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Wherever the art of medicine is loved, there is
also a love of humanity.
- Hippocrates

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Editorial

Statins in COVID-19 Era

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Several experts believe that statins are wonder drugs, similar to what aspirin used to be. Although originally approved for lowering blood cholesterol, over the years, statins were found to have a myriad other benefits that go beyond their lipid-lowering effect. Statins have many properties that condition our bodies to minimize the pathological effects of Coronaviruses. Let us dissect those and evaluate their value in the COVID-19 Era, which has just begun, and no one knows when it will effectively end.

Epidemiological data from 72,314 COVID-19 patients reported by Chinese Center for Disease Control and Prevention show that while the overall case-fatality rate (CFR) was 2.3%, the CFR was elevated among those with pre-existing comorbid conditions—10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer (1). Since CVD and diabetes are on the top of the list of comorbid conditions, these numbers call for a rigorous control of lipid abnormalities, as seen below. In the context of CVD, it should be noted that apart from the well-known effect of decreasing LDL cholesterol, statins also reduce the plasma ADP levels, and thus suppress platelet activation and thromboembolic episodes (2). An intriguing recent study that was posted on bioRxiv, a pre-print server jointly run by the Cold Spring Harbor Laboratory, BMJ and the Yale, on May 29, 2020 sheds more light on the relationship between cholesterol and COVID-19 lethality (3). Basically, the study shows that loading cells with cholesterol enhances the endocytic entry of pseudotyped SARS-CoV-2. The cholesterol concomitantly traffics angiotensin converting enzyme-2 (ACE2) to the viral entry site. Decreasing the cellular cholesterol has the opposite effect. The authors posit that as cholesterol content of tissues increases with age and inflammation, the cell surface of elderly people is coated with more viral entry points thus making them more susceptible to COVID-19 mortality (3). Statins reduce cholesterol synthesis in the liver, improve the HDL levels and reduce LDL cholesterol. These may protect against SARS-CoV-2 infection by scavenging tissue cholesterol, especially if combined with healthy dietary habits and losing weight.

Statins do not exhibit anti-viral properties in acute settings. However, epidemiological and clinical data suggest that statin use is associated with less severe viral pneumonia and influenza mortality (4-6). This may be related to the protective effect

on innate immunity. Toll-like receptors (TLRs) are sensors that recognize molecular patterns from viruses, bacteria and fungi to initiate immune responses to invading pathogens. It was shown that MyD88 (myeloid differentiation primary response 88), an adapter protein necessary for signaling by multiple TLRs, is a required component of the innate immune response to mouse-adapted SARS-CoV infection. Data from mice genetically deficient in different TLRs suggest that a balanced immune response operating through TLRs and MyD88-driven pathways likely provide the most effective host cell intrinsic antiviral defense responses to severe SARS-CoV disease (7). It is more interesting that statins are effective in stabilizing MyD88 during hypoxia. Based on this, it has been suggested that an early and high dose of a statin might be a good treatment strategy for MERS-CoV infection, as a deficiency in MyD88 expression resulted in high mortality rates after MERS-CoV infections (8). It is possible that a similar strategy may work in early stages of SARS-CoV-2 infection, although the efficacy of statins in later stages when the cytokine storm sets in is questionable.

Another interesting aspect of statins is their anti-inflammatory effect. Statins are known to reduce inflammatory markers, such as C-reactive protein, an independent risk factor in disease (9). Statins also modulate the immune system by inhibiting the rate-limiting enzyme of the L-mevalonate pathway. L-mevalonate pathway downstream products play critical roles in the different steps of an immune response, including immune cell activation, migration, cytokine production, immune metabolism and survival (10). The ability to inhibit protein prenylation through the mevalonate pathway enhances antigen presentation and adaptive immune responses. And so, it has been suggested that a new application for statins is vaccine adjuvants and in cancer immunotherapies (11). In fact, due to their anti-inflammatory and antioxidant properties, in combination with conventional psychotropic medications, statins have been proposed for use in various psychiatric disorders, including depression, schizophrenia, and dementia (12).

