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Management of COVID-19: the risks associated with treatment are clear, but the benefits remain uncertain

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Abstract

Even though the early reports from China provided advance warning of what was to come, the COVID-19 pandemic has spread throughout the world with devastating consequences. Emergency measures are being implemented to reduce the magnitude of the public health crisis, prevent healthcare facilities from becoming overwhelmed and reduce the death toll of the disease. Containment strategies to mitigate viral transmission and emergency measures to increase the capacity of each country to provide intensive care are at the forefront of the public health management of the epidemic, even though the detrimental social and psychological effects of quarantine are evident on a global scale. Optimal management of critically ill patients with COVID-19 is also unclear, and the initial suggestion for early intubation as in typical ARDS may have caused significant harm. The management of mild cases of confirmed infection is another point of controversy, as drugs which may be repurposed for COVID-19 treatment have significant, potentially irreversible toxic effects and their use in mild cases of a viral illness which is typically self-limited may be harmful.

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Introduction

During the past 4 months, new major epidemic foci of coronavirus disease 2019 (COVID-19), some without traceable origin, have been identified and are rapidly expanding in Europe, North America, Asia, and the Middle East. The COVID-19 pandemic is currently the most important health policy issue throughout the world, with thousands of new cases and hundreds of deaths being recorded every day. Fears that the impact of this outbreak may be similar to that of the 1918 H1N1 influenza (Spanish flu) pandemic which resulted in over 20 million casualties are gaining ground and the lockdown measures instituted by governments worldwide, despite their necessity, seem to be contributing to public mistrust in the health care system and in the priorities of the administration. A similar degree of scepticism may be present among healthcare professionals on the front lines, as at present there is little evidence in support of any of the measures taken to manage the outbreak.

Containment measures and capacity for intensive care

The pandemic presented an unprecedented challenge for hospitals around the world, requiring a profound reorganization of the emergency department and the inpatient wards. In Italy, emergency department visits initially declined before returning to pre-pandemic levels at the peak of the pandemic, whereas the proportion of patients who were admitted to the hospital greatly increased [1,2]. Admission is necessary even for mildly symptomatic patients if they present with desaturation, due to the need to provide supplemental oxygen. Initial response to oxygen therapy would determine what level of care the patients would subsequently require (general inpatient, sub-intensive with non-invasive ventilation or intensive care). The need to triage and separate suspected COVID-19 cases from other patients was another issue which had to be addressed. Hospitals' capacity to provide all levels of care was strained, with particular emphasis being placed on a potential shortage of intensive care unit beds [1,3]. The reasoning behind the quarantine measures is that they will limit the growth of the pandemic sufficiently so as to prevent the healthcare system from being overwhelmed (flattening the curve). By spreading out the new cases over a longer period, hospitals can adjust to ensure that inpatient and Intensive Care Unit (ICU) level care is available to all those who require it. At the moment however there is no conclusive evidence that treatment in the ICU (including lung protective ventilation, prone position ventilation, dialysis,

vasopressor and inotropic support, even extracorporeal membrane oxygenation) or in the inpatient wards alters the disease course in any way. Given that severe COVID-19 infection is characterized primarily by a subtype of Acute Respiratory Distress Syndrome (ARDS) it would make sense to manage the disease in a similar manner, with mechanical ventilation being the mainstay of treatment [4]. However, the evidence that has been published up to this point suggests that once ARDS develops in COVID-19 patients the prognosis is far worse than ARDS due to other causes, with a fatality rate greater even than ARDS due to sudden acute respiratory syndrome (SARS) or Middle East Respiratory Syndrome (MERS) [5]. The data that is currently available sheds light upon risk factors for early death and for the development of ARDS, but the outcomes of those who survive for prolonged periods after intubation are unclear [6]. Recent research which has highlighted the role of coagulopathy in the pathogenesis of severe COVID-19 may in fact favour the use of non-invasive ventilation or high flow nasal oxygen over early intubation, as the prolonged immobility associated with mechanical ventilation could worsen a hypercoagulable state [7]. Respiratory failure in COVID-19 may be characterised by normal lung compliance and hyperperfusion of hypoventilated tissues in contrast to typical ARDS, and such a pathophysiology would be exaggerated by the use of high levels of positive end-expiratory pressure (PEEP). The inappropriate use of high PEEP as is recommended for typical ARDS may have contributed to the high mortality rates observed in the first cohorts of severely ill patients [8,9] It remains however uncertain if a different ventilator management strategy would lead to significantly improved outcomes.

