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HAS UNDERTREATMENT OF SEVERE COVID ILLNESS BEEN WIDESPREAD? A PEDIATRIC RHEUMATOLOGIST'S PERSPECTIVE

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Abstract: This article addresses the possibility that undertreatment of patients with severe COVID illness has been widespread and has resulted in a high number of preventable COVID deaths. In most cases of COVID infection (perhaps as many as 98% of those infected) the immune system safely and efficiently neutralizes the virus, such that the patient is either asymptomatic or experiences only mild-moderate symptoms (which may be temporarily miserable, but not life-threatening or organ threatening and do not require hospitalization). A small percentage of patients with COVID experience severe illness, and in most of these cases the most threatening aspects of the illness appear to be due to an excessive immune reaction to the virus — hyperinflammation and "cytokine storm." This hyperinflammatory state/cytokine storm is not new or unique to COVID infection. For years it has been known that life-threatening hyperinflammation and cytokine storm occur with many bacterial infections and with many other viral infections, including seasonal influenza infection. Over the past four decades, pediatric rheumatologists have developed extensive experience with excessive immune reactions (hyperinflammation/cytokine storm), including how to bring them under control. Much of this experience has come from managing systemic onset juvenile idiopathic arthritis that has become complicated by macrophage activation syndrome and "cytokine storm." The pediatric rheumatology approach to hyperinflammatory states is characterized by: early, appropriately compulsive, anticipatory, serial monitoring; prompt and appropriately bold immunosuppression of hyperinflammation, carefully using corticosteroid and anti-cytokine therapies (e.g. anakinra); and careful, anticipatory, tailored adjustments along the way — always balancing concerns about risks versus benefits. In this article it is suggested that the pediatric rheumatology approach to control of hyperinflammatory states be applied to the management of severe COVID illness.

Key words: COVID-19, Hyperinflammation, Cytokine Storm, Corticosteroid, Anti-Cytokine Treatment

БЫЛО ЛИ ШИРОКО РАСПРОСТРАНЕНО НЕАДЕКВАТНОЕ ЛЕЧЕНИЕ ТЯЖЕЛЫХ СЛУЧАЕВ КОВИД-19? МНЕНИЕ ПЕДИАТРА-РЕВМАТОЛОГА

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Резюме: Настоящая статья поднимает вопрос о том, насколько широко распространено недостаточно адекватное лечение пациентов с тяжелым КОВИД-19, и не привело ли это к большому числу смертей от КОВИД, которых можно было бы избежать. В большинстве случаев КОВИД-инфекции (возможно, у 98% инфицированных) иммунная система благополучно эффективно нейтрализует вирус и, таким образом, у пациента или вовсе нет никаких симптомов, или присутствуют симптомы легкой или умеренной тяжести (которые достаточно неприятны, однако не угрожают жизни, нормальной работе органов и не требуют госпитализации). Небольшой процент пациентов с КОВИД-19 болеют тяжело, и в большинстве этих случаев наиболее угрожающий аспект болезни связан с избыточной иммунной реакцией на вирус — гипервоспалением и «цитокиновым штормом». Это гипервоспалительное состояние и цитокиновый шторм встречаются отнюдь не только при КОВИД-инфекции. Много лет известно, что жизнеугрожающее гипервоспаление и цитокиновый шторм имеют место при многих бактериальных инфекциях, а

также при многих вирусных инфекциях, включая сезонный грипп. За последние сорок лет педиатры-ревматологи накопили огромный опыт по проблеме избыточных иммунных реакций (гипервоспалению/цитокиновому шторму) и научились брать их под контроль. Большая часть этого опыта получена благодаря работам по лечению системного начала ювенильного идеопатического артрита, который осложняется синдромом активации макрофагов и «цитокиновым штормом». Педиатрически-ревматологический подход к гипервоспалительным состояниям должен быть: ранним, достаточно упорным, упреждающим, включать серийное мониторирование, своевременную и достаточно агрессивную иммуносупрессию гипервоспаления, осторожное использование кортикостероидов и анти-цитокиновой терапии (например, анакинра); а также осторожный, опережающий индивидуальный подбор конкретных приемов «на ходу», постоянно имея в виду необходимость балансировать риски и преимущества. В настоящей статье делается предположение, что педиатрически-ревматологический подход к лечению гипервоспаления можно применить для того, чтобы справиться с тяжелыми случаями КОВИД-инфекции.

Ключевые слова: КОВИД-19, Гипервоспаление, цитокиновый шторм, кортикостероиды, анти-цитокиновая терапия

"Human experience, which is constantly contradicting theory, is the greatest test of Truth."
Samuel Johnson

«Изначально противоречивый человеческий опыт — это величайший критерий Истины»
Сэмюэл Джонсон

MAIN TEXT

To what extent have patients with severe COVID illness been under-treated? This is an under-reported, under-investigated aspect of the COVID epidemic in the USA. The hypothesis of this article is thatunder-treatment of patients with severe COVID illness has been widespread and has resulted in a large number of COVID deaths that could have been prevented? Whether this hypothesis is true remains to be determined. It is a high priority hypothesis to test.

