Choosing Among Unproven Therapies for the Treatment of Life-Threatening COVID-19 Infection: A Clinician's Opinion from the Bedside

Robert A. Raschke, MD

HonorHealth Scottsdale Osborn Medical Center
Scottsdale, AZ USA

We are clearly in unprecedented times. As clinicians watch patients die from COVID-19 infection in the ICU, many feel they cannot wait for clinical trials to prove that various proposed therapies are efficacious. Treatments for which *any* rationale suggest the possibility of benefit are being administered to patients and the literature abounds with reports of case series or poorly-designed observational trials in which small numbers of patients seem to have favorable outcomes when given these unproven therapies (1). In many cases, these reports are made globally available via social networking without the benefit of peer-review or are being published despite severe methodological flaws that would not have been acceptable prior to the COVID-19 outbreak.

Standard therapy for COVID-19 has recently been published by the Surviving Sepsis Campaign, which have taken a conservative, evidence-based approach (2). But many clinicians are not able to maintain such equipoise in the face of catastrophe. Therefore, I propose an approach to consideration of bedside implementation of *unproven* therapies for life-threatening COVID-19 for comment and criticism. None of the therapies discussed below have even marginally-acceptable empirical evidence of clinical benefit in patients with COVID-19, so let us put critical appraisal of the literature aside for the moment, and accept that we cannot evaluate these therapies using the normal rules of evidence-based practice (3), application of which would exclude all from further consideration were this any other disease than COVID-19.

I will focus on four unproven therapies that are currently being given to patients with COVID-19 infection: hydroxychloroquine (4), tissue plasminogen activator (tPA) and heparin for presumed pulmonary microthrombosis (5), immunosuppressive treatment of "cytokine storm" (6), and transfusion of convalescent serum (7).

I based my opinions on these four unproven therapies on the following principles:

1. COVID-19 is a viral pneumonia. Although it may prove to have some distinctive features, it is likely to be similar to other viral pneumonias (such as SARS CoV-1, MERS, and H1N1 influenza) in terms of its clinical manifestations and response to therapy. We are more likely to gain helpful insights by looking at previous clinical data related to viral pneumonia than to data regarding various noninfectious entities such as high-altitude pulmonary edema or pulmonary venous occlusive disease, as some authors have suggested. COVID-19 viral pneumonia is unlikely, a priori, to respond to therapies that have never shown *clinical* benefit in the treatment of other viruses, particularly viral pneumonias.

2. Demonstration of *in-vitro* activity rarely translates into clinical efficacy (8,9). *In-vitro* activity should be a basis for clinical trials, not bedside implementation.
3. If unproven therapies are to be given, their safety must be an important consideration. First do no harm.
4. We should be willing to apply any treatment recommendation we make for patients to ourselves or beloved family members.

Based on these principles, I propose the following:

Hydroxychloroquine. The non-specific anti-viral properties of chloroquine and hydroxychloroquine were demonstrated in cell cultures 40 years ago. Although active *in vitro* against Dengue, HIV, Ebola, Influenza and other viruses, this has never convincingly translated into clinical effectiveness (9). A large cohort study focusing on prevention of influenza pneumonia included over 4000 patients receiving HCQ, and showed that they had an *increased* risk of hospitalization for pneumonia compared to controls (10). Given this long track record, it seems unlikely that hydroxychloroquine will suddenly be found to have clinical anti-viral benefit in 2020. When it is nevertheless given, care should be exercised to monitor QTc, especially if used in conjunction with other QTc-prolonging drugs like azithromycin and/or in patients with cardiomyopathy.

tPA and heparin. A high incidence of venous thromboembolism has been observed in some cohorts of COVID-19 patients, as has previously been described in patients with H1N1 pneumonia (11). Standard thromboprophylaxis should be employed and venous thromboembolism should be diagnosed and treated in patients with COVID-19 infection. However, some clinicians are administering tPA and therapeutic-dose heparin to patients with COVID-19 and elevated D-dimer *in the absence* of documented DVT or PE, based on the theory that these patients have microvascular thrombosis requiring treatment. Several large multicenter RCTs examined the use of human activated protein C (Xigris®) to prevent/treat microvascular thrombosis in patients with severe sepsis and convincingly demonstrated no clinical benefit (12). There is no other infectious disease for which the use of tPA or treatment-dose heparin has been proven to be clinically beneficial in the absence of standard indications related to documented venous thromboembolism. Lytic/antithrombotic therapy has a relatively high potential for causing life-threatening hemorrhage. In my opinion, it should not be employed without support from well-designed clinical trials.

Cytokine Storm or HLH. The terms cytokine storm and hemophagocytic lymphohistiocytosis (HLH) have been used to describe similar (perhaps identical) maladaptive immune responses to viral infections. HLH has been well-described in H1N1 pneumonia, SARS-CoV-1 and MERS. There is a rich history of (mostly) observational clinical research supporting the use of immunosuppressive therapies including steroids, anakinra and tocilizumab to treat HLH secondary to viral infection (13). Although immunosuppression can be associated with life-threatening secondary opportunistic infections, treating secondary HLH in selected patients is an approach with

a long track record and could be considered standard therapy in Covid19 patients fulfilling HLH diagnostic criteria.

Convalescent Serum. The use of convalescent serum is supported by low-quality observational data going back over 100 years. Although never proven effective in well-designed clinical trials, prior reports in patients with Spanish influenza, SARS-CoV-1 and H1N1 all suggest potentially significant reductions in mortality with acceptable safety (14-16). This therapy is more difficult to operationalize, requiring (expedited) FDA approval, collection, processing and testing of neutralizing antibody titers by a licensed blood bank (17), however based on the principles outlined above, its benefit/harm ratio seems to support its use as an investigational therapy in patients with life-threatening COVID-19.

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