These issues are crucial because intubation and mechanical ventilation is extremely resource intensive and typically avoided if the chances of recovery are low, similar to resource intensive procedures such as organ and bone marrow transplantations. In the United States where advance directives which may include do not intubate and do not resuscitate orders are common [10], informed consent must be obtained prior to intubation and many patients would not consent if they knew that they were far more likely never to regain consciousness than to recover. The fatality rates of patients intubated due to SARS or MERS unfortunately lend credence to this pessimistic outlook [11,12]. This should not be misinterpreted as an argument against offering optimal ICU care to critically ill COVID-19 patients; of course, such care should be made available to all who require it and wish to receive it. However, if mechanical ventilation success rates are unacceptably low (Table 1) as we have previously noted [13], broadening access to ventilators in a resource-limited setting should not be prioritized over other measures to reduce the impact of the outbreak, such as containment measures and antiviral treatment which could lead to clinically relevant improvement in all who are ill (not just those in critical condition) and reduce the transmissibility of the disease.

Containment measures are the response of choice at the early stages of an epidemic and seem to have worked well in the past, in the case of SARS and the most recent Ebola virus outbreak**.** However**,** isolation and quarantine restrict individual liberties, are difficult to implement on a mass scale and are not well tolerated by the public. Moreover, the effects observed in the economy are detrimental. In this case it is highly unlikely that they will halt the spread of pandemic entirely, they could however slow its progression sufficiently to allow the development of effective management strategies for the disease or, in the most optimistic scenario, to reduce transmission temporarily while waiting for the epidemic to die out on its own over the spring and summer [14].Despite the positive results of containment measures in China, South Korea and Japan, the same policies in Europe and North America do not appear to be as effective, being perceived mostly as necessary harm reduction measures to reduce the impact of the outbreak to manageable levels, rather than halt its spread completely. There is substantial concern that containment measures have failed entirely in this case, and the observed reduction in the number of new cases in the regions with the highest prevalence of COVID-19 may be attributed to the fact that a significant proportion of the population has been infected, with most cases being either asymptomatic or mild enough to not seek medical attention. Widespread serological testing for the presence of specific antibodies against sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is required to test this assumption [15]. An enzyme linked immunosorbent assay (ELISA) to quantify levels of SARS-CoV-2 specific IgM, IgG and IgA could be used to detect past infection and current immunity against the virus, but this test is not suitable for initial diagnosis of COVID-19 as there may be a lag of up to 2 weeks from infection until antibodies against the virus are produced. Such a test would also be of limited use to detect past infection in immunocompromised individuals who would be unable to sustain a humoral immune response [16]. Rapid serological tests for point of care diagnosis of infection are controversial at this point due to substantial false negative and false positive rates, so reverse transcriptase polymerase chain reaction (RT-PCR) remains the gold standard for the diagnosis of COVID-19. Rapid tests are substantially faster (results are available within minutes) and less costly than RT-PCR, so such a test would be preferred if its sensitivity and specificity was similar to the gold standard [16,17].

Antiviral treatment of mild COVID-19

A primary care focused strategy designed to identify cases early and offer antiviral treatment has received considerable attention in the past few weeks. However, antiviral treatment may only alter the course of the disease when it is initiated shortly after exposure, at the onset of symptoms or even during the incubation period. Initiation once severe disease with desaturation develops may be considerably less effective. While there is no definitive evi-

Table 1. Mortality of patients on mechanical ventilation for COVID-19 and related coronavirus associated diseases.

Author, year, journal, disease	Deaths/total number of patients on mechanical ventiation	Mortality for mechically ventilated patients
Zhou, 2020, Lancet, COVID-19	32/33	97%
Yang, 2020, Lancet Resp Med, COVID-19	30/37	81%
Arabi, 2017, Crit Care Med, MERS	204/281	73%
Lew, 2003, JAMA, SARS	24/39	61.5%

