Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinics in Dermatology (2021) **39**, 107–117

Clinics in Dermatology

What we have learned from the COVID-19 pandemic: Time to think outside the box, maybe far outside

W. Clark Lambert, MD, PhD, FRCP Edin[a,b,*], Albert Alhatem, MD[b], Muriel W. Lambert, PhD[b], Robert A. Schwartz, MD, MPH, DSc (Hon), FRCP Edin[a,b]

[a] *Department of Dermatology*, Rutgers New Jersey Medical School, Newark, New Jersey, *USA*
[b] *Department of Pathology, Immunology and Laboratory Medicine*, Rutgers New Jersey Medical School, Newark, New Jersey, *USA*

Abstract. The coronavirus disease 2019 pandemic has had a profound effect on our lives and careers; this presentation explores some of the lessons we have learned from it and others that it may yet teach us. Socioeconomic effects have been profound, not all of them favorable. Travel and meeting activities, as well as many other activities, have been severely restricted. Social unrest has become intense, and it may have questionable political consequences, as the United States is undergoing a contested election result.

Introduction

Much of the entire biomedical science community has devoted itself to developing a vaccine against this virus, and over 17 are now in various stages of testing, at least three in advanced stages, with many others in development. A number of promising medical treatments are currently in development as well, including antiviral medications and medicines directed at the cellular point of entry of the virus, which happens to be the angiotensin converting enzyme-2 (ACE-2) receptor. Other medications that show promise at present include plasma from recovered patients and monoclonal antibodies directed against the virus, which is used presently as a stopgap for prophylaxis until a vaccine(s) is/are developed; yet other medications are directed against the "cytokine storm," an intense inflammatory reaction triggered by the virus that is extremely destructive, affecting many organs, especially the lungs. We explore the likelihood that similar cytokine storms are responsible for some adverse effects seen in other disease settings, such as malaria, sepsis, and trauma, and are responsible for events appearing, and currently thought to be unavoidable, in surgery settings, both dermatologic and nondermatologic.

Socioeconomic effects

The socioeconomic effects of the coronavirus disease 2019 (COVID-19) pandemic have been profound and, in many respects, difficult to interpret and understand[1,2]; however, several aspects appear to have become clear:

1. Young patients with COVID-19, especially very young patients, usually, but not always, experience only mild disease, whereas elderly patients, particularly those with comorbidities, in particular cardiopulmonary disease including asthma and/or diabetes mellitus, often experience severe disease and even death.
2. Among COVID-19 patients the overall death rate is approximately 0.5% to 1.0%[3]; however, two nonmedical factors may significantly inflate this statistic:

* Corresponding author.
E-mail address: lamberwc@njms.rutgers.edu (W.C. Lambert).

https://doi.org/10.1016/j.clindermatol.2020.12.020
0738-081X/

A: "Do not resuscitate" (DNR) status is currently strongly associated with death rate among patients hospitalized for COVID-19 disease[4]; this may have an effect on this statistic, because such patients are often not offered treatment with a respirator even when physicians feel that it is indicated.[4] This increased death rate in COVID-19 patients with a DNR status, irrespective of other factors, is reported, for the first time, elsewhere in this journal (*Clinics in Dermatology*[4]).

B: In the United States, and likely elsewhere, hospitals and other health care facilities can receive considerably increased funding based on the number of patients they have who have COVID-19 and/or on how many of them die of it. As a result, there is an economic pressure for them to maximize their death tolls from COVID-19. This is particularly an issue in patients who die of other causes but also have COVID-19 at the time of death (ie, who die *with* COVID-19 rather than *of* COVID-19) or even who tested positive for COVID-19 in the recent or not-so-recent past but who have recovered at the time of death, which is from another cause.

3. Wearing protective masks when in the company of others, especially indoors, significantly decreases one's risk of contracting the virus. Earlier information from the U.S. Centers for Disease Control and Prevention (CDC) was not clear on this and even could be understood as indicating that wearing masks is useless or even harmful, increasing the risk of infection. Apparently, this advice was based on a need at that time to reserve masks for certain high-risk individuals until they became more readily available, which is now the case.
4. Touching one's face, especially the eyes, should be rigorously avoided during this pandemic. These touch points provide portals of entry for the virus, which is adept at attacking mucous membranes. This may be challenging, especially if one has not had a haircut for weeks because commercial venues for this are not open.
5. Maintaining a distance of at least 1.5 meters (6 feet) from others when in the company of other people significantly decreases one's risk of contracting the virus.
6. After development of signs and clinical manifestations suggestive of COVID-19, or a positive test for COVID-19 infection (there are a number at present), individuals should self-quarantine themselves for a period of 14 days. This measure is believed to limit dissemination of the virus. [While this paper was in press this was reduced by the CDC to 10 days.]
7. As a further preventative measure, some states in the United States currently have laws or edicts requiring that all individuals entering those states from other locales where the rates of COVID-19 are deemed to be high must self-quarantine themselves for 14 days after entry into those states.
8. Infected individuals can become infectious before development of signs or clinical manifestations of the disease, and before becoming positive in some tests.
9. The provision of medical care is changing to protect patients and health care workers (HCWs) alike. Those most at risk of serious complications from COVID-19 are often encouraged to use telemedicine.[5] As a result, the practice of medicine is changing for patients and physicians alike in response to the pandemic.
10. In addition to flu-like signs and clinical manifestations, pyrexia (fever) above 97.5°F, sometimes above 104°F, is a distinctive sign of the disease, but is seen in less than 10% of affected individuals. Pyrexia may also be due to other causes, particularly in children.
11. Measures, such as lockdown of large social gatherings, are effective in limiting the spread of the disease, but this can come at such staggering social, political, and economic costs that, if overapplied, they can actually be counterproductive. Such measures should therefore be used with discretion. Good public policy involves more than superb physician input. Politicians and other public officials, including accountants, statisticians, and economists, as well as the news media, must take part. Should any one of these groups err or fall short, there may be additional unexpected consequences, perhaps important or even catastrophic.
12. Avoidance of some social gathering situations, such as air travel and incarceration, may or may not be necessary.

    A: The air quality of commercial and some private aircraft is said to usually be better, and more likely to be free of the COVID-19 virus, than one's home environment. This clearly must be either verified or debunked; we are astounded that the airline industry has not aggressively pursued this issue. One would have expected, for example, that one or more of them would have inserted an extra device or filter into the air scrubbers on their aircraft and then advertised this aggressively, even if they were unnecessary. We believe that people primarily avoid air travel for fear of becoming infected with the COVID-19 virus while on the aircraft or at the airports. If this is true and the fear is unfounded, or the situation can be overcome, this needs to be shared with the public. We suggest that, if flying is indeed safe, some top airline executives should take long flights on their airlines to prove that they are safe, and then advertise this as well.

