

**Title: SARS-CoV-2 : First do no harm.**

Grant W. Waterer

MBBS PhD

University of Western Australia and Northwestern University, Chicago

[grant.waterer@uwa.edu.au](mailto:grant.waterer@uwa.edu.au)

Jordi Rello

MD PhD

Centro de Investigación Biomedica en Red (CIBERES), Instituto de Salud Carlos III, Madrid, España

Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain

Clinical Research, CHU Nîmes, Université Montpellier-Nîmes, Nîmes, France

Richard G. Wunderink

MD

Northwestern University Feinberg School of Medicine, Chicago

Word count: 1137

Editorial on Blue-202002-0445OC and Blue-202003-0543OC

Key words: SARS, Covid-19, ARDS, Pneumonia, RCT, Precision medicine, Coronavirus, therapy

In his book “Of the Epidemics” Hippocrates advises physicians that they must “have two special objects in view with regard to disease, namely, to do good or to do no harm”.(1) Facing the challenge of the SARS-COVID-19 pandemic, this advice remains as pertinent now as it was over 2400 years ago. In response to the 1919 Spanish flu pandemic, physicians in desperation turned to the antimalarial quinine.(2) It is disappointing that one hundred years later, despite the emphasis on evidence-based medicine, the same strategy was adopted due to the highly emotional need to treat patients with “something”.

Faced with a new disease, numbers of patients that have in many cases vastly overwhelmed healthcare resources, and no available effective treatment, an extraordinary array of experimental therapies have been given to critically ill patients, often in combination.

Whether this approach has harmed more patients than it has helped remains to be seen.

Desperate times are felt to justify desperate measures. However, the case series of Du et al(3) in this issue demonstrates that access to basic critical care support, not experimental therapies, is the most important determinant of the high mortality reported in some SARS-CoV-2 series. Despite acute respiratory distress syndrome in 74% and shock in 81%, only 21% of cases received invasive mechanical ventilation.

Many physicians across the world are recommending treatments even while researchers and regulators claim that the evidence of benefit is limited, and therapies should be tested in a randomised, controlled trial. These physicians believe that the chance of potential benefit outweighs the chance of harm. However, safety concerns may be significantly underestimated since most of these drugs have never been properly studied in critically ill patients. For example, many of the experimental therapies used are potentially cardiotoxic, including hydroxychloroquine, ritonavir, lopinavir, interferon alpha-2-beta, azithromycin and methylprednisolone. As myocarditis is reported as a potential complication of SARS-CoV-2, if all these agents are used in combination, is it a surprise that very high rates of cardiac

complications such as the 60% incidence of arrhythmia reported in the case series from Du et al(3) in this issue and by others?(4) Interferons are generally pro-inflammatory and may be deleterious in patients with hyperinflammation with high plasma interleukin 6 (IL-6). Anti-IL-6 monoclonal antibodies have been associated with cytomegalovirus re-activation, episodes of bacterial septic shock and bowel perforation, particularly when combined with high dose corticosteroids.(5, 6) Many of these experimental agents have pharmacologic interactions with a large list of drugs commonly used in critical care, hampering overall management and increasing the risk of toxicity. High-dose steroids, associated with superinfections like invasive pulmonary aspergillosis and increased mortality in influenza pneumonia(7) and worse outcomes in the 2009 influenza A pandemic,(8) were used in 75% of fatal cases in the series by Du et al,(3) and 74% of critical cases in the multi-center study of Feng et al.(9) Like hydroxychloroquine, high dose corticosteroids may be associated with delirium, agitation and psychosis that often is complicating the weaning of SARS-CoV-2 intubated patients. Patients and their families have a clear right to being informed of the risks of all these experimental therapies so they can provide informed consent for compassionate use. That this is routinely occurring seems unlikely.

Treating all patients with the same therapy regardless of stage of disease or clinical phenotype is also perilous and properly conducted trials are necessary to select patient characteristics associated with a beneficial response. It is very clear that patients are presenting with different clinical phenotypes causing respiratory failure,(10) both with and without evidence of “cytokine storm”.(11) It would clearly be unreasonable to expect patients with such different phenotypes to respond similarly to the same experimental interventions. The recent report on compassionate use of remdesivir among 53 patients with severe SARS-CoV-2 showed an improvement in oxygen support in 36 (68%) whereas 8 (15%) showed worsening; Clinical improvement was less frequent among intubated patients

(hazard ratio of 0.33) and patients older than 70 years (hazard ratio of 0.29).(12) With serious adverse events reported in 23%,(12) personalized therapy is clearly going to be required.

Another serious problem with routine use of unproven agents for SARS-CoV-2 is that clinical equipoise is lost and an experimental agent becomes *de facto* standard of care, potentially seriously compromising the ability to do placebo controlled trials. Inability to complete a controlled trial because of loss of clinical equipoise is a two-edged sword. Even if the intervention has true benefit it is unlikely detractors will be convinced and lives will be lost because the treatment is still not given. If the intervention has adverse effects not revealed because of the absence of a placebo arm then lives may be lost because it continues to be used. If experimental agents are given in combination, attribution of effects, both beneficial and adverse, to one of them becomes nearly impossible, given the significant variability in critical care outcomes as a baseline.