dence that any drug actually attenuates the complications of the disease or reduces transmissibility, it may not matter if the regimen recommended for universal treatment is well tolerated. A number needed to treat (NNT) of 5 or even 10, while unacceptable for ICU care or surgical procedures, would exceed all expectations of efficacy in the context of primary care. The combination of hydroxychloroquine and azithromycin which is available and affordable throughout the world has been recommended for outpatient treatment, with interferon, remdesivir (a drug not currently available outside of clinical trials) and either anakinra (an interleukin-1 antagonist) or tocilizumab (an interleukin-6 antagonist) potentially being reserved for inpatients enrolled in clinical trials [18]. Aside from the randomized trials that are underway, the combination of hydroxychloroquine and azithromycin is also supported by an open label study that was recently published, but the small sample size and methodological flaws in the study preclude its consideration as high level evidence [19]. Lopinavir/ritonavir, a combination of protease inhibitors for the treatment of (human immunodeficiency virus) HIV was initially used in the treatment of COVID-19 but will likely fall into disfavour due to the negative results from a randomized trial [20]. Other drugs which have received attention for the treatment or prophylaxis of COVID-19 include mefloquine (an antimalarial drug), colchicine (an anti-inflammatory compound used for gout and pericarditis) and ivermectin (an antiparasitic) [21]. While there is no evidence that these drugs are clinically useful for the treatment of COVID-19, their toxicity profile and the risks associated with their use are clear.

Ensuring that these drugs are readily available and offered to all who may benefit is definitely less costly than opening new ICUs or mandating lockdown for entire countries, and steps are being taken in that direction throughout the world, both to ensure the supply of drugs and to publish guidelines regarding their use in COVID-19, even in the absence of strong evidence. Such an approach does however pose risks as the drugs currently used for COVID-19 treatment do not have a safety profile that would justify prophylactic use in asymptomatic individuals; in fact, they may not even be acceptable for use in mild cases, given the self-limiting natural course of the disease. Chloroquine and its derivative hydroxychloroquine have an extremely narrow therapeutic index, with overdose being characterised by life-threatening cardiac conduction abnormalities and electrolyte disorders which can prove fatal even with prompt management in the ICU [22]. The risk of fatal arrhythmias may be increased when co-administered with azithromycin as both drugs prolong the QT interval. Mefloquine has been associated with severe neuropsychiatric adverse effects which may persist even after discontinuation of treatmen t[23], colchicine may cause gastrointestinal adverse effects and electrolyte disturbances at therapeutic doses, whereas toxicity manifests as multi-organ dysfunction [24] and ivermectin acts a positive allosteric modulator of gamma-aminobutyric acid-A (GABA-A) receptors (similar to barbiturates) and is prone to accumulation in the brain following prolonged use or p-glycoprotein dysfunction [25,26] (Table 2).

Conclusions

The treatment of mild cases of COVID-19 is controversial due to the unproven efficacy and concerns regarding the safety of the drugs which could be used. The use of effective antiviral drugs to limit disease complications and transmissibility is probably the best approach at this stage of the pandemic, but the drugs currently being recommended may cause more harm than the disease itself, especially in outpatients with mild disease. At present a great number of clinical trials to investigate the potential efficacy therapies for COVID-19 are being conducted, highlighting the urgent need for an effective treatment and safe treatment backed by high quality evidence [19]. Public perception that the disease is currently incurable puts immense pressure on physicians to utilize experimental pharmacotherapy to ensure the best outcomes for patients and demonstrate that COVID-19 can be effectively managed. However, if the experimental treatments utilized outside of a clinical trial setting are associated with excess morbidity and mortality, the public will regard all healthcare providers with greater scepticism and there will be considerable backlash against all entities (individuals, corporations and public institutions) that advocated in favour of this approach. Drug repurposing efforts at this point should perhaps focus on screening

Table 2. Safety profile of drugs which may be recommended for the treatment of COVID-19 in outpatients.

Drug	Propensity for drug interactions	Clinical manifestations of toxicity	Lethal in overdose
Azithromycin	Increased risk of arrythmia when co-administered with other drugs which prolong QT interval	GI disturbances, QT prolongation	No
Chloroquine/hydroxychloroquine	Increased risk of arrythmia when co-administered with other drugs which prolong QT interval. Metabolism by CYP3A4, CYP2D6	Arrhythmias, electrolyte disturbances, altered mental status, seizures. Similar to the tricyclic antidepressant toxidrome but without anticholinergic effects	Yes
Lopinavir-Ritonavir, Darunavir-cobisistat	Strong inhibition of CYP3A4	GI disturbances, lipodystrophy in chronic use	No
Colchicine	Toxic concentrations may be attained when coadministered with CYP3A4 inhibitors, P glycoprotein inhibitors. Contraindicated in renal failure	Diarrhea and electrolyte disturbances at commonly used dose; multi-organ dysfunction and death in overdose	Yes
Mefloquine	QT prolongation, arrythmogenic similar to other quinoline drugs	Severe and potentially irreversible neuropsychiatric adverse effects	Unknown
Ivermectin	Toxic concentrations may be attained when coadministered with CYP3A4 inhibitors, P glycoprotein inhibitors	Central nerous system depression	Unknown

