

Emergency Management of Severe Covid-19 Cases: A Narrative Review

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Abstract

Introduction: With several media and public health agencies warning of a continued global outbreak and possible pandemic, there is a high probability United States hospitals will see a large influx of severe cases of COVID-19, which will overwhelm many health systems. This review aimed to collect the evidence about emergency management of severe COVID-19 cases.

Methods: We searched PubMed and preprint archives for research articles published up to 21 February 2020 using the following terms: "COVID-19", "SARS-CoV-2", "2019-nCoV", "n-CoV", and "coronavirus." At the initial stage of screening, any articles that were published before 1 December 2019 were excluded. Research titles were independently reviewed by two authors to eliminate studies that did not meet our inclusion criteria before the full review of abstracts and full-text of selected studies. At least two authors independently extracted data using the CHARMS (critical appraisal and data extraction for systematic reviews of prediction modelling studies) checklist.

Results: Owing to the widespread availability of diagnostic testing capacity after the summer of 2020, this living review has now focused on the therapeutic models. Of these, 29 had low risk of bias, 32 had unclear risk of bias, and 545 had high risk of bias. The most common causes for high risk of bias were inadequate sample sizes and inappropriate or incomplete evaluation of model performance. Several medications were newly developed, and many have been under investigation.

Conclusions: As with MERS and SARS, steroids should be avoided. Data from both the SARS and MERS epidemics have demonstrated worse long-term outcomes with the use of corticosteroids, and the use of steroids should only be reserved for patients requiring treatment for other disease processes. Ribavirin, however, resulted in worse SARS outcomes when compared

to case-matched control patients. In contrast, based upon limited data Ribavirin seems to be associated with improved MERS survival. Similar randomized trials evaluating lopinavir/ritonavir for MERS have been designed, but are not yet completed.

Keywords: COVID-19, Emergency, Severity, Management

Introduction

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), previously referred to as 2019-nCoV, is the virus responsible for causing Coronavirus Disease 2019 (COVID-19). The COVID-19 is the seventh identified human coronavirus, and appears to have notable similarities to 2 other highly pathogenic human respiratory coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), 2 both of which have generated large-scale public health responses in the last 2 decades. The majority of initial COVID-19 cases were associated with travel to Hubei Province China; however, a growing number of cases due to person-to-person transmission have been reported both in and outside of China [1]. Three major trajectories for COVID-19 have been described: mild disease with upper respiratory symptoms, non-severe pneumonia, and severe pneumonia complicated by acute respiratory distress syndrome (ARDS) necessitating aggressive resuscitative measures [2].

Most patients with confirmed COVID-19 have had a subjective or confirmed fever and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing) [3]. An absolute majority of all critically ill COVID-19 patients present with severe respiratory insufficiency. Concerning clinician judgment regarding patient presentations compatible with COVID-19, Center of Communicable Diseases (CDC) guidelines prioritize patients from defined populations for further evaluation and testing as persons under investigation (PUI) [4]. The CDC has developed a real time reverse transcription polymerase chain reaction (RT-PCR) assay for detecting SARS-CoV-2 in upper and lower respiratory specimens obtained from COVID- PUIs [5]. With several media and public health agencies warning of a continued global outbreak and possible pandemic, there is a high risk in the United States hospitals will see a large influx of

cases of COVID-19, which will overwhelm many health systems. On ultrasound, severe cases with COVID-19 typically demonstrate an irregular/thickened pleural line, scattered/confluent B lines, consolidations of various sizes, and both non-translobar and translobar consolidations [6]. Radiological appearance is characteristic in chest x-ray with ground glass appearance [7]. Laboratory findings include high levels of ferritin and hemophagocytosis are related to inflammation severity and are present in several diseases with different etiologies: macrophage activation syndrome, hemophagocytic lymphohistiocytosis (HLH), sepsis, multisystem inflammatory syndrome (MIS), staphylococcal toxic shock, and severe cases of COVID-19, suggesting that these are different phenotypes of the same inflammatory process [8]. Although COVID-19 is less severe and less frequent in children, as the pandemic progresses, there are reports of a worrying clinical picture in the pediatric age group.

Symptoms similar to Kawasaki disease and toxic shock that require assertive conduct by pediatricians, especially those working in emergency services [9]. Similar reports have been reported in several countries under the name "multisystem inflammatory syndrome in children" (MIS-C) temporarily associated with COVID-19. Society of Critical Care Medicine (SCCM) Surviving Sepsis COVID-19 guidelines recommend performing endotracheal intubation under airborne precautions, including use of a fitted N95 respirator and placement of the patient in an AIIR [10]. Based on prior cases of HCPs infected with SARS-CoV-1 while using N95 respirators, some experts recommend using a PAPR. The most experienced provider should intubate. Using eye protection (safety goggles or visor) in addition to normal safety equipment has been proven to provide a significant reduction of nosocomial transmission in the SARS

epidemic and is thus suggested in the care of COVID-19 patients. Extracorporeal membrane oxygenation (ECMO) was approved by the FDA as a therapy during the COVID-19 pandemic, and the WHO suggests its use for COVID-19 patients with refractory hypoxemia despite the use of protective ventilation, emphasizing that it is a very limited resource that must be rationed in a pandemic situation [11].