We are not talking here about patients who have not received hydroxychloroquine, azithromycin, zinc, or vitamin D. We are talking about patients with life-threatening and organ-threatening "cytokine storm" and other immune-mediated complications of COVID who may not have received prompt, needed, appropriately aggressive immunosuppressive/immunomodulatory treatment (e.g. corticosteroid and specific anti-cytokine therapies) for these well-known immune-mediated phenomena. As will be explained in this article, effective treatments for these phenomena have long been available (before COVID), but, apparently,have been offered to only a minority of patients with severe COVID illness — often received belatedly when offered.

Among the several questions that beg investigation and answers:

1. What percentage of the patients who have died of true COVID illness could have been saved if harmful immune-mediated aspects of their disease had been detected early and promptly treated with appropriately aggressive immunosuppression/immunomodulation?
2. What percentage of patients who have survived severe COVID illness, but sustained irreversible organ damage, could have been spared that damage, if harmful immune-mediated aspects of their disease had been detected early and promptly treated with, appropriately aggressive immunosuppression/immunomodulation?
3. What percentage of the reported "COVID deaths" have truly been definite or probable COVID deaths? This question needs to be answered to accurately answer the first two.

BACKGROUND

In most cases of COVID infection (perhaps as many as 98% of those infected?) [1] the immune system safely and efficiently neutralizes the virus, such that permanent viral damage is prevented and the patient is either asymptomatic or experiences only mild-moderate symptoms (which may be temporarily miserable, but not life-threatening or organ threatening and do not require hospitalization). In these cases, the two main phases of immune reactivity work remarkably well together: First, the relatively primitive innate immune system (e.g. Type 1 interferon) quickly senses danger and creates an immediate local anti-viral milieu that thwarts viral replication — thereby diminishing the viral load. Secondly, the innate immune system (again, notably, Type 1 interferon) activates the more sophisticated adaptive immune system (e.g. B cells and T cells) which then produce viral-specific antibodies (first IgM, then IgG), activate cytotoxic T cells (which kill virus-infected cells in order to slow viral propagation to other cells), and create memory B and T cells for future protection against that virus (and, to a lesser extent, against similar viruses). In order for this sequential two-phase process to be safe, efficient, and successful, just the right amount of type 1 interferon needs to be promptly made available; just the right amount of activation of the adaptive immune system needs to occur; and the timing of these two processes needs to be just right. Too little (or too late) or too much Type 1 interferon can be harm-

ful; and too little (or too late) or too much of an adaptive immune response can be harmful. It is all about timing and balance — a careful, coordinated, timely balance.

A small percentage of patients with COVID experience severe illness, and in most of these cases the most threatening aspects of the illness are due to an excessive immune reaction to the virus [2–8]. It is possible that in some cases the type 1 interferon reaction is too slow or otherwise inadequate, such that the virus gets the upper hand and overwhelms the patient. But, most often the problem in patients with severe COVID illness is that their innate immune system,or their adaptive immune system, or both, have become excessively active. Instead of mounting an appropriate, timely, well-coordinated immune reaction, the immune system appears topanicand excessively activate much of its armamentarium — both the innate armamentarium and the adaptive armamentarium. Great imbalance, discoordination, dysfunction, and hyperactivity characterize this "hyperinflammatory state." The immune system, for example, excessively activates macrophages (a powerful and explosive primitive component of our innate immunity);excessively releases an array of potentially harmful cytokines (resulting in a "cytokine storm"); may excessively activate cytotoxic T cells (which may be dysfunctional, as well);and excessively triggers complement and coagulation cascades. These activations feed-back on each other, accelerate each other, and create vicious cycles that further escalate and perpetuate the excessive immune reactions.

Quite soon, these excessive immune reactions start damaging human cells/tissues: for example, the endothelial cells that line the pulmonary microvasculature may become immunologically injured (my hypothesis) and swell, potentially partially occluding the lumen of these vessels, thereby reducing blood flow to the lung's air sacs; the lung's air sacs may become is chemically and immunologically injured, inflamed,and potentially fibrosed; the storm of cytokines causes fever, clinical and laboratory signs of systemic inflammation, and immune-mediated injury to multiple organs; and activated coagulation cascades result in micro and macro thrombi, potentially throughout all vasculatures. All organs, including the brain, can be affected by these unfortunate immune-mediated phenomena. Respiratory failure, multi-organ failure, cardiac failure, strokes, and death often result, particularly if these excessive immune reactions are allowed to progress untreated or inadequately treated, as opposed to being detected early and promptly and adequately suppressed.

Indeed, the leading cause of life-threatening/organ threatening complications of COVID appears to be the above-mentioned cytokine storm/hyperinflammation [7]. Development of cytokine storm has appeared to be the major determinant of COVID outcome. Clinical and lab features of cytokine storm have correlated well with poor outcome in COVID [2–8]. Elevated cytokine levels (e.g. IL-6) have been found in most patients dying of COVID [7].