    B: Incarceration, if done properly (eg, without overcrowding), is already geared against social contact among prisoners and should therefore be amenable to social distancing. If done properly (emphasis, if done properly) incarceration need not increase the risk of transmission of the COVID-19 virus. In many places in the United States, prisoners have simply been set free to lessen their risk of acquiring the COVID-19 virus,

with the result that many of them are again committing crimes, often for the same offenses for which they were previously convicted. We believe that a better way can and should be found.

13. Some large social gathering situations may be modified, rather than eliminated.
    A: Several, such as some church services, may be carried out in settings resembling drive-in theaters, with patrons remaining in their cars. Drive-in theaters themselves may make a resurgence.
    B: Sports events may be played before limited but dispersed audiences, or even before empty stadiums, especially if they are televised. In sports events that are associated with a significant risk of transmission of the virus among the players and/or officials and coaches, and so on, special rules, such as requiring all participants to wear face masks or face shields, perhaps specially designed for the sport in question, could perhaps be introduced, with special penalties enforced against teams that fail to comply. Better this than canceling the sports events altogether.
14. A complete return to the "normal" state of things before the pandemic after it has passed is unlikely. It has changed many things for keeps, and it has hastened changes in others that had already begun, such as working at home.[6]
15. Social unrest, stemming from individuals being isolated and unable to attend social gatherings and events over long periods of time due to fear of contracting the virus, eventually leads to, or at least contributes to, bizarre social behavior, sometimes bordering on panic, on a massive scale.[1] Public monuments are overturned, courthouses and other public buildings defaced or even destroyed, and public spaces taken over by mobs who entrench themselves for months on end. One public building was even set afire with police trapped inside (they escaped). Large-scale freeing of prisoners to protect them from acquiring the virus while incarcerated as well as widespread antipolice sentiment, much of it irrational, contribute to the problem. We do not know how this will turn out.

Medical care

Development of vaccine(s) against COVID-19

It is currently widely believed that development of a safe, effective vaccine is the only way that the COVID-19 virus, which is currently wreaking havoc throughout much of the world, will be defeated. If a vaccine is, indeed, the only solution to our current dilemma, however, then we are likely to be in for a long haul. Although a vaccine may be the best long-term solution, the lead time for development and testing of a vaccine is usually much longer than that for a safe, effective treatment. These authors (WCL and RAS) are more optimistic, because a number of very promising drugs, such as remdesivir, are already available or are under study (see below), some drugs already long in use off-label, such as chloroquine and hydroxychloroquine, may prove to be effective, particularly in combination with other agents,[7-10] and because, as more and more patients contract the disease and recover, sources for convalescent and postdisease serum and antibody are certain to become more numerous.[13–18] Development of a safe, effective treatment, or of more than one such treatment, has another distinct advantage: Should another virus emerge, the same or a similar treatment is more likely to be effective against it than a vaccine, which tends to be specific for a particular pathogen. As an example, consider the vaccinations against the influenza virus, which must be modified each year to keep abreast of new viral mutations, sometimes with limited results. Hopefully, and we think probably, both a vaccine and a treatment will emerge from our massive worldwide reaction to the COVID-19 pandemic.

Regarding development of a safe, effective vaccine, there is much cause for optimism as well. Currently, there are over 17 such vaccines in various stages of testing (not just in development, in testing, some of them already in stage three of testing[19]).

Previous American experience with vaccinations against Asian respiratory viruses: Maurice Hilleman and the Asian Influenza Pandemic of 1957

During the Asian Influenza Pandemic of 1957, Maurice Hilleman of the Walter Reed Army Institute of Research was able to expedite vaccine development. The result was that not only had a vaccine been developed and tested but also 40 million doses had been administered by the time this pandemic from Asia hit America. The end result was that America was barely grazed by this viral threat.[20,21]

Complications of vaccines

Vaccines are not perfect.[22,23] In addition to the fact that they simply may fail to provide significant protection against the targeted virus, additional known complications are as noted:

1. The vaccination may actually make subsequent encounter with the targeted virus significantly worse for the vaccinated individual.[23] This problem has been encountered in vaccination against dengue, causing the vaccine to be withdrawn and replaced by another one. Theoretically, a "cytokine storm" (see below) may even be induced by a vaccine, although this has not been observed with any vaccine to date.
2. Systemic complications, such as the Guillain-Barré syndrome (G-BS), may occur. This is a rare condition but may be life-threatening. Vaccination against a previous viral invasion from China, the H1 N1 virus, also known as known as "swine flu," turned out to

be unnecessary, because the virus was contained. Approximately 500 individuals developed G-BS or a related serious complication of the vaccination, however.[23] Approximately 200 patients were permanently paralyzed from this vaccination.

3. During the process of scaling up production of the vaccine, it may come to lose its potency against the pathogen against which it is directed. This loss of potency may be heterogenous, so that large groups of vaccines may receive ineffective vaccinations, while others receive effective ones.
4. The target virus or other pathogen may mutate to a form that is less susceptible to immunization by the vaccine, or even to a form that is not protected against by the vaccine at all. Theoretically, the vaccine may even have an adverse effect, such as carrying another pathogen or making the target disorder worse.

Development of medical treatments for COVID-19 patients

Natural course of COVID-19 disease without treatment

Before considering the changes in the course of this disease we hope to achieve with treatment, let us first consider the course of the disease without it.