Furthermore, recent *in vitro* studies conducted on COVID-19 have found that remdesivir and chloroquine inhibit viral infection of cells with low micromolar concentration with a high selectivity index. While there are multiple other ongoing studies exploring lopinavir/ ritonavir in COVID-19, none utilises a double-blind methodology to address this limitation. Siltuximab, another monoclonal antibody, binds directly to IL-6 and can be considered a second-line treatment for COVID-19 cases resistant to tocilizumab, although there is no adequate evidence of its effectiveness [12]. Due to the similarities between the cytokine release syndrome and the cytokine storm in COVID-19, studies are underway to evaluate the safety and efficacy of this therapeutic modality. The FDA has issued emergency use authorization for remdesivir for the treatment of severe COVID-19 in adults and children [13]. Moreover, prophylactic anticoagulation with low molecular weight heparin has been a standard recommendation for all cases that require hospitalization for COVID-19 and have no contraindications. Although there is no evidence of a correlation between serum IL-1 levels and COVID-19 severity. Ongoing multicenter studies have evaluated the role of anakinra associated with emapalumab in reducing hyperinflammation in patients with severe SARS-CoV-2 infection [14].

Pre-existent liver and kidney diseases, impairment of these organs in older adults, and the presence of comorbidities can elevate the risk of clinical complications in COVID-19. Liver and kidney injuries in COVID-19 may alter the pharmacokinetics of drugs currently prescribed to treat the disease. Due to the lack of definitive protocols, the management of COVID-19 has been primarily supportive. Owing to the increase in the number of patients coming to the ED, the diversion of ambulances from the main hospital that was housing the majority of COVID-19

patients and the opening up of more areas being manned by the ED, shortage of ED manpower became a real concern. This review aimed to collect the evidence about emergency management of severe COVID-19 cases [15].

Methods

We searched PubMed and preprint archives for research articles published up to 21 February 2020 using the following terms: “COVID-19”, “SARS-CoV-2”, “2019-nCoV”, “n-CoV”, and “coronavirus.” At the initial stage of screening, any articles that were published before 1 December 2019 were excluded. Research titles were independently reviewed by two authors to eliminate studies that did not meet our inclusion criteria before the full review of abstracts and full-text of selected studies. We selected research articles that contain estimates for at least one of the following epidemiological parameters: (i) the severity of cases, (ii) the management strategies, which is defined as the time it takes for the number of protocols in the epidemic. At least two authors independently extracted data using the CHARMS (critical appraisal and data extraction for systematic reviews of prediction modelling studies) checklist.

Results

The current potential for global dissemination of the COVID-19, given the co-occurrence of Lunar New Year celebrations, in addition to the growing number of reported cases, adds urgency to understanding this outbreak. The confirmation of cases in 29 countries as of February 8, 2020 underscore the potential for COVID-19 to rapidly evolve into a global pandemic. The remaining identified human coronaviruses (HCoV-229E HKU NL OC43) are limited in their severity of disease and often fail to produce symptoms greater than the common cold in immunocompetent hosts. MERS appear to have had higher case-fatality rates and worse severity of illness [16]. In comparison to seasonal influenza globally, coronaviruses represent a smaller burden of disease, and fall well short of the Influenza pandemic. Inoculation via “fomite-to-face” contact is also likely a significant contributor to the spread of the virus. This development raises concerns that the COVID-19 may be similar to other viruses

such as chickenpox and measles in that transmission may be possible during the incubation period or by patients with mild disease. As of February 9, 2020, the mortality and morbidity rates of COVID-19 remain in flux.

Mortality among COVID-19 victims seems highest for the elderly and those with multiple comorbidities, seasonal Influenza [17]. These models and the virus's behavior, thus far suggest the capability for sustained human-to-human transmission. Current rates of transmission are likely underestimated and will continue to evolve as the virus continues its spread, reporting practices evolve, and more data accrue. Because the signs and symptoms of COVID-19 are similar to other viral respiratory syndromes, health care professionals must obtain a detailed travel history in any patient presenting to the emergency department with fever and respiratory symptoms. More widely available testing is anticipated to be available soon. After identifying a PUI, both hospital infection control and the local health department should be contacted immediately to prevent further spread amongst patients and health care workers. Surgical face masks may be helpful for larger fluid droplets associated with coughing and sneezing, but they are unlikely to help with small airborne contaminants. Where available, respirators with an adequate seal and air movement directed through filters should be more effective [18].