Take Home Message: Although statins may not act as antiviral agents in acute settings, their overall properties and effects may markedly improve the body's ability to prevent or counter SARS-CoV-2 infection and even reduce severity of the COVID-19 disease. Hence, regular intake of statins may be beneficial. In addition, cholesterol reducing diets and avoiding overweight and obesity will help us largely. Furthermore, considering the fact that COVID-19 will not disappear in the near future, and the effectiveness of a vaccine is yet to be established, and potential therapy is still in the research stage, it is essential that we need to protect ourselves by strengthening our immune system.

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A Piece of My Mind

Does SARS-CoV-2 Affect Differently the Immunocompromised Individuals vs. Those on the Immunosuppressant Drugs?

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COVID-19 Coronavirus has shaken up the entire world by creating a pandemic involving over 213 countries with close to 5,611,597 infections and over 348,330 deaths as of May 26, 2020. In normal healthy human beings, with no underlying health ailments, the pathogenesis of COVID-19 disease is primarily due to lung infections, followed by the autoimmune syndrome due to patient's own overactive immune system (Reddy, 2020). The lack of a sufficient number of T-regulatory cells and the inflammation reducing interleukins is one of the reasons for the uncontrollable overactive immune system, resulting in dangerous life-threatening auto-immune syndrome, with respiratory system failure. In the case of elderly population, the pathophysiology of the onset of COVID-19 disease is different because of the immune senescence i.e. lack of sufficient immune response, to start with, due to old age. Even in the older population, the immune system can be ramped up using the multiple mixed strains of probiotics with their diverse immunomodulins, and immune boosting antioxidants.

Now let us look into the naturally immunocompromised individuals, immunocompromised due to disease, and induced immunocompromised condition to eliminate organ rejection as in the case of organ transplant subjects. Physicians naturally prescribe the immunosuppressive medications to suppress the immune response which will induce the transplant organ rejection. What exactly do immunosuppressant drugs do? Mainly these drugs suppress the T-cells, which operate as functional cell mediated cytotoxic adaptive immunity agents. In addition, they also significantly suppress the B-cells, which are responsible for humoral antibody driven adaptive immunity. These immunosuppressant drugs may also partly inhibit the natural killer cells which function in cell mediated cytotoxic innate immunity. All of the above outlined adaptive immune systems have to be simmered to eliminate the rejection of the transplanted organs, such as liver, kidney etc.

Now let us analyze what happens to the innate immune system which constitutes macrophages, neutrophils, basophils, eosinophils, etc. When immunosuppressant drugs are administered, apparently the innate immune system activity cannot be totally reduced, since they are nonspecific in nature and will act as the first line of defense to ward off infections, including both viral and bacterial. Based on these facts, let us analyze what happens to the organ transplant recipients, who are on the immunosuppressant drugs, if he or she is infected with SARS-CoV-2 causing COVID-19 disease.

As I have outlined earlier, the COVID-19 disease results in more damage due to host's overactive immune system, more than primary damage due to the virus on lung tissue. One of the lines of treatment for COVID-19 is through the use of immunosuppressant drugs to simmer the autoimmunity due to the overactive host's immune system. If it is so, organ transplant recipients who are on the immunosuppressant drugs should not have severe secondary lung damage due to the host's overactive immune system. It is good news. However, the COVID-19 virus can also do primary damage to the lungs since the adaptive immune response is slow or none in these patients. Yet, if COVID-19 viral infection level is low, the transplant patient's innate immune system, perhaps to some extent, should be able to suppress the infection to protect the patient, due to the activity of lung tissue associated macrophages.