1. The most common port of entry appears to be the lungs, where the virus is inhaled as an aerosol. The virus may enter by directly invading other areas, however, particularly mucous membranes and conjunctivae
2. The virus enters the host lung parenchymal cells.
3. After approximately 6 days, the virus undergoes a burst of replication and dissemination into the victim's blood.
4. A potentially substantial but very variable "cytokine storm" occurs in response to the massive replication of the virus. This may cause major damage to numerous internal organs.
5. The lungs are the most important target organ of the cytokine storm and of the virus, but the damage does not occur all at once; in the beginning, the lungs remain compliant, but later they become quite stiff and noncompliant.[24,25]
6. Individuals with certain comorbidities, especially congestive heart failure or lung disease, including asthma, and the elderly are at increased risk to develop serious lung problems and to die of the disease, especially if they also carry the designation DNR (see below)[4]; however, younger patients in apparently perfect health may also become sick and die of the disease.
7. It is becoming increasingly apparent that a virus-associated coagulopathy is an important component of COVID-19 disease, and it is a poor prognostic sign when it is discovered.[26-34]
8. Skin signs of COVID-19 are important and may be diagnostic or at least suggestive of the diagnosis.[11,12,35–37] Especially noteworthy are lesions due to thrombosis in the skin, such as "covid toes."
9. As noted and documented elsewhere in *Clinics in Dermatology,*[4] patients with the designation DNR on their medical chart are at significantly increased risk of death from COVID-19 disease. The designation is typically placed at the discretion of the patient and/or their family to prevent prolonged (ie, even, sometimes, for months or even longer) and/or extreme (eg, use of a respirator) measures being used to prolong life, when there is no reasonable chance of recovery once these measures are withdrawn or reduced to a tolerable level. Once applied, the designation DNR is routinely interpreted by physicians in a very different way, such that a respirator is not offered to a DNR patient with COVID-19 even when the patient's physicians feel that it is indicated for treatment of their COVID-19, which usually requires application of a respirator for only a few days or one or two weeks.[4] The end result is that mortality is significantly higher in patients with a DNR designation on their chart who develop COVID-19 disease, even though they may very well survive if treated with a respirator, which can be withdrawn later if the patient is judged to be terminal. As a result, the mortality rate in these patients is probably unnecessarily much higher than it needs to be.[4]
10. A special concern for patients with significant lung disease, including COVID-19 disease, is superinfection in the lungs with another pathogen, notably the fungus *Candida cruris.*[40]
11. The disease does not progress to all of these stages in every patient. It may stop at any of the above stages and does so in the vast majority of cases.
12. After recovery from COVID-19, some patients develop sequelae of the disease and/or of the treatment for it and/or the actual experience of being very ill (eg, post-traumatic stress disorder [PTSD]) or any combination of these. Significant neuropsychiatric and thromboembolic sequelae, which may arise even while the disease is ongoing, are a particular concern.[26-34,41-44] More or less similar neuropsychiatric sequelae were noted following previous viral pandemics with this class of pathogens.[45,46]

In assessing drugs and other treatment modalities, it is very important to consider not only the extensive patient-to-patient variability, but also the stage of the disease at which the treatment/modality is administrated. What is very effective at one stage or in one patient may be ineffective, or even counter effective, if administered at another stage or in another patient. This factor may also cause drugs/agents evaluated in blinded studies to be judged as ineffective when they may, in fact, be beneficial, if used at a different time or stage of the disease.

Treatments

Development of best ways to manage care of patients with disease related to the SARS-CoV2 (COVID-19) virus is a major problem, especially because the virus only emerged in late 2019.[1,47-55] Eventually, one or more vaccines should become available, which, together with resulting herd immunity following widespread immunization, should reduce the problem, hopefully dramatically, but in the meantime practices, such as quarantine, social distancing, wearing face masks, and cancellation of sports events, live theater, opera, wedding receptions, indoor restaurant dining and other social events, as well as many forms of travel with their enormous and societal and economic costs, are likely to persist. Although many among us hardly know that they have been infected with this pathogen, others suffer severe disease and statistical studies have shown a significant number, approximately 0.3% to 1.5% overall, die as a result.[3] As noted above, however, this number may be inflated by overreporting deaths due to COVID-19 and by failing to offer patients with a DNR status a respirator when this is indicated.[4]

In the absence of an effective vaccine, the optimal treatment plan includes prevention. Accordingly, those most at risk should be protected from COVID-19. These individuals include elderly patients and others with serious comorbidities, as well as health care workers (HCWs). Those over 65 years of age should be strongly encouraged to telecommute,[5] unless they are immune from COVID-19, presumably after surviving an infection, assuming that postinfection immunity can be proven.[5] HCWs over 70 years of age should probably avoid or limit physical presence at public health care facilities and medical centers.

Previous much more limited spread of similar viruses, notably those responsible for the severe acute respiratory syndrome (SARS) and the closely related virus responsible for the Middle Eastern respiratory syndrome (MERS), have provided medical virologists and physicians caring for these patients opportunities to learn lessons that appear to be useful in attacking this one.[20,21,45,46] Because the viruses are similar, much about the structure and biology of this virus has already been learned, although more remains to be studied. We have many promising drugs and other agents; what we do not have are randomized, double-blinded, statistically blinded study results with large numbers of subjects. Most of the proposed agents for treating severely ill patients are supported as such only by very limited data, if any. These agents are grouped into several categories, as follows.

Development of agents that bind to the angiotensin converting enzyme-2 receptor

It has been discovered that the virus responsible for COVID-19 invades human cells by binding to the receptor on the cell surface for angiotensin converting enzyme-2 (ACE-2). ACE-2 is part of the renin-angiotensin pathway in which blood pressure, measured at least in part by the rapidity and volume of blood flow into the kidneys, stimulates the kidneys to secrete more or less of renin, a hormone that acts on the adrenal glands and other tissues to initiate a complex system that controls blood pressure. It follows that inhibitors of this pathway that act by binding to the same receptor may be of value as anti-COVID-19 agents[56]; however, this is far from proven to be actually true.[56] At present, this is an interesting avenue for research, but this proposal is far from developing into a useful treatment modality for COVID-29 at present.

Medicines for treatment of COVID-19

Hydroxychloroquine administered with azithromycin and zinc or with doxycycline and zinc

Chloroquine (CQ) and hydroxychloroquine (HCQ) are antimalarial drugs widely used by dermatologists and rheumatologists to treat inflammatory disorders such as collagen-vascular ("connective tissue") diseases. Extensive clinical experience has supported their administration in severely ill COVID-19 patients, as well,[7-10] based only on very limited experimental data. Those who use these drugs emphasize that they should be begun very early in the course of the disease. Hydroxychloroquine is thought to act by preventing the virus from entering the cell and again later to prevent it from replicating within the cell. No one knows the mechanism by which these drugs provide a beneficial effect, if any, in these inflammatory disease states. An intriguing idea is that they modulate the effects of a poorly understood but potentially devastating immunologic phenomenon known as the cytokine storm (reviewed below) induced by the virus, either directly or indirectly. This phenomenon is thought, based on less than perfect evidence, to be a major player in the pathogenesis of lung and other internal organ disease in COVID-19 patients. Notably, it does not affect all COVID-19 patients.