only compounds with an established safety profile, low risk for adverse events and minimal toxicity in overdose for activity against COVID-19. As both resources and time are in short supply, the individuals responsible for public health policy will have to decide how best to allocate both to manage this crisis; at the moment however, there is no hard evidence upon which to base such a decision. One could assert that we are all flying blind.

References

1. Casagranda I, Coen D, Paolillo C, et al. Changing Emergency Department and hospital organization in response to a changing epidemic. Emerg Care J 2020;16:8969. doi: 10.4081/ecj.2020.8969.
2. Comelli I, Scioscioli F, Cervellin G. Impact of the COVID-19 epidemic on census, organization and activity of a large urban Emergency Department. Acta Biomedica doi: https://doi.org/10.23750/abm.v91i2.9565
3. Mirco N, Andrea C, Angelo G, et al. At the epicenter of the Covid-19 pandemic and humanitarian crises in Italy: Changing perspectives on preparation and mitigation. Catalyst 2020. doi: 10.1056/CAT.20.0080
4. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788-800.
5. Guan W, Ni Z, Hu Y, et a.l Clinical Characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. doi: 10.1056/NEJMoa2002032
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020. doi: 10.1016/S0140-6736(20)30566-3.
7. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.
8. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020;24:154.
9. Gattinoni L, Coppola S, Cressoni M, et al. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020. doi: 10.1164/rccm.202003-0817LE.
10. Stream S, Nolan A, Kwon S, Constable C. Factors associated with combined do-not-resuscitate and do-not-intubate orders: A retrospective chart review at an urban tertiary care center. Resuscitation 2018;130:1–5.
11. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160:3 89-97.
12. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003;289:2801-9.
13. Zareifopoulos N, Lagadinou M, Karela A, et al. Intubation and mechanical ventilation of patients with COVID-19: what should we tell them? Monaldi Arch Chest Dis 2020;90:1296. doi: 10.4081/monaldi.2020.1296
14. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of respiratory viral infections. Annu Rev Virol 2020. doi: 10.1146/annurev-virology-012420-022445
15. Ioannidis JPA. Coronavirus disease 2019: the harms of exaggerated information and non-evidence-based measures. Eur J Clin Invest 2020;50:e13222.
16. Abbasi J. The promise and peril of antibody testing for COVID-19. JAMA 2020. doi: 10.1001/jama.2020.6170.
17. Lippi G, Mattiuzzi C, Bovo C, Plebani M. Current laboratory diagnostics of coronavirus disease 2019 (COVID-19). Acta Biomedica 2020. doi: 10.23750/abm.v91i2.9548
18. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
19. Gautret P, Lagier J-C, Parola P, et a. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print].
20. Cao B, Wang Y, Wen D, et al. A Trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020. doi: 10.1056/NEJMoa2001282
21. Fan H-H, Wang L-Q, Liu W-L, et al. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus (2019-nCoV) related coronavirus model. Chin Med J (Engl) 2020. doi: 10.1097/CM9.0000000000000797.
22. Clemessy J-L, Taboulet P, Hoffman JR, et al. Treatment of acute chloroquine poisoning: A 5-year experience. Crit Care Med 1996;24:1189-95.
23. Nevin RL, Leoutsakos J-M. Identification of a syndrome class of neuropsychiatric adverse reactions to mefloquine from latent class modeling of FDA Adverse Event Reporting System Data. Drugs R D 2017;17:199-210.
24. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila) 2010;48:407-14.
25. Chandler RE. Serious neurological adverse events after ivermectin-do they occur beyond the indication of onchocerciasis? Am J Trop Med Hyg 2018;98:382-8.
26. Menez C, Sutra J-F, Prichard R, Lespine A. Relative neurotoxicity of ivermectin and moxidectin in Mdr1ab (-/-) mice and effects on mammalian GABA(A) channel activity. PLoS Negl Trop Dis 2012;6:e1883.