Reflections on Progress at the Dog Days of Summer in the year 1 of Covid-19

C Nicodemus 16 August 2020

Despite the politics and disagreements, much has been learned about Covid since its February-March arrival in North America. I encourage readers to look at my earlier posts for context.

Progress has been made with breath taking speed on most fronts. Vaccines are rapidly progressing into advanced clinical study, diagnostic tests to confirm infection and confirm prior infection are established and the infectiousness of the organism now fully appreciated. Institution of social distancing has been demonstrated to break episodes of exponential spread, but opening up safeguards also prone to reignite the spread of disease. Several agents have been found to benefit patients with severe disease, but not surprisingly reversing SARS covid remains difficult and unsatisfactory.

Both corticosteroid treatment and early administration of beta interferon in the treatment of severe covid have demonstrated benefit, and the use of chloroquine to prevent symptomatic infection or to improve outcomes in patients suffering SARS has been demonstrated ineffective. Many additional studies are ongoing. Resistance to the concept of a community actionable intervention study which I called for back in March has been driven by the difficulty in accurately selecting a suitable population and uncertainty what the true denominator of case definition of disease ought to be. For many individuals the natural course of infection is asymptomatic or mild. It is only a small minority that progress to severe disease. Therefore, my call for community actionable intervention studies to seek a simple way to avoid dysregulated immunity leading to SARS is believed to require very large numbers of study subjects making the approach impractical. The recent reports from Bulware, et. al. in *New England Journal of Medicine*, and Skipper et. al. in *Annals of Internal Medicine* looking at different aspect of chloroquine intervention illustrate the challenge Thousands of patients with known exposure to the virus are needed to attempt a definitive early intervention study as the natural history of disease evolution is inconsistent.

The impression I have voiced that severe covid is a form of dysregulated immune response is a concept that now has increasingly strong support. Patients developing severe covid have a relative deficiency in their type I Interferon response profile as reported by Blanco-Melo and colleagues in Cell in May. Interestingly, a deficient IFN response pattern is also associated with the post covid pattern of chronic fatigue that has emerged this summer at significant incidence. The syndrome closely resembles Myalgic Encephalopathy which is also characterized by a hyporesponsive type I interferon pattern. These disorders of immunity may be systemic or perhaps local and organ specific. Signs and symptoms of either the SARS covid pattern or the Chronic Fatigue pattern would appear to be the by-product of the local and disseminated immune response patterns on an organ specific basis.

I remain as concerned now as in April about the pandemic and our global response to the crisis. With the northern hemisphere once again turning to indoor activities in the coming months the infectivity of the virus will increase in northern latitudes and risk for further for exponential spread expanded.

The observation that Clients at the Pine Street Inn homeless center in Boston experienced a low rate of clinical disease but a high prevalence of infection is both unexpected and important in considering the nature of immune regulation. More than 400 individuals spend their days on the street but return to crowed sleeping quarters at Pine Street for the overnight. It has been suggested that sun exposure and Vitamin D may be the protective factor. Similar patterns have been reported in other homeless populations, and whether vitamin D is the protective factor remains to be proven, but the outdoor environment may be protective via vitamin D or perhaps a less well defined immune stabilizing effect of sun exposure to the body.

Actionable Interventions: The objections to a community actionable intervention model are tied to the difficulty establishing index cases and a desire for definitive statistical demonstration of marginal treatment effects in a population that may have very heterogeneous natural outcomes. I believe the need remains urgent, but suggest the name, "Community Actionable Intervention *Screening* Study" (CAI*S*S) may be preferred. The actionable intervention must be a widely available remedy already distributed to regional pharmacies. The anticipated immune modulatory activity may or may not be widely recognized, but candidate interventions must have established and acceptable toxicity profiles. It must be appreciated that schedule and dose may be as important as the choice of agent itself. Failure of a candidate agent may result in rejection, however consideration for adjustment of dosing parameters and schedule relative to onset of disease should also be considered before drawing definitive conlusions.

Interventions that modify the character of a host response to infection may be disease aggravating or disease ameliorating. For community and the economic consequence of lock down, for an intervention to be meaningful a useful intervention cannot have a subtle benefit. Likewise, it absolutely should not be disease aggravating. Therefore, the screening of possible alternative interventions can proceed in small initial groups as long as the incidence of progression to severe disease is sufficient. Since random chance might yield provocative outcomes in small studies with low incidence of severe disease, replication of provocative outcome in duplicate community studies is more compelling than detection of a subtle effect in a larger study. If subtle effects are missed, they probably are not meaningful for community outcomes.

I had and still advocate for assessment of an early self-limited outpatient series of oral corticosteroids and a short course of oral antibiotic with known anti-inflammatory activity as potential approaches, but other commonly available approaches might also be considered. Since the successful approach is unknown, more important is the establishment of the scientific model that would enable such pilot clinical studies to be conducted rapidly in community settings using facilitated and simplified but robust components of institutional oversight and data management that do not require dedicated staff supervision or disrupt clinical practice.

A key to the approach is simplified patient selection criteria. Also, the data collection tool must be simple making the study possible to conduct as part of a routine triage clinic practice. Internet based studies that recruit patients who think they might have covid, suffer from dilution of actual disease. A CAISS study should seek patients presenting with acute symptoms within onset with 48 hours in known hotbeds of active disease and a history of potential exposure. A simple symptom score tool, presence of respiratory symptoms and fever should be recorded. Treatment should be provided immediately, prior to confirmatory lab results and patients testing negative for active infection included for safety assessment. Patients would receive a short (perhaps 3 to 5 day) intervention and record severe aggravation if it occurs, and symptoms at end of treatment and week 1 and 2 following treatment. Development of severe disease requiring hospitalization and mortality at month 1and 2 should be collected for all patients, but data gathering should be minimized. A simple tool using smart phone technology might supplement the primary data. Central management and data oversight collection could allow the study to simply happen at participatory primary care centers and if the alternative treatments were provided as simple outpatient kits, local pharmacy participation could be avoided or minimally disruptive.

If development of severe complications of infection was indeed a rare outcome of Covid-19, our society could get back to work and school while we await the emergence of a curative safe treatments.