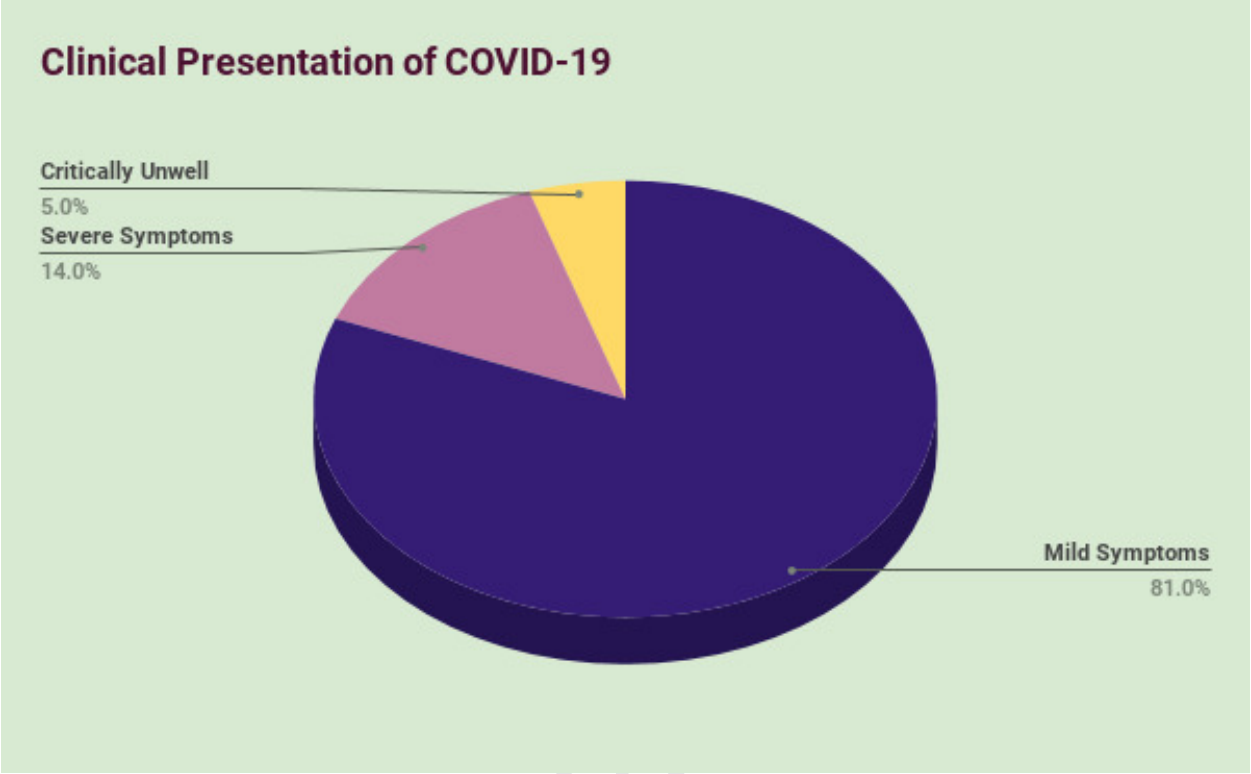
***In infants Heart Rate(HR) <90 bpm or > 160 bpm and children HR <70 bpm >150 bpm