Side effects of deoxychloroquine are extremely uncommon, but they do exist. The most important is probably a serious cardiac arrhythmia, occurring especially in patients with a prolonged Q–T interval on their electrocardiogram, which may be fatal.[57-64] Others include blindness, renal failure, worsening of psoriasis,[61] and an occasional severe cutaneous adverse drug reaction, known as generalized pustular figurate erythema.[11,12]

Similarly, azithromycin is widely used and is generally regarded as safe. It also has very uncommon but potentially serious side effects, however, including cardiac arrhythmias in the elderly and in those with pre-existing Q–T interval prolongation, bradycardia, low serum potassium, or low serum magnesium.[62-65] Azithromycin also is an effective drug against the closely related pathogenic viruses, influenza A (H1 N1)[66] and zika.[67,68]

Despite widespread use for these conditions, these applications are almost completely "off-label" in the United

States. This means that the drug is approved for use by the U.S. Food and Drug Administration (FDA), but not for this usage. Licensed health care providers in the United States are allowed to prescribe such drugs for treatment of diseases other than those approved by the FDA as long as the drug itself is approved. Currently, the FDA has banned HCQ for outpatient use, a decision that is extremely controversial. HCQ is presently still approved by the FDA for inpatient use.

Chloroquine, hydroxychloroquine, and ivermectin are also reviewed as possible treatments for COVID-19 patients elsewhere in this special issue.[7]

Antiviral agents including monoclonal antibodies

Drugs known to be effective against the hepatitis C virus (HCV), such as sofosbuvir, may be a potential option in the treatment of COVID-19 patients.[69,70] This speculation is based on the similarity between the replication mechanisms of the HCV and of the coronaviruses. There is only limited experimental evidence for this, but it has been hypothesized that sofosbuvir may be a potential option for care of patients with COVID-19, especially at the onset of the infection and before invasion of the virus into lung parenchymal cells. It has also been suggested that sofosbuvir and velpatasvir could be used in combination, which would be anticipated to have strong potential activity against SARS-CoV2 (COVID-19) infection.[70] These are but two potential approaches that use direct-acting antivirals as broad-spectrum antiviral agents against this virus. There are many steps involved in development of this viral illness, and most of them are attacked by one or more of these drugs/agents, including, in addition to the above, ribavirin, remdesivir, tocilizumab and lopinavir/ritonavir.[71-73] In addition to these steps, creation of agents that attack the endocytic pathway and the autophagic process in cells has been suggested to develop possible agents against COVID-19.[74]

Remdesivir

Separate recent clinical studies have shown impressive positive results using remdesivir, an antiviral antimetabolite, to treat severe cases of this disease.[73] This drug was introduced years ago to treat other viral illnesses. It is possible that it, used with other medications, would be even more effective. Recent studies of remdesivir have been particularly promising; notably, Australia has recently declared this the drug of choice for their citizens with severe illness due to COVID-19. Among the numerous antiviral drugs currently under study for treatment of COVID-19, remdesivir appears to be the clear winner at this point in time[73]; however, this may change.

Corticosteroids

Dexamethasone is a corticosteroid that has impressive reports about its effectiveness for treatment of severely affected patients with COVID-19.[75] It has the disadvantage that it is significantly more expensive than other corticosteroids. It may act by preventing or ameliorating the cytokine storm (see below); however, use of corticosteroids to treat infectious disease is not without risk, and caution has been advised.[76] The authors suspect that the stage of the disease at the time of treatment determines its effectiveness, lack of effectiveness, or counter-effectiveness. It may be advisable to use corticosteroids only in combination with other agent(s).

Nonsteroidal antiinflammatory drugs (NSAIDs)

Much of what was said above regarding corticosteroids may also be said about nonsteroidal antiinflammatory agents, which have also been suggested as potential anti-COVID-19 virus agents.[77] It is likely that their effectiveness, if such is observed, will be due to countering the cytokine storm.

Antibodies/serum from recovering COVID-19 patients

Use of serum or of extracted antibodies from recovering or convalescent COVID-19 virus disease patients has been used widely for treatment of especially ill COVID-19 patients.[13-18] As more and more patients are diagnosed and then recover, the supply of this reagent should increase dramatically, allowing more and more patients access. It should also allow much more objective evaluation of the value, or lack thereof, of treatment of these patients.

Monoclonal antibodies

Monoclonal antibodies directed against the COVID-19 virus, generated in animals, are in current use, primarily as prophylaxis against infection as a stopgap until a vaccine becomes available.[78]

Immunotherapeutic agents

A number of immunotherapeutic agents have been proposed for treatment of COVID-19 patients.[79-81] This approach may be especially useful to control a cytokine storm type reaction or an associated disease such as psoriasis, which is known to emerge, re-emerge, or become worse in COVID 29 patients.[82]

Antibiotics

As every physician knows, antibiotics are generally of little or no value against viruses. Despite of this, however, some antibiotics are of use against certain viruses, perhaps because they have activities other than as an antibacterial agent, perhaps because they have antibacterial properties that combat

bacterial superinfections encountered with the virus in question. Antibiotics such as azithromycin, tetracycline,[83] and doxycycline,[83] especially when combined with other medications, such as chloroquine and hydroxychloroquine, are already in use on an off-label basis by numerous physicians. (Azithromycin is also discussed separately, above.) Numerous clinical trials with azithromycin, although usually in combination with HCQ, are listed for the United States alone on the ClinicalTrials.gov U.S. governmental website. A particularly innovative one, entitled "Azithromycin for COVID-19 Treatment in Outpatients Nationwide (ACTION)," is based at the University of California San Francisco (ClinicalTrials.gov Identifier: NCT04332107), in collaboration with the Bill and Melinda Gates Foundation, Pfizer, and Stanford University. Officially entitled "Azithromycin for Prevention of Disease Progression in Patients with Mild or Moderate COVID-19," it hopes to prevent COVID-19 progression to hospitalization. Others have suggested formal clinical trials with the prepackaged preparation of azithromycin, which is administered at the first sign of a COVID-19 infection over a 5-day period with 500 mg the first day and 250 mg for the remaining 4 days, for a total of 1.5 g for adults over 18 years of age, and for children 5 to 18 years of age, 10 mg/kg on the first day and 5 mg/kg for the following 4 days.