Since we do not know the exact number of viral particles involved in each infection, the transplant patients must be extremely careful not to contact the disease. This can be accomplished through social distancing, regular washing of hands with soap, using the appropriate face mask, and not shaking hands and giving hugs, and finally keeping away from crowded places and from people who have the COVID-19 disease symptoms.

In addition to the above listed prophylactic practices, I strongly recommend consuming fresh yogurt (fully fermented) with multiple probiotics on a daily basis to strengthen their gastrointestinal microbiota. In addition, consumption of at least one ounce of aged cheese per day (one-year old) made of pasteurized milk is the best way to strengthen their intestinal microbiota or microflora. Contrary to people's thinking, aged cheese is easy to digest, and it is loaded with natural and highly beneficial probiotics. Even lactose intolerant people can consume aged cheese without any discomfort due to significantly reduced or absence of lactose in them. One can question the efficiency of probiotics in terms of improving the immunity of organ transplant recipients to override the Coronavirus infection. Multiple Mixed Strain Probiotics and their growth end products (immunomodulins) induce the production of defensins (natural antimicrobial peptides with 29-35 amino acids), by the host epithelial cells, which can inactivate infective viruses and bacteria. This is an indirect way of inactivating viruses without having to involve the elaborate immune system. It is proven that probiotics significantly enhance the systemic activity of macrophages. Collectively the probiotic induced defensins and the fully operative innate immune system, including stimulated macrophages, will ward off both the viral and bacterial infections, without having to involve the adaptive immune systems i.e. specifically the effector T-cells and B-cells. Based on the publication by D'antiga (1) I posit that multiple mixed strain probiotics induce selectively the production and activation of T-regulatory cells without having to stimulate the effector T-cells, which have been suppressed deliberately by the immunosuppressant drugs, in the case of organ transplant recipients, to reduce the overall inflammation. This is a plus for the organ transplant individuals. As I have discussed earlier, the adaptive immune systems have to be suppressed with the aid of immune suppressants in the case of organ transplant recipients, to prevent organ rejection.

Organ transplant patients should not abuse the use of alcohol, since alcohol has a significant effect on slowing lung tissue associated macrophages, which are essential for fighting COVID-19 infections. It is also extremely important to keep up good oral hygiene, and the hygiene of the nasopharyngeal orifices to protect from yeast (*Candida albicans*), Herpes (*Herpes simplex*), and respiratory viruses including the SARS-CoV-2 Coronavirus. In addition to the regular intake of active fresh yogurt and the aged cheese, (to derive maximum amounts of implantable natural probiotics), it is good to take nutritional supplements such as vitamin C, vitamin E, vitamin D, and zinc to significantly reduce the oxidation of the tissues. As you all know, oxidation is the core cause of any disease. I strongly recommend consulting with your physician before taking any of these supplements. Above all, the stress, anxiety, and fear should be curtailed since they significantly diminish the innate immune system and also induce dysbiosis (Reddy, 2017). Good restful sleep will replenish the organs and also significantly improve the physiological functions of the specialized tissues, such as bone marrow (which produces white blood corpuscles) in a synchronized fashion to protect and maintain good health.

The latest medical journal article published from Italy, (where the highest death rate was encountered due to COVID-19), distinctly proved that the COVID-19 infection did not hamper the health of the organ transplanted persons receiving immunotherapy, confirming my hypothesis that the COVID-19 mortality may be solely due to the secondary auto immunity, due to patient's overactive immune system (D'antiga, 2020).

Since the immune senescence in the older population will have similar immune deficiency patterns, as in the case of organ transplant patients who are on the immunosuppressant drugs, the proactive precautions and nutritional modalities, outlined in this article, should be followed to override or reduce the chances of picking up SARS-CoV-2 infections.

Disclosure: Author is a scientist heavily involved in probiotic research, has published over 130 research articles, and holds over 150 US and International patents. His company (IMAC, Inc.) manufactures and sells all over the United States, Canada, Europe, and South East Asia and South American countries, food grade microbial cultures and other high tech essential enzyme fortified functional products, which go into the manufacture of cheese and other dairy products.