Unquestionably, much of the pathogenesis and optimal therapy of SARS-CoV-2 remains unknown, but we strongly believe that it is critically important that when faced with uncertainty clinicians stick to standards of care that are proven and robust. The SARS-CoV-2 pandemic is an opportunity to learn how to treat patients and test therapies at the same time.(13) Trials of experimental therapies are certainly justified, but only in properly conducted, randomized controlled trials where their risks and benefits can be accurately assessed, and certainly not in untried combinations which greatly increase the risk of harm.

Concerns that results from conventional trials can take years is proving false with hundreds of patients enrolled within six weeks in at least two SARS-CoV-2 specific clinical trials.

Adaptive multicentre trials with interim analyses have the ability to determine if an intervention is superior to placebo, adjust the standard of care and move on to test new

therapies in rapid succession. Once a new intervention has become standard of care, it can be tested against alternatives or combinations of drugs. For sites that don't have the capacity to generate local trials, participation in platform trials like REMAP-CAP(14) should be encouraged.

In summary, we believe that the widespread use of clearly experimental therapies being reported in patients with SARS-CoV-2 is dangerous and unjustified. There is a real risk that mortality rates are higher than they need to be because of toxic, ineffective therapy.

Clinicians must not succumb to the impulse to “do something else” but instead stick to evidence-based therapies and if possible, enrol their patients into adaptive clinical trials.

SARS-CoV-2 is likely to be a problem for years and we need to develop precision approaches based on high quality clinical data as fast as we can. Equally, and unfortunately, SARS-CoV-2 will not be the last serious viral pneumonia epidemic humanity faces and only by having a scientific approach this time can we avoid going back to 1919 era desperation treatments the next time we are faced with this challenge.

1. Adams F. The genuine works of Hippocrates. The Sydenham Society, London.; 1849.
2. Shors T, McFadden SH. 1918 influenza: a Winnebago County, Wisconsin perspective. *Clin Med Res* 2009; 7: 147-156.
3. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P, Li T, Cao F, Chang C, Hu Q, Jin Y, Xu G. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. *Am J Respir Crit Care Med* 2020.
4. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in Covid-19 patients. *J Cardiovasc Electrophysiol* 2020.
5. Ogata A, Kato Y, Higa S, Yoshizaki K. IL-6 inhibitor for the treatment of rheumatoid arthritis: A comprehensive review. *Mod Rheumatol* 2019; 29: 258-267.

6. Komura T, Ohta H, Nakai R, Seishima J, Yamato M, Miyazawa M, Kaji K, Marukawa Y, Kagaya T, Kitagawa K, Kawashima A, Kaneko S, Unoura M. Cytomegalovirus Reactivation Induced Acute Hepatitis and Gastric Erosions in a Patient with Rheumatoid Arthritis under Treatment with an Anti-IL-6 Receptor Antibody, Tocilizumab. *Intern Med* 2016; 55: 1923-1927.
7. Moreno G, Rodriguez A, Reyes LF, Gomez J, Sole-Violan J, Diaz E, Bodi M, Trefler S, Guardiola J, Yebenes JC, Soriano A, Garnacho-Montero J, Socias L, Del Valle Ortiz M, Correig E, Marin-Corral J, Vallverdu-Vidal M, Restrepo MI, Torres A, Martin-Loeches I, Group GS. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med* 2018; 44: 1470-1482.
8. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019; 23: 99.
9. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, Xiong W, Yang D, Chen R, Lu F, Lu Y, Liu X, Chen Y, Li X, Li Y, Summah HD, Lin H, Yan J, Zhou M, Lu H, Qu J. COVID-19 with Different Severity: A Multi-center Study of Clinical Features. *Am J Respir Crit Care Med* 2020.
10. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2020.
11. Ye Q, Wang B, Mao J. Cytokine Storm in COVID-19 and Treatment. *J Infect* 2020.
12. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E, Oda R, Yo K, Quiros-Roldan E, Studemeister A, Redinski J, Ahmed S, Bernett J, Chelliah D, Chen D, Chihara S, Cohen SH, Cunningham J, D'Arminio Monforte A, Ismail S, Kato H, Lapadula G, L'Her E, Maeno T, Majumder S, Massari M, Mora-Rillo M, Mutoh Y, Nguyen D, Verweij E, Zoufaly A, Osinusi AO, DeZure A, Zhao Y, Zhong L, Chokkalingam A, Elboudwarej E, Telep L, Timbs L, Henne I, Sellers S, Cao H, Tan SK, Winterbourne L, Desai P, Mera R, Gaggar A, Myers RP, Brainard DM, Childs R, Flanigan T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med* 2020.
13. Angus DC. Optimizing the Trade-off Between Learning and Doing in a Pandemic. *JAMA* 2020.
14. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, Bhimani Z, Bonten M, Broglio K, Brunkhorst F, Cheng AC, Chiche JD, De Jong M, Detry M, Goossens H, Gordon

A, Green C, Higgins AM, Hullegie SJ, Kruger P, Lamontagne F, Litton E, Marshall J, McGlothlin A, McGuinness S, Mouncey P, Murthy S, Nichol A, O'Neill GK, Parke R, Parker J, Rohde G, Rowan K, Turner A, Young P, Derde L, McArthur C, Webb SA. The Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) Study: Rationale and Design. *Ann Am Thorac Soc* 2020.