But, this hyperinflammatory state/cytokine storm is certainly not new or unique to COVID infection. For many years it has been known that life-threatening hyperinflammation/cytokine storm occurs with many bacterial infections and with many other viral infections, including seasonal influenza infection [9–17]. In fact, usual seasonal influenza viruses are major triggers of cytokine storm [2]. In one study of patients who died of H1N1 influenza, 81% had features of cytokine storm [13].

THE PEDIATRIC RHEUMATOLOGY APPROACH TO HYPERINFLAMMATORY STATES(E.G. "CYTOKINE STORM")

For many years, pediatric rheumatologists have known a great deal about these excessive immune reactions (hyperinflammation/cytokine storm) and how to bring them under control [18–39]. Their knowledge has been the result of extensive individual and collective experience and extensive collaborative international study, including thoughtful development of strict diagnostic and classification criteria and uniform treatment protocols [18, 19, 20, 26, 27] and randomized clinical trials [32–34]. Pediatric rheumatologists have led the way, because many childhood autoimmune diseases (e.g. systemic onset juvenile idiopathic arthritis) become complicated by excessive macrophage activation (macrophage activation syndrome) and "cytokine storm" [18–39].

Nearly 40 years ago, when I was a visiting pediatric rheumatologist at Beijing Children's Hospital, I vividly remember discussing (with Beijing pediatricians) the excessive macrophage activation and massive cytokine release associated with systemic onset JIA and how to treat it (with high dose corticosteroid, at that time). The concept of excessive macrophage activation/excessive release of cytokines was very new at that time in the USA and Europe and was largely unknown in China. Since then, pediatric rheumatologists around the world have been routinely and successfully treating hyperinflammatory reactions (e.g. macrophage activation syndrome, "cytokine storm," secondary HLH, and systemic inflammatory response syndrome) with corticosteroid and, more recently, withspecific anti-cytokine treatments — either anti-IL-1 treatment (anakinra) or anti-IL-6 treatment (tocilizumab) [32–39]. These treatments have been life-saving and organ-saving, particularly when these hyperinflammatory reactionsare recognized early,treated promptly with appropriately aggressive immunosuppression, and monitored compulsively with serial lab testing, with nuanced adjustments being made along the way.

An important lesson learned by pediatric rheumatologists is that if the clinician acts too slowly or too timidly, the patient loses. Early detection, prompt and appropriately bold immunosuppressive treatment, compulsive serial monitoring, and careful adjustments, have been the keys to success. Failure to detect early, failure to promptly treat appropriately aggressively, failure to compulsively monitor, and failure to make wise adjustments can, each by themselves, cause preventable mortality and damage. Personal experiences, collective clinical observations, carefully studied collaborative case series, and, ultimately, randomized clinical trials [32–34] have documented the value of the pediatric rheumatology approach to hyperinflammatory states associated with childhood rheumatic diseases — diseases which, by the way, are often much more explosively hyperinflammatory and life-threatening than their counterparts in adults.

This experience of pediatric rheumatologists has been applied to the recognition and treatment of cytokine storm/hyperinflamma-

tory states triggered by bacterial and viral infection, in adults and children [40–46]. Historically, for many years, Emergency Departments, hospitalists, and ICU pediatricians in children's hospitals have commonly consulted pediatric rheumatologists for help in recognizing and treating infection-triggered cytokine storm. Randomized controlled trials (RCT) of immunosuppressive treatment of infection-related hyperinflammation have been conducted [40–41]. In other words, for many years before COVID arrived on the scene, pediatricians and pediatric rheumatologists (and physicians for adults) had developed considerable experience with the diagnosis and treatment ofinfection-triggered cytokine storm/hyperinflammation. We learned to serially and anticipatorilytest patients for elevated levels of CRP, serum ferritin, D-dimer, PT, PTT, triglycerides, and liver transaminases; and lowered levels of platelets, lymphocytes, albumin, and fibrinogen — early markers of an evolving hyperinflammatory state. And we learned to treat aggressively and promptly, but carefully, with corticosteroid and specific anti-cytokine therapies, such as anakinra — all the while worrying about administering immunosuppression in the context of infection, but not being paralyzed by that worry.

In the beginning, we did not have randomized clinical trials that proved that this treatment for infection-related hyperinflammation was effective, safe, and necessary. We quickly learned, though, that these children were likely to die or sustain irreversible multi-organ damage, if not treated aggressively with immunosuppressive medications. Knowing that these children were faced with a life-threatening and organ-threatening disease process, we (and the child's parents and grandparents) felt morally and ethically obligated to boldly treat these children, despite absence of randomized clinical trials. The alternative, watching them suffer and die, was obviously unacceptable. It seemed to be obviously unethical to withhold corticosteroid and anakinra treatment that had worked so well for hyperinflammatory states associated with childhood rheumatic diseases, simply because no randomized clinical trials had yet been conducted to prