

Use of specific antimicrobials for COVID-19: Should we prescribe them now or wait for more evidence?

As the number of Coronavirus disease 2019 (COVID-19) cases worldwide rises exponentially, clinicians and healthcare systems are faced with a difficult dilemma. Should they focus on supportive care and wait for the results of clinical trials or join other clinicians who are already prescribing specific antimicrobials which may be active against the virus?

COVID-19 was initially identified as the cause of an outbreak of infection in Wuhan, China at the end of December 2019. Since then, the virus has spread rapidly to most countries in the world and resulted in over a million infections and 50,000 deaths as of the 3rd of April 2020.¹ Most patients with mild disease recover within 1-2 weeks, whilst patients with severe disease may require 3-6 weeks.² Eighty percent of patients have mild infection (often symptoms of an upper respiratory tract infection), 15% developed severe illness, and 5% required critical care admissions for organ support.³ Mortality is currently estimated to be 1-3%.¹ Older patients (> 80 years old) and patients with comorbidity such as respiratory disease, diabetes, stroke, cardiac disease and cancer are more likely to die from the illness.² Mortality for a patient admitted to critical care is estimated to be about 50% however this may be dependent on access to and quality of critical care services. So far, no vaccine or drug has been approved to treat human coronaviruses including COVID-19. In addition, there is no validated clinical tool or test to predict patients who are likely to develop complications.

There are currently multiple ongoing trials of specific antimicrobials for treatment and prevention of COVID-19. The most common agents proposed are chloroquine, ritonavir boosted lopinavir, ribavirin, favipravir, remdesivir, interferon, nitazoxanide. These agents have been proposed as specific therapy for COVID-19 based on previous in vitro evidence of activity against Middle East Coronavirus and recent evidence of in vitro activity against COVID-19.^{4,5} In support of their use, there have been case reports and observational studies of patients treated with these therapies who have improved and survived. In addition, a small sized controlled trial from France suggested significant improvements in viral load in patients treated with hydroxychloroquine and Azithromycin compared to supportive care. We eagerly wait to see whether other large trials will validate the results from the French study. Interestingly, despite suggestions of good invitro activity a recently published trial of use of ritonavir boosted lopinavir in patients from China did not show in improvement in outcomes. This highlights the importance of doing and waiting for results of well conducted clinical trials before widespread use of these agents.

Anecdotal and uncontrolled data have suggested that early treatment with specific antimicrobials may reduce the risk of patients developing severe complications. This has prompted empirical use these drugs outside of clinical trials in the hope of preventing patients from developing critical illness – eg use of hydroxychloroquine or chloroquine as pre-exposure prophylaxis for at-risk contacts or healthcare workers. The desire to 'do something' for patients and colleagues is entirely understandable in the current pandemic, where conventional treatments have seemed so powerless. Moreover, some argue that drugs such as chloroquine have been used to treat infections such as malaria and HIV for many years with minimal safety concerns. All these reasons may encourage clinicians to prescribe these antimicrobials without restrictions.

We know that supportive therapy is currently recommended as the mainstay of treatment for COVID19. Epidemiological data suggests low mortality rates when high quality supportive care is provided for patients with COVID-19.² Justifying use of experimental treatments outside of clinical trials for the majority of patients who have mild disease or no symptoms seems to us overly aggressive,

especially if they are given at high doses which may increase the risk of serious side effects such as hepatotoxicity and cardiotoxicity. Patients with multiple morbidities are also at increased risk of drug interactions.

There is currently no specific approved treatment for COVID-19, nor are there large well conducted trials suggesting improvement in outcomes when treated with anti-infective agents. Therefore, the mainstay of treatment is supportive. Experimental therapies are being investigated as part of clinical trials. We believe that the widespread use of unproven drugs in desperation to vulnerable individuals may cause harm and discourage patients and healthcare providers from participating in clinical trials. Without a control group to compare, it is impossible to know whether use of these drugs helps or causes harm. We therefore strongly recommended that novel or repurposed use of these is only done on compassionate grounds or as part of an ethically approved clinical trial such as the WHO Solidarity trial. Despite the pressure to do all possible to save lives during the COVID-19 pandemic, we recommend that clinicians and especially Infectious Disease Physicians and clinical pharmacists should continue to promote and champion antimicrobial stewardship.

References

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² Huang C. L., Wang Y, Li X, et al; Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China - The Lancet 395.10223 (2020): 497-506.

³ Wu Z, McGoogan J. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. [Publish Online Ahead of Print February 24, 2020] JAMA.2020 <https://doi.org/doi:10.1001/jama.2020.2648>

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⁵ Wang M, Cao R, Zhanget L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020 Feb 4. Available at <https://www.nature.com/articles/s41422-020-0282-0>. Accessed March 14, 2020.