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Scientific Basis for Opening Up After Lockdown due to COVID-19

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The Covid-19 pandemic has infected over 5.5 million patients globally and caused over 350,000 deaths. Many countries have been on lockdown for at least 2 to 3 months, including India, which has been on lockdown from March 25th. This pandemic has led to severe economic downturns with millions of people unemployed. Thus, it is essential to follow scientific guidelines when opening up the economy to mitigate further suffering and financial crisis. India is a country with millions of people still below the poverty line and several millions are in the lower middle class that depend on day-to-day earnings to provide two square meals for their family and children. COVID-19 is a new disease and a lot is still unknown about the virus causing this disease. Our information on COVID-19 has change from what was initially known about this virus in the beginning of the pandemic. Initially, it was reported that "Coronavirus can live on some surfaces for up to three days and up to three hours in the air. Some studies reported that the virus can live up to four hours on copper, up to 24 hours on cardboard, and up to 2-3 days on plastic and stainless steel." These statements have spread a lot of fear and misinformation about the methods of transmission. Now we know that catching the Coronavirus from boxes delivered by Amazon or on your takeout food bags is highly unlikely because of the poor survivability of Coronaviruses on these surfaces. Thus, the emphasis should be on strategies that help maintain physical distance, hand hygiene, avoid touching the face and wearing masks in crowded places. These can mitigate most of the spread of the virus.

Evidence supporting spread from pre-symptomatic or from asymptomatic cases has been discussed in literature and by media outlets. It may be recalled that in the initial days of reporting on COVID-19, a letter published in the NEJM in January 2020 reported that early cases in Germany may have spread from an asymptomatic business person from Shanghai, which was found to be incorrect on a later date (1). As a result, epidemiologists and infectious disease experts were worried that asymptomatic carriers could potentially increase the spread of this infection. Presently, the US Centers for Disease Control and Prevention reports that around 13% of transmission may be from asymptomatic individuals in children and in adults the transmission of COVID-19 is possibly highest when patients are symptomatic (2). It is hard to clearly suggest what proportion of COVID-19 transmission is due to asymptomatic or pre-symptomatic infections when compared to symptomatic infections. While it is clear that symptomatic individuals spread most infections, yet the possibility of some percent of spread coming from completely asymptomatic and pre-symptomatic individuals cannot be ruled out. Thus, when countries open up, they have to ensure that every symptomatic person is quarantined, especially if found positive for COVID-19 after testing. This step will let the vast majority of people to resume normal life while maintaining social distancing.

SARS-CoV-2, the virus causing COVID-19, is seen in higher numbers in densely populated areas and can be contained where social distancing and practicing hand hygiene can be maintained. This is an encouraging finding because it suggests that restriction of gatherings where super spreading is likely to occur will have a significant impact on transmission (3). This finding has essential ramifications-by maintaining social distancing people can go to their jobs; small businesses can be reopened, and people can participate in outdoor activities as long as crowding can be avoided and face masks are used when appropriate. Retail markets that employ thousands can also be opened with restrictions implemented to prevent overcrowding and having effective ventilation systems. All of these might help to ease financial distress. Scientists have been trying to find out the infectivity pattern of this virus using various models (4). Present knowledge dictates that if lockdown and social distancing is not maintained, the SARS-CoV-2 virus can spread to up to 3 people (the "R" factor), with an estimated range of 1.97 to 5.7. R is the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection. R provides an average estimate of spread by individual patients (5). But, some people may spread the infection to a larger number of people, while some do not spread the infection. To understand how infection spreads, scientists introduced "K", which provides a value called dispersion factor. K describes how much a disease clusters

(5). The lower the K is, the more transmission comes from a small number of people. Lloyd-Smith and co-authors (3) estimated that SARS—in which superspreading played a major role—had a K of 0.16. The estimated K for MERS, which emerged in 2012, is about 0.25. In the flu pandemic of 1918, in contrast, the value was about one, indicating that clusters played less of a role. In a recent paper, authors from the London School of Hygiene and Tropical Medicine report that the K factor for COVID-19 is 0.10. Based on this article "Probably about 10% of cases lead to 80% of the spread" (6).

