Response to the WHO recommendation on convalescent plasma use in Covid-19 from the National CCPP19 Convalescent Plasma Project Leadership Team

On December 6, the World Health Organization (WHO) updated its recommendations on COVID-19 management and recommended against the use of COVID-19 convalescent plasma (CCP) in treating any stage of COVID-19 disease. This recommendation was based on an analysis of aggregated randomized trial (RCT) data that, in the view of the WHO, did not show clear clinical benefits of CCP, although the recommendations did acknowledge evidence that CCP was effective in reducing the viral load in treated patients.

As a mechanical and largely statistical exercise in which the results of all RCTs are simply tabulated and summarized, the WHO analysis is exemplary. But as a scientific examination and assessment of these RCTs, an exercise that requires digging below the surface to ask critical questions, the WHO recommendations are seriously wanting. Most importantly, the WHO recommendation ignores patient groups who may derive substantial benefit from CCP.

In every RCT, the first issue to address is whether the core hypothesis motivating the RCT was in fact appropriately tested. Had the WHO dug deeper into the RCTs it would have discovered that most RCTs did not test CCP appropriately. Decades of experience have shown conclusively that for convalescent plasma to work, it must be provided early in the course of illness and with sufficient antibody content, , a principle that is supported by robust biological evidence and animal models (1).

Had the WHO dug deeper into the RCTs it would have noted that nearly all RCTs were conducted in heterogenous hospitalized patient populations, often including patients who had already progressed from the viral to the inflammatory phase of COVID-19, manifested by prolonged duration of symptoms and/or a requirement for invasive oxygen supplementation. Had the WHO dug deeper into the RCTs, it also would have noted that some RCTs used CCP with an insufficient amount of antibody.

Unfortunately, many CCP RCTs did not, and by virtue of their study designs could not, test the hypothesis that CCP works if provided early and in a sufficient dose. Given the catastrophic conditions caused by a global pandemic, the drive to focus treatments on the sickest of hospitalized patients was understandable, but it has been known for decades that most such patients do not benefit from convalescent plasma.

The WHO chose to ignore multiple signals of CCP efficacy found in subgroups of patients in the RCTs who were treated early or in less severe stages of illness and received high titer CCP (2). The WHO chose to ignore multiple observational studies, some much larger than any published randomized RCT (3), in which careful propensity matching was employed, and CCP efficacy was demonstrated (4, 5). The WHO chose to ignore studies that showed the particular value of CCP in immunosuppressed patients (6,7).

The WHO chose to ignore a carefully conducted randomized RCT of CCP from Argentina, conducted in elderly outpatients shortly after their diagnosis, that reduced progression of disease by half (8). This finding has just now been replicated in another out-patient RCT in the United States (Sullivan et al), although we recognize that this finding was not available to the WHO on December 6.

A most unfortunate consequence of the WHO recommendation on CCP is that it discourages use of CCP, including in low and middle-income countries (LMIC), where it may be the only antiviral available. In comparison to all other drug or in-patient therapies, CCP is safe, relatively inexpensive and widely available, well worth the investment in making it accessible in resource-limited settings. In addition, convalescent plasma is the only treatment that can be employed rapidly in any new epidemic situation as soon as there are survivors. Its success in this setting for COVID-19 has recently been demonstrated in

a large RCT (9). We urge the WHO to revisit its recommendation on CCP by reviewing the totality and consistency of the evidence supporting its benefit, taking account of the pandemic conditions and the features of RCT design that affected the findings of most large RCTs. The first step should be to examine in detail the RCTs that replicated the circumstances under which convalescent plasma has worked effectively in the past. This means focusing on RCTs that administered high titer CCP early in the disease course. Such trials are consistent with both the historical use of convalescent serum and the contemporary employment of monoclonal antibodies in COVID-19. They are the most appropriate RCTs upon which any recommendation for CCP use should be based.

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