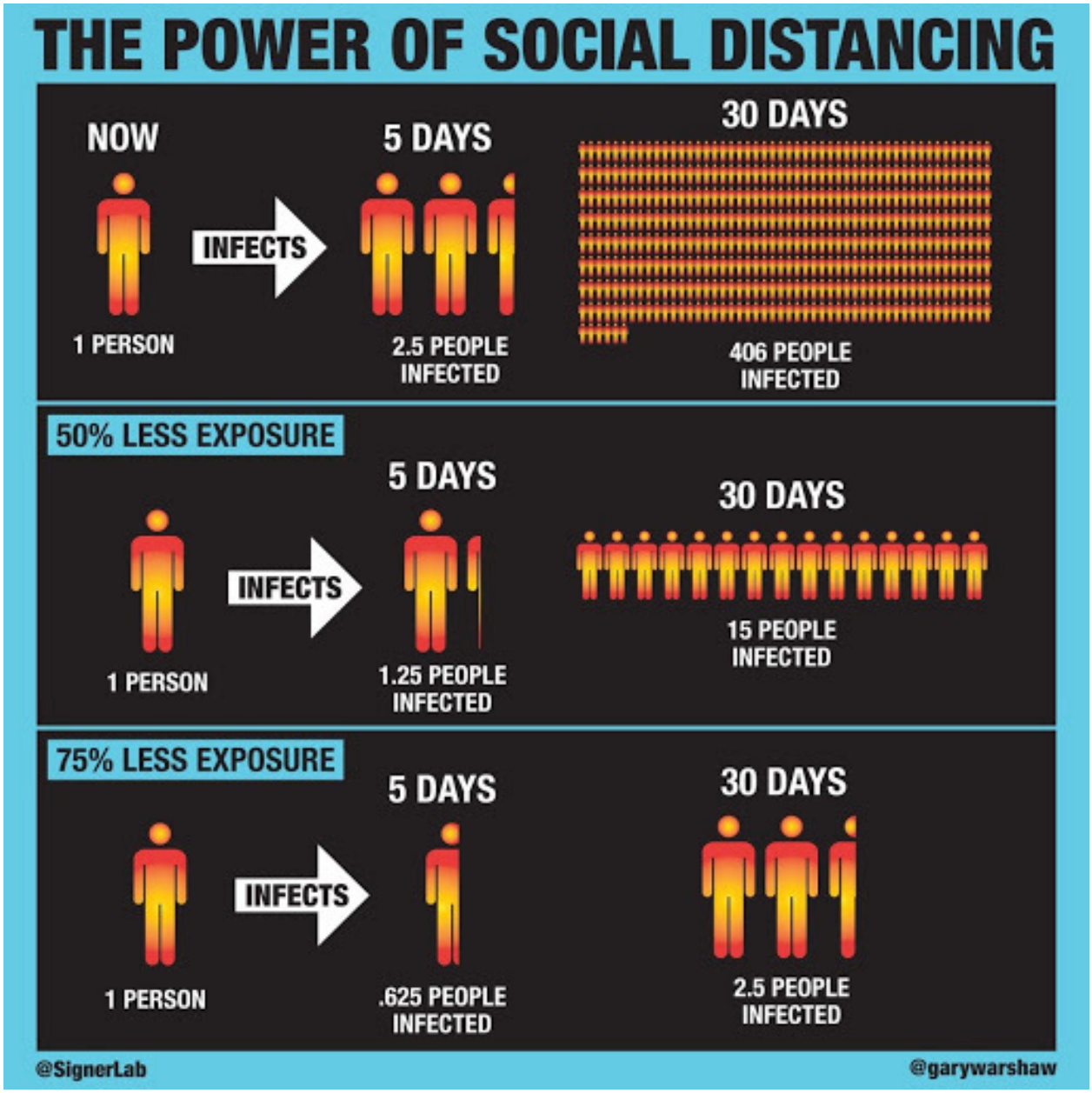
Table 3: Parameters for recognition of septic shock in adults and children (58)