Antiparasitic agents

Antiparasite drugs, such as ivermectin, are also already in use on an off-label basis by some physicians. Oral ivermectin is widely and safely used in mass treatment programs in Africa for onchocerciasis.[84] This antiparasitic medication has shown broad-spectrum antiviral activity *in vitro*. It has been shown to inhibit SARS-CoV-2 in viral cell culture.[86] The addition of ivermectin to HCQ may prove synergistic in chemoprophylaxis and treatment of COVID-19.[85,86] Chloroquine, hydroxychloroquine, and ivermectin are reviewed as possible treatments for COVID-19 patients elsewhere in this special issue.[7]

Zinc

Zinc (Zn) has the ability to enhance innate and adaptive immunity in the course of a viral infection. In addition, Zn used as an adjuvant can enhance the effect of COVID-19 treatment for a wide range of drugs; for example, the effectiveness of Zn can be enhanced when administrated together with chloroquine, which acts as an ionophore, whereas Zn inside the infected cell can stop SARS-CoV-2 replication. Given those potential benefits, Zn should be considered as a possible adjuvant therapy with other prescribed treatments for COVID-19 patients.[87,88]

Vitamins C and D

Various vitamins have been suggested as possible treatments for COVID-19 disease, mostly as an agent to be used with something else. Among these, vitamins C and especially D appear to be the leading contenders.[89] No definitive studies have been carried out to date.

Mesenchymal stem cell therapy

Mesenchymal stem cells have been introduced to COVID-19 patients as a possible treatment. Reports have been sporadic and difficult to assess.[90,91]

Melatonin

Melatonin has been recommended as an adjuvant therapy for COVID-19.[92] Because it can aid in inducing sleep, we expect it should be helpful for that reason alone.

Chinese and herbal medicine

Chinese and herbal medicines have been recommended for COVID-19 disease, but by their very nature, they are not supported by laboratory or clinical studies. As a result, we are unable to evaluate them.

Heterogeneity of COVID-19 patients

Even though this virus has only been evident since late 2019, and we have much to learn about it and the disease states it produces, there is much we do already know. The disease in humans is quite mild, or even entirely asymptomatic, in the vast majority of patients, but in a significant minority, it leads to severe disease, sometimes even death. Although some patients are predictably prone to bad outcomes from infection with this virus, such as the elderly and those with diabetes mellitus or cardiac or pulmonary disease, especially those with a DNR status,[4] some severely affected victims are young and in apparent good health when infected. Considering only skin and mucous membrane manifestations, the disease is again extremely heterogeneous,[35-39] as we have noted elsewhere in this issue.[35][While this paper was in press, a more infectious mutant variant of the virus appears to heve emerged; however it does not appear to be more likely to cause severe disease and does appear to be susceptible to vaccines already in development.]

Sequelae of COVID-19 disease/viral infection and its treatment

Among the significant unknowns regarding this new virus and the disease it causes are the sequelae that may follow the disease or even an asymptomatic infection of the virus. Such sequelae have been observed after infection with West Nile virus, Ebola virus, and H1 N1 influenza, as well as SARS and MERS, both of which are also caused by a coronavirus. Like the COVID-19 itself, the occurrence and course of sequelae, which appear to be due, at least in part, to side effects of

the treatments applied for the COVID-19, appear to be very heterogeneous.[41,42,44]

Why the heterogeneity?

From numerous medical and autopsy studies of patients who have died from COVID-19, the answer to at least some of its heterogeneity becomes clearer. The disease does not progress in most patients, but in others it induces reactive processes that cause catastrophic destruction. It is not clear whether it is the virus or the reaction against it, gone out of control, that causes the most damage. It appears most likely that it is the latter. This is discussed in more detail below.

Cautionary note

Notably, it is important that we proceed with all deliberate speed in pursuing effective treatment(s) and/or vaccine(s) against this pandemic. Wise heads among us are urging caution.[93] Also notably, statistical studies to evaluate drugs and vaccines often make the critical, and unstated, assumption that the subjects of the studies are homogeneous. Because this is not at all true of COVID-19 patients, statistical significance becomes more difficult to attain. It is well to recall the wise adage, "Failure to prove a difference does not prove lack of a difference." It may be best to conclude that if such studies show a difference, it is likely to be correct, but if they do not, it may be best to conclude that we simply do not yet know the answer.

Gained insights into other medical and biomedical issues and problems

The cytokine storm

The cytokine storm, otherwise known as the cytokine release syndrome (CRS)[80] or the COVID-19-related systemic inflammatory response,[8,21] is believed to be the cause of the severe visceral reaction that causes the catastrophic course of this disease in some patients. It is essentially an autoimmune type of response that depends not so much upon recognition of self-antigens, as it does on release of destructive influences that damage or destroy some critical, as well as some non-critical organs and activates potentially self-destructive processes such as inflammation and coagulation. The systems that can be activated by COVID-19 are present in all of us, but their activities vary depending on such factors as HLA type, accounting for the great variability of the signs and clinical manifestations of the disease.

Upon reflection, it is apparent that other diseases also depend upon activation of similar systems to cause their characteristic signs and clinical manifestations. The collagen-vascular diseases (connective tissue diseases) come to mind, as well as a myriad of other diseases. In dermatology, one thinks of autosensitization ("id") reactions, various reactive entities such as elephantiasis nostra, and the "angry back syndrome" that complicates clinical patch testing. The human body's reactions to various disease states are not necessarily beneficial, and may actually be quite counterproductive and harmful.

Cytokine storms are, of course, quite variable, depending on multiple factors, including their causes. Let us consider clinical situations that, on reflection, appear to depend heavily on this type of reaction in some form to produce adverse outcomes.

Malaria

At least part of the reason that antimalarial drugs, such as chloroquine and deoxychloroquine, are effective against malaria may be because in that disease, with its various forms, cytokine storms arise and are part of the etiopathogenesis. Malaria is known to give rise to crises.[94] We posit that these are actually cytokine storms. If we are correct, it may be that the cytokine storm may in turn be studied using animal models of the various types of malaria.

Sepsis

Sepsis has long been considered to be associated with uncontrolled release of immunologically active substances and endogenous inflammatory agents, even before many of the ones known and studied today were identified. These investigations are ongoing.[95,96] One known aspect is that sepsis due to different organisms is clinically different.

Surgery

Although, as dermatologists, we rarely perform major surgery, we not infrequently are exposed to it and the patients involved either in our training or practice. Minor surgery is, of course, a staple of current-day dermatology. Aseptic procedures and anesthesia, local or systemic, are, of course, critical underpinnings of both kinds of surgery, and their introduction dramatically changed surgery for the better; however, we strongly suspect that there is a third leg that should also be underpinning surgery: control of the resulting cytokine storm. We suspect that this leg, once introduced, will have an effect as great as or perhaps even greater than the former two.