The proper usage of respirators and other personal protective equipment (PPE) including donning, fit, and frequent changing combined with proper hand hygiene represent the most effective method of preventing transmission in health care settings. Isolation rooms and care processes should be configured to minimize the number of health care personnel exposed to the patient as well as the duration of contact. It is paramount that all health care professionals use standard, contact, droplet, and airborne precautions in addition to an eye shield. Not all COVID-19 exposed or afflicted patients will need hospital admission. However, the decision to discharge a PUI for home isolation should be made in consultation with the local public health authorities. Patients should be directed to use appropriate hand hygiene, wear a simple facemask when around others, and remain isolated to a single room in the house

whenever possible. Patients should only leave the house for medical attention after calling in advance to inform the medical office of their COVID- PUI status. Therefore, discharge may be inappropriate for patients who are unable to adhere to recommendations, return precautions, self-monitoring, or those with inadequate housing. In patients suspected of COVID-19 infection, viral testing should be initiated early for disease confirmation and symptomatic treatment initiated as needed [19]. Intravenous fluids should be used judiciously in patients without overt signs of fluid depletion as they may worsen oxygenation with increasing disease severity. With the predicted number of cases set to rise significantly, this represents a prodigious acute unmet medical need. The swift genomic sequencing of COVID-19 has facilitated this process, allowing comparison with MERS-CoV SARS-CoV, and other moribund viruses . Blinding reduces the risk of bias in the outcome of a trial. The introduction of this requirement and other initiatives to increase clinical trial transparency has contributed to an increasing number of trials being recorded in online registries. The logging of trials on registries has vastly facilitated the dissemination of information across several domains, including intervention, methodology, patient group, and outcome measures. Furthermore, in the event of the nonpublication of results, it means that trial information remains freely available for analysis.

Randomization reduces the risk of bias in a trial outcome. We hope that this will clarify current investigational advances and guide potential future strategies. Thus, ritonavir is given concomitantly to inhibit this, significantly boosting the half-life of lopinavir. However, efficacy was not seen in a randomized open-label study (lopinavir/ritonavir versus standard care) in 199 patients with COVID-19 [20]. Several other antiviral drugs are being investigated, predominately those with activity against various influenza subtypes and other RNA viruses. Many trials are focusing on drugs typically used in the management of RNA viruses, such as HCV and HIV. These include danoprevir/ritonavir, azvudine, sofosbuvir/ledipasvir, sofosbuvir/ daclatasvir, darunavir/cobicistat, and emtricitabine/tenofovir [21]. This study is limited by its lack of randomization and blinding, and small sample size. Furthermore,

postexposure prophylaxis is an attractive strategy for both healthcare workers and household contacts exposed to COVID-19. Later on, six studies are looking at the use of antivirals, such as umifenovir, antimalarials, such as hydroxychloroquine and chloroquine, and the use of recombinant human interferon alpha (a)1b spray for the prevention of infection [22].

Most of clinical trials (excluding TCM) for either the prevention and/or treatment of COVID-19 have been registered in China, which is not surprising given that the country saw the outbreak of the disease first. Public health initiatives have thus far successfully curtailed the previously exponential growth of COVID-19 cases in China. This has reduced the number of potential participants for clinical trials in China and the registration of new clinical trials has since declined. The wider global community has been slower to react. The rapid escalation of trial registrations in response to increasing disease incidence seen in China has unfortunately not occurred in Europe. Despite this, there are now encouraging signs. Initiatives focused on pan-European collaboration are being championed by the European Union with a priority on larger patient studies compared with the smaller studies registered in China [23]. However, this may in part reflect a higher proportion of preventative studies currently being carried out that include large numbers of participants. Hopefully, larger studies will provide higher quality evidence, although may take longer to generate results in the context of this escalating public health crisis. Studies registered in the USA have generally placed an emphasis on larger participant numbers than China and on an adaptive trial design for both the treatment and prevention of COVID-19.

Conclusions

In patients presenting with severe respiratory symptoms with radiographic findings, broad spectrum antibiotics should be administered early, since it is often not possible to differentiate between bacterial pneumonia and COVID-19 infections. As with MERS and SARS, steroids should be avoided. Data from both the SARS and MERS epidemics have demonstrated worse long-term outcomes with the use of corticosteroids, and the use of steroids should only be

reserved for patients requiring treatment for other disease processes. Ribavirin, however, resulted in worse SARS outcomes when compared to case-matched control patients. In contrast, based upon limited data Ribavirin seems to be associated with improved MERS survival. Similar randomized trials evaluating lopinavir/ritonavir for MERS have been designed, but are not yet completed.

Conflict of interests

The authors declared no conflict of interests.

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