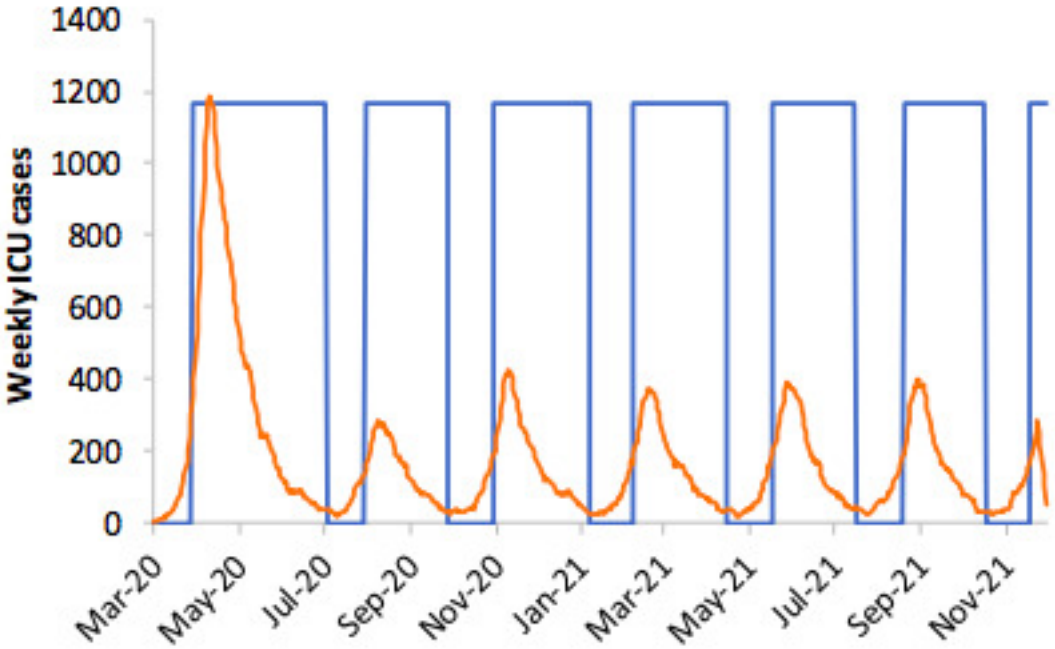
	Baricitinib	Ruxolitinib	Fedratinib
Daily dose (mg)	2-10	25	400
Affinity and Efficacy: K_d or IC_{50}, nM*			
AAK1			
Cell free	17	100	32
Cell	34	700	960
GAK			
Cell free	136	120	1
Cell	272	840	30
BIKE			
Cell free	40	210	32
Cell	80	1470	960

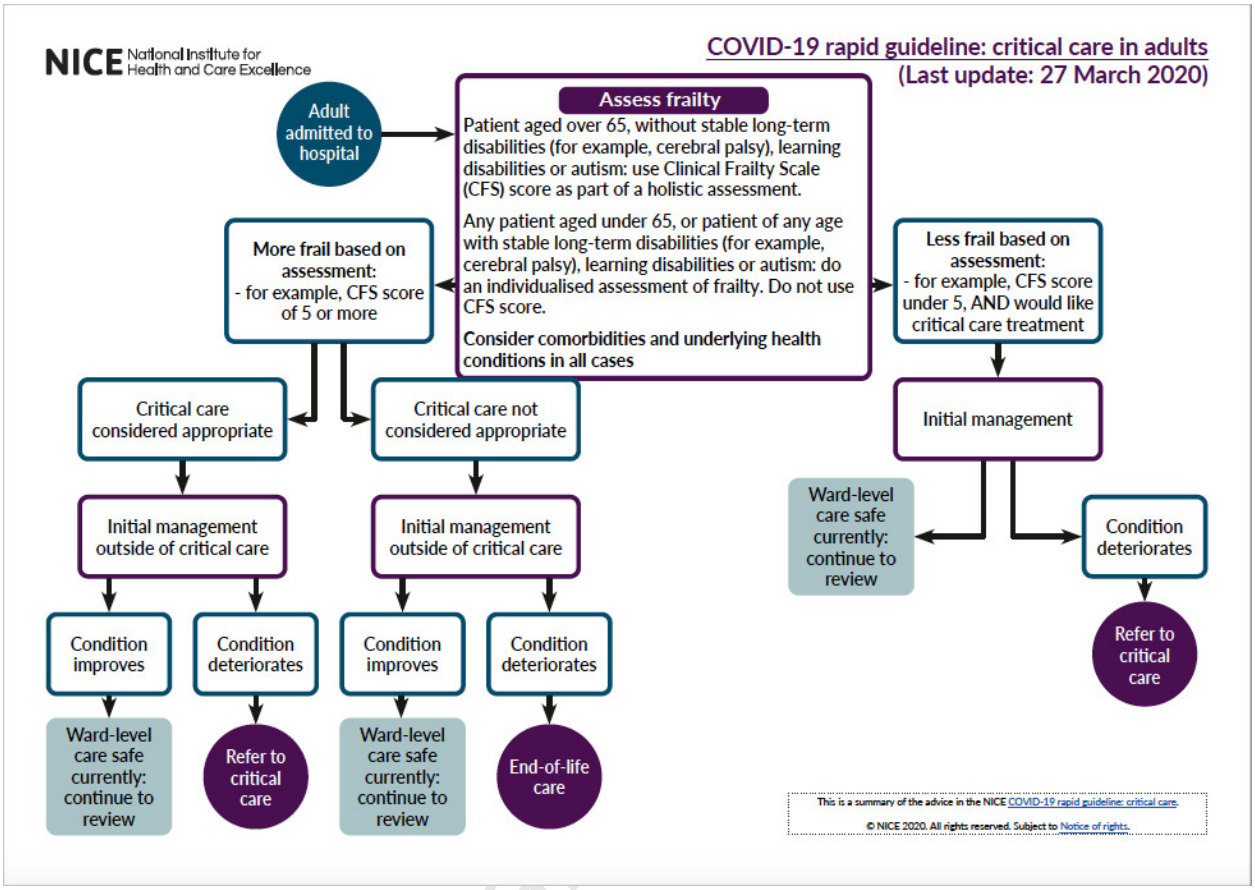
JAK1			
Cell free	6	3	20
Cell	12	20	600
JAK2			
Cell free	6	3	3
Cell	11	21	100
JAK3			
Cell free	>400	2	79
Cell	>800	14	2370
TYK2			
Cell free	53	1	20
Cell	106	7	600
Pharmacokinetics			
Plasma protein binding	50%	97%	95%
C_{max} (unbound)	103	117	170
Safety:tolerated dose	?10 mg/day	?20 mg twice daily	?400 mg/day