Why do we suspect this? Surgery involves cutting or destroying tissue, or both. Were the patient conscious and also able to feel this process, we are well aware of the anticipated reaction. This would fall into the category of "flight or fight." Just because the patient does not feel the trauma, however, does not mean that he or she is not reacting to it at an unconscious level. Surgery textbooks note various stages of recovery from major surgery, including a catabolic and an anabolic phase. These stages are considered unavoidable by many surgeons, but we suggest that they be, at least in part, the result of a massive cytokine response to the procedure.

Part of that response is likely to redirect blood flow away from vital organs and toward muscle and parts of the brain, to enable "flight or fight." A patient undergoing a procedure or a recovering surgery patient needs just the opposite. Reversal of this process, perhaps by administering other cytokines or drugs, may profoundly reduce the stress of surgery.

We do not yet have a safe and effective treatment that would completely reverse this counterproductive reaction, but we do have:

1. Laboratory tests that detect systemic inflammation, such as C reactive protein
2. Drugs with antiinflammatory properties, such as chloroquine and hydroxychloroquine, that would be good candidates to suppress it
3. Opportunities abound to test the following hypotheses, which arise from the above rationale:

Hypothesis: Surgery, whether major or minor, induces cytokine reactions that are not necessarily beneficial or desirable.

Hypothesis: Surgery patients could benefit significantly from amelioration of some or all these reactions.

One might expect that the best opportunities to test these hypotheses lie in major surgery settings, but the opposite may be true. Major surgery may produce such massive reactions that they may actually be more difficult to study. *As a result, the best opportunities may lie in dermatologic surgery settings.* Chloroquine and hydroxychloroquine are already FDA-approved medications (see above), and widespread studies are currently ongoing on them and other antiinflammatory agents due to the COVID-19 pandemic and their proposed value in treating this disease; these studies should provide additional information useful for anyone using them for other purposes. (Take care to take necessary precautions for such complications as cardiac arrhythmias when administering these drugs.) Laboratory studies of systemic inflammation and cytokine reactions to minor surgery are routinely available and usually require only a few blood draws (at least three; one before, one during and one following the procedure). Those with access to basic science investigators and their laboratories may wish to pursue more complex studies.

Trauma and shock

Much of what may be said of cytokine storm type reactions following and/or during surgery may also be said of trauma situations and patients undergoing shock, whatever the cause. These situations are also opportunities for study and possible antiinflammatory intervention, but they are generally uncontrolled and therefore more difficult to study.

Conclusions

The COVID-19 pandemic took the world by surprise and has drastically altered it. There are numerous ongoing socioeconomic consequences, some arguably even worse than the viral disease itself. Medically there has been a magnificent response on the part of medical personnel, and a somewhat mixed one on the part of politicians and regulators, some responses excellent, some not so excellent. The biomedical community, backed by government funding, has mobilized itself to find vaccines and effective treatments with impressive, one could reasonably state amazing, results, but more are needed. Detection, prevention, and treatment strategies for COVID-19 are essential. Good public policy needs to advanced and refined, probably individualized to specific localities, communities, and situations, in what appears to be a rapidly changing landscape. Political instability has drastically increased and, we suspect, will continue to do so as the pandemic takes its toll, particularly if some of these measures are not taken and/or are not done properly.

There is much that we can, and should, learn from this pandemic. Routine procedures and protocols, such as assignment of DNR status to some patients, may have unanticipated and even adverse consequences in a pandemic. Development of new drugs, reapplication of old ones, and development of new vaccines need not take nearly as long as in the even recent past, partially as a result of new and emerging technologies. We must use this pandemic to learn more about a phenomenon that has plagued humankind for centuries but has been little studied or taught: the cytokine storm.

This phenomenon has importance in many areas of medicine, especially infectious disease, trauma, and surgery, including dermatologic surgery. We have the means, as well as the interest and motivation, to study it and learn how to moderate it. Through all of this, we must not abandon the one attribute human has to cope with even massive problems: Thinking.

References

1. Ladapo JA. Fear and loathing in COVID America. *The Wall Street Journal*. August 4, 2020:A15.
2. Otani A. *Coronavirus is a puzzle that Wall Street can't solve.* The Wall Street Journal. June 27-28, 2020:B4.
3. Abbott B, Douglas J. Research reveals fatality rate for Covid-19. *The Wall Street Journal*. July 22, 2020:A1.
4. Alhatem A, Lambert WC, Schwartz RA. "Do Not Resuscitate (DNR)" status markedly influences death rate in COVID-19 patients. Clin Dermatol, in press.
5. Almutairi N, Schwartz RA. COVID-19 with dermatologic manifestations and implications: An unfolding conundrum. *Dermatol Ther*. 2020;33:e13544. doi:10.1111/dth.13544.
6. Komisar E. COVID-19 hastens the work-at-home revolution. *The Wall Street Journal*. August 4, 2020:A15.
7. New uses for old wine. Clin Dermatol. 2020. This issue.
8. Meo SA, Klonoff DC, Aliram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. *Eur Rev Med Pharmacol Sci*. 2020;24:4539–4547.
9. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. *Diabetes Metab Syndr*. 2020;14:241–246.