In my opinion, India should slowly start opening up in regions that are not hotspots for Coronavirus. Determining areas for opening can be based on multiple factors, including cases that have shown a static or downward trending curve in the last two weeks. A slow step-ladder approach to opening up the economy may be taken with a change in course if the number of COVID-19 cases increases. While hotspots will need to be under extended lockdown, I recommend increased testing along with isolation to prevent rapid spread. A recent Columbia University study reports that the Indian Government has done an excellent job in implementing the lockdown. In fact, modeling studies have shown that even just one or two weeks of early implementation of control measures have a large impact on the number of infections and deaths (7).

Finally, hydroxychloroquine (HCQ) and its use in the prevention of COVID-19 remain very contentious despite multiple research efforts. Chinese and French studies that have unfortunately not followed the strictest guidelines for clinical trials have shown efficacy for HCQ in treating COVID-19 (8). However, small American studies and a large observational study from the Veteran Administration Hospitals here in the United States, failed to substantiate such claims (9, 10). It is thus apparent that HCQ may or may not have any role as preventive medicine for this epidemic. On the contrary, it is documented that HCQ, either alone or in combination with azithromycin, has an extremely dangerous side effects and can lead to death. HCQ, as well as the much-advertised combination, can initiate electrical changes inside the heart, resulting in a fast heartbeat that can kill patients within a few minutes technically called Sudden Cardiac Death. Thus, it is not recommended that these medicines be taken without specific physician's advice and close monitoring, which is almost impossible when taken by self-prescription or at people's homes where medical supervision is not possible.

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Pioneers in Medicine and Healthcare

Late Dr. Dodda Bhaskara Rao

M.D., Ph.D., FACP, Diplomate of ABIM & ABFP

A Pioneer in Geriatric Medicine in the USA

In November 1973, Dr. Rao moved to the United States from Scotland, where he also obtained a Ph.D. in Geriatric Medicine. At that time, Geriatric Medicine was not a well-established medical speciality in the United States and there were virtually no training centers or fellowship programs in Geriatric Medicine. By virtue of his training and skills in Geriatric Medicine acquired in the United Kingdom, Dr. Rao became Associate Professor of Medicine and Associate Chief of Geriatric and Chronic Diseases at the Johns Hopkins University in Baltimore, Maryland. Later, he became the Chairman of Geriatrics and Chronic Diseases at the Oak Forest Hospital, Illinois. There, he successfully established a fellowship program in Geriatric Medicine and trained a number of young doctors in that specialty. By virtue of his excellence in Geriatric Medicine, Dr. Rao soon became an advisor to many state and international health care bodies as a specialist. Under his constant guidance and advice, Geriatric Medicine expanded in the United States as a distinct specialty. He often chaired programs at the United Nations and WHO, representing the United States. He served as a member of the medical team for President Ronald Reagan. Such a noble person suddenly left this world in February 1984 at the age of 56 years, leaving behind a unique and rich career as Chairman of a Department in one of the most prestigious institutes in the world. Please watch the following video clip of a TV interview Dr. Dodda Bhaskar Rao gave during the early years of his career in the United States of America.



Presentation on Dr. Dodda Bhaskar Rao by WCN Community Affairs TV
Anchor: Virginia Gale

https://www.youtube.com/watch?v=k_qXKLxjxY



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Saurabh Aggarwal, Nelson Garcia-Telles, Gaurav Aggarwal, Carl Lavie, Giuseppe Lippi, Brandon Michael Henry *Diagnosis (Berl)* 2020 May 26;7(2):91-96

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