Table 4: Properties of three anti-viral and anti-inflammatory drugs (64).




THE POWER OF SOCIAL DISTANCING
NOW
5 DAYS
30 DAYS
INFECTS
1 PERSON
2.5 PEOPLE INFECTED
406 PEOPLE INFECTED
50% LESS EXPOSURE
5 DAYS
30 DAYS
INFECTS
1 PERSON
1.25 PEOPLE INFECTED
15 PEOPLE INFECTED
75% LESS EXPOSURE
5 DAYS
30 DAYS
INFECTS
1 PERSON
.625 PEOPLE INFECTED
2.5 PEOPLE INFECTED
@SignerLab
@garywarshaw




NICE National Institute for Health and Care Excellence
COVID-19 rapid guideline: critical care in adults
(Last update: 27 March 2020)
Adult admitted to hospital
Assess frailty
Patient aged over 65, without stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism: use Clinical Frailty Scale (CFS) score as part of a holistic assessment.
Any patient aged under 65, or patient of any age with stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism: do an individualised assessment of frailty. Do not use CFS score.
Consider comorbidities and underlying health conditions in all cases
More frail based on assessment: - for example, CFS score of 5 or more
Less frail based on assessment: - for example, CFS score under 5, AND would like critical care treatment
Critical care considered appropriate
Critical care not considered appropriate
Initial management
Initial management outside of critical care
Initial management outside of critical care
Ward-level care safe currently: continue to review
Condition deteriorates
Condition improves
Condition deteriorates
Condition improves
Condition deteriorates
Refer to critical care
Ward-level care safe currently: continue to review
Refer to critical care
End-of-life care
This is a summary of the advice in the NICE COVID-19 rapid guideline: critical care.