10. Ferner RE, Aronson JK, Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. *Br Med J*. 2020;369:m1432.
11. Schwartz RA, Janniger CK. Generalized pustular figurate erythema. A newly delineated severe cutaneous drug reaction linked with hydroxychloroquine. *Dermatol Ther*. 2020;33:e13380.
12. Adadías-Granado I, Palma Ruiz AM, Cerro PA, et al. Generalized pustular figurate erythema. First report in two COVID-19 Spanish patients on hydroxychloroquine. *J Eur Acad Dermatol*(in revision).
13. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. *J Clin Invest*. 2020;130:4791–4797.
14. Rajendran K, Krishnasamy N, Rangarajan J, et al. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. *J Med Virol*. 2020;92:1475–1483.
15. Alzoughool F, Alanogreh L. Coronavirus drugs: Using plasma from recovered patients as a treatment for COVID-19. *Int J Risk Saf Med*. 2020;31:47–51.
16. Joob B, Wiwanitkit V. Convalescent plasma and COVID-19 treatment. *Minerva Med*. 2020 In press. doi:10.23736/S0026-4806.20.06670-7.
17. Brown BL, McCullough J. Treatment for emerging viruses: Convalescent plasma and COVID-19. *Transfus Apher Sci*. 2020;59.
18. Marcus AM. Survivors' plasma found to cut covid mortality. *The Wall Street Journal*. August 5, 2020:A5.
19. Pancevski B. Biotech is upbeat on vaccine. *The Wall Street Journal*. July 11-12, 2020:A6.
20. Hilleman MR, Flatley FJ, Anderson SA, Lueking ML, Levinson DJ. Antibody response in volunteers to Asian influenza vaccine. *J Am Med Assoc*. 1958;166:1134–1140.
21. Cavanaugh Simpson J. *The Man Who Beat the 1957 Flu Pandemic Pioneering virologist Maurice Hilleman, who is little remembered today, also helped develop nine of the 14 children's vaccines that are now recommended*; April 19, 2020. Available at: https://blogs.scientificamerican.com/observations/the-man-who-beat-the-1957-flu-pandemic/. Accessed June 20, 2020.
22. Zukerman G, Walker J. Vaccines have a lot to prove. *The Wall Street Journal*. August 5, 2020:A6.
23. Loftus P. Vaccine researchers aim to stem side effects. *The Wall Street Journal*. July 13, 2020:A6.
24. Polidoro RB, Hagan RS, de Santis, Santiago R, Schmidt NW. Overview: Systemic inflammatory response derived from lung injury caused by SARS-CoV-2 infection explains severe outcomes in COVID-19. *Front Immunol*. 2020;11:1626.
25. Marini J. Management of COVID-19 respiratory distress. *JAMA*. 2020;323:2329–2330.
26. Singh P, Schwartz RA. Disseminated intravascular coagulation: A devastating systemic disorder of special concern with COVID-19. *Dermatol Ther*. 2020.
27. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19 implications for the cardiovascular system. *Circulation*. 2020;142:68–78.
28. Spyropoulos Alex C, Weitz Jeffrey L. Hospitalized COVID-19 patients and venous thromboembolism. *Circulation*. 2020;142:129–132.
29. Helms J, Tacquard C, Severac F. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. *Intensive Care Med*. 2020;46:1089–1098.
30. Bikdeli B, Madhavan MV, Jimenez D. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Col Cardiol*. 2020;75:2950–2973.
31. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoC-2 infection. *Clin Chem Lab Med*. 2020;58:1116–1120.
32. Zhang Y, Cao W, Xiao M, et al. Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. *Zhonghua Xue Ye Xue Za Zhi*. 2020;41:E006.
33. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in Covid-19: The first autopsy series from New Orleans. *MedRxiv*. 2020.
34. Miller HI. Covid's harrowing complications. *The Wall Street Journal*. July 21, 2020:A13.
35. Schwartz RA, Lambert WC. COVID-19 specific skin changes related to SARS-CoV-2: Visualizing a public health challenge. *Clin Dermatol*. 2020, in press.
36. Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: A rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;183:71–77.
37. Gisondi P, PIaserico S, Bordin C, et al. Cutaneous manifestations of SARS-CoV-2 infection: A clinical update. *J Eur Acad Dermatol Venereol*. 2020;34:2499–2504.
38. Kanitakis J, Lesort C, Danset M, Jullien D. Childblain-like acral lesions during the COVID-19 pandemic ("COVID toes"): Histologic, immunofluorescence and immunohistochemical study of 17 cases. *J Am Acad Dermatol*. 2020.
39. Andina D, Noguera-Morel L, Bascuas-Arribas M, et al. Chilblains in children in the setting of COVID-19 pandemic. *Pediatr Dermatol*. 2020.
40. Schwartz RA, Kapila R. Cutaneous manifestations of a 21st century worldwide fungal epidemic possibly complicating the COVID-19 pandemic to jointly menace mankind. *Dermatol Ther*. 2020.
41. Kapila R, Schwartz RA. Post-pandemic neuropsychiatric complications: von Economo's disease, the Kapila syndrome and more: Linkages in view of the new Covid-19 pandemic. *Indian J Med Sci*, in press.
42. Ellul M, Varatharaj A, Nicholson TR, et al. Defining causality in COVID-19 and neurological disorders. *J Neurol Neurosurg Psychiatry*. 2020;91:811–812.
43. Leira Enrique C. Preserving stroke care during the COVID-19 pandemic: Potential issues and solutions. *Neurology*. 2020;95:124–133.
44. Garcia CAC, Sanchez EBA, Huerta DH, Gomez-Arnau J. COVID-19 treatment-induced psychiatric adverse effects. *Gen Hosp Psychiatry*. 2020.
45. von Economo C. Encephalitis lethargica. *Wien Klin Wochenschr*. 1917;30:581–585.
46. Kapila CC, Kaul S, Kapur SC, Kalayanam TS, Banerjee D. Neurological and hepatic disorders associated with influenza. *Br Med J*. 1958;2:1311–1314.
47. Fauci AS, Lane HC, Redfield RR. COVID-19. Navigating the uncharted. *N Engl J Med*. 2020;382:1268–1269.
48. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: The reality and challenge. *J Microbiol Immunol Infect*. 2020;53:436–443.
49. Robby MII. Current drugs with potential for treatment of COVID-19: A literature review. *J Pharm Pharm Sci*. 2020;23:58–64.
50. Baden LR, Rubin EJ. COVID-19: The search for effective therapy. *New Engl J Med*. 2020;382:1851–1852.
51. Muillard A. Flooded by the torrent: The COVID-19 drug pipeline. *Lancet*. 2020;395:1245–1246.
52. Kupferschmidt K, Cohen J. Race to find COVID-19 treatment accelerates. *Science*. 2020;367:1412–1413.
53. Guy RK, DiPaola RS, Romanelli F, Dutch RE. Rapid repurposing of drugs for COVID-19. *Science*. 2020;368:829–830.
54. Potì F, Pozzoli C, Adami M, Poli E, Costa LG. Treatments for COVID-19: Emerging drugs against the coronavirus. *Acta Biomed*. 2020;91:118–136.
55. Barlow A, Landolf KM, Barlow B, et al. Review of emergency pharmacotherapy for the treatment of coronavirus disease. *Pharmacotherapy*. 2020;40:416–437.
56. Khashkhusha TR, Chan JSK, Harlsy A. ACE inhibitors and COVID-19: We don't know yet. *J Card Surg*. 2020;35:1172–1173.
57. Gérard A, Romani S, Fresse A, et al. French Network of Pharmacovigilance Centers. "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapie*. 2020.