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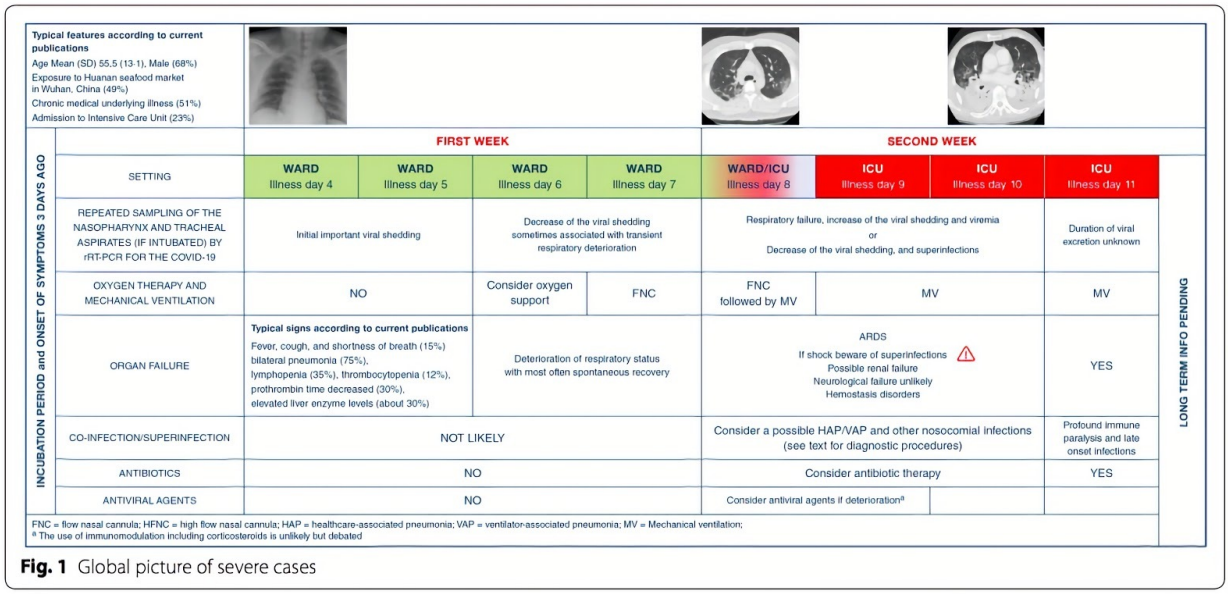
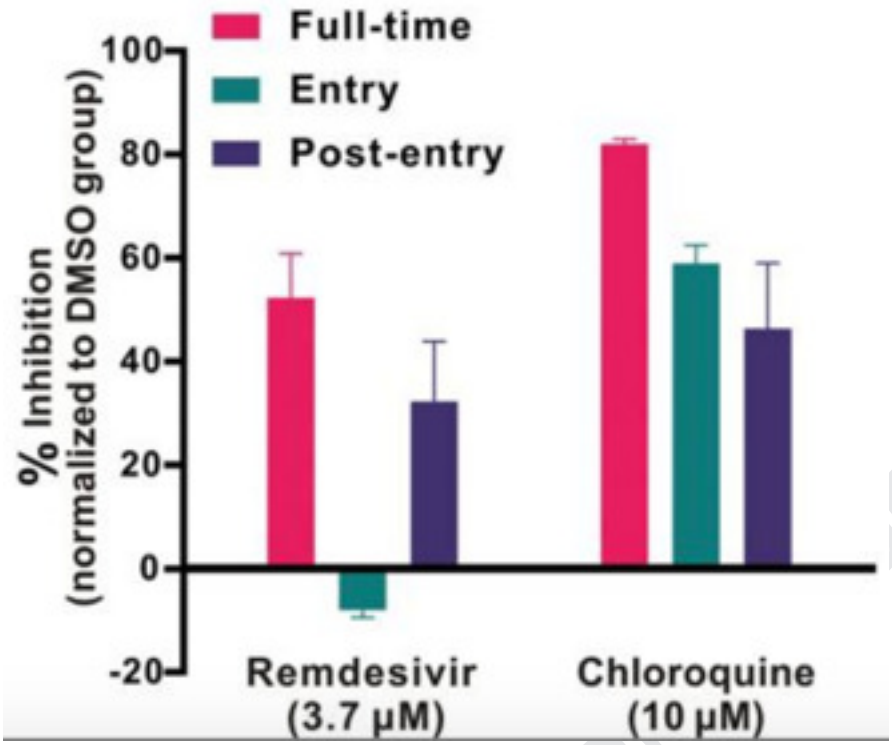


Fig. 1 Global picture of severe cases



Highlights:

- COVID-19 has recently been declared a pandemic by WHO
- Increased cases globally have highlighted the need for updated management guidelines
- Currently, supportive management is the first-line treatment
- New medical therapies are currently in phase 1 and 2 trials

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

Please state any conflicts of interest

None

Please state any sources of funding for your research

None

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

None required

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry, the hyperlink to the registration and the unique identifying number of the study. You can register your research at http://www.researchregistry.com to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Maria Nicola : significant role in concept production and writing of manuscript, editing and approval of final draft

Niamh O'Neill : significant role in writing of initial manuscript, editing and approval of final draft

Catrin Sohrabi : contribution to writing of manuscript, approval of final draft

Mehdi Khan : contribution to writing of manuscript, approval of final draft

Riaz Agha : senior author, role in supervising concept production, collection of papers and approval of final draft

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

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Data Statement

The data in this review is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.