58. Uzelac I, Travanian S, Asjikaga H, et al. Fatal arrhythmias: Another reason why doctors remain cautious about hydroxychloroquine for treatment of COVID-19. *Heart Rhythm*. 2020.
59. Natsuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug treatment: A review and proposed protocol. *Eur Heart J Acute Cardiovasc Care*. 2020;9:2015–2021.
60. Lo'ai A, Alzoughool F, Atoum M. Risk of using hydroxychloroquine as a treatment of COVID-19. *Int J Risk Saf Med*. 2020.
61. Sachdera M, Mufti A, Maliyar K, Lytvyn Y, Yeung J. Hydroxychloroquine effects on psoriasis: A systemic review and a cautionary note for COVID-19 treatment. *J Am Acad Dermatol*. 2020.
62. Schwartz RA, Suskind RM. Azithromycin and COVID-19 prompt early use at first signs of this infection in adults and children: An approach worthy of consideration. *Dermatol Ther*. 2020.
63. Arshad S, Kilgore P, Chaudhry ZS, et al. Henry Ford COVID-19 Task Force. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020.
64. Asensio E, Acunzo R, Uribe W, Saad EB, Sáenz LC. Recommendations for the measurement of the QT interval during the use of drugs for COVID-19 infection treatment. Updatable in accordance with the availability of new evidence. *J Interv Card Electrophysiol*. 2020.
65. Gbinigie K, Frie K. Should azithromycin be used to treat COVID-19? A rapid review. *BJGP Open*. 2020.
66. Tran DH, Sugamata R, Hirose T, et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1 N1)pdm09 virus infection by interfering with virus internalization process. *J Antibiot*. 2019;72:759–768.
67. Retallack H, Di LE, Arias C, et al. Zika virus cell tropism in the developing human brain and inhibition by Azithromycin. *Proc Natl Acad Sci U S A*. 2016;113:14408–14413.
68. Bosseboeuf E, Aubry M, Nhan T, et al. Azithromycin inhibits the replication of Zika virus. *J Antivir Antiretrovir*. 2018;10:6–11.
69. Nourian A, Khalili H. Sofosbuvir as a potential option for the treatment of COVID-19. *Acta Biomed*. 2020;91:236–238.
70. Izzi A, Messina V, Rinaldi L, Maggi P. Editorial - Sofosbuvir/Velpatasvir as a combination with strong potential activity against SARS-CoV2 (COVID-19) infection: How to use direct-acting antivirals as broad-spectrum antiviral agents. *Eur Rev Med Pharmacol Sci*. 2020;24:5193–5194.
71. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 in patients with tocilizumab. *Proc Nat Acad Sci U S A*.. 2020;117:10970–10975.
72. Antwi-Amoabeng D, Kanji Z, Ford B, et al. Clinical outcomes in COVID-19 patients treated with tocilizumab: An individual patient data systematic review. *J Med Virol*. 2020.
73. Li Z, Wang X, Cao D, et al. Rapid review for the anti-coronavirus effect of remdesivir. *Drug Discov Ther*. 2020;14:73–76.
74. Yang N, Shen HM. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. *Int J Biol Sci*. 2020;16 1724-1721.
75. Oxford University. *Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19*; 2020 Available at: *https://www.recoverytrial.net/files/recovery_dexamethazone_statement_160620_v2final.pdf* Accessed June 17,.
76. Tang C, Wang Y, Lv H, Guan Z, Gu J. Caution against corticosteroid-based COVID-19 treatment. *Lancet*. 2020;395:1759–1760.
77. Little P. Non-steroidal anti-inflammatory drugs and COVID-19. *Br Med J*. 2020.
78. Solomon F. Scientists enlist antibody treatment in fight against COVID-19. *The Wall Street Journal*. August 5, 2020:A6.
79. Jamilloux Y, Henry T, Belot A, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev*. 2020;19.
80. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J Autoimmun*. 2020.
81. Arnaldez FI, O'Day SJ, Drake CG, et al. The Society for Immunotherapy of Cancer perspective on regulation of interleukin-6 signaling in COVID-19-related systemic inflammatory response. Version 2. *J Immunother Cancer*. 2020;8.
82. Ayhan E, Murat Öztürk M, An I, Abdelmaksoud A, Araç E. Potential role of anti-interleukin-17 in COVID-19 treatment. *Dermatol Ther*. 2020.
83. Sodhi M, Etminan M. Therapeutic potential for tetracycline in the treatment of COVID-19. *Pharmacotherapy*. 2020;40:487–488.
84. Schwartz RA, Al-Qubati Y, Zieleniewski L, Shah R, Kapila R. Onchoceriasis (river blindness): Larva-induced eczema (onchodermatitis) from an important oculocutaneous tropical disease spilling over into North America and Europe. *Int J Dermatol*. 2019.
85. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020;178.
86. Patrì A, Fabbrocini G. Hydroxychloroquine and ivermectin: A synergistic combination for COVID-19 chemoprophylaxis and/or treatment? *J Am Acad Dermatol*. 2020.
87. Rahman MT, Idid SZ. Can zinc be a critical element in COVID-19 treatment? *Biol Trace Elem Res*. 2020;26:1–9.
88. Kumar A, Kubota Y, Cherver M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. *Med Hypothesis.*. 2020.
89. Hemilä H, Chalker E. Vitamin C as a possible treatment for COVID-19. *Infect Chemother*. 2020;52:222–223.
90. Atluri S, Manchikanti L, Hirsch JA. Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically ill COVID-19 patients: The case for compassionate use. *Pain Physician*. 2020;23 E71-E83.
91. Golchin A, Seyedjafari E, Ardeshiryajimi A. Mesenchymal stem cell treatment for COVID-19: Present or future. *Stem Cell Rev Rep*. 2020;16:427–433.
92. Zhang R, Wang X, Ni J, et al. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci*. 2020;250.
93. Jiang S. Don't rush to deploy COVID-19 vaccines and drugs without safety guarantees. *Nature*. 2020;579:329.
94. Maxmen A. How to defuse malaria's ticking time bomb. *Nature*. 2018;599:458–465.
95. Chausterman BG, Swirski FK, Weber GP. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol*. 2017;39:517–528.
96. Nowill AE, Fornazin MC, Spago MC, et al. Immune response resetting in ongoing sepsis. *J Immunol*. 2019;203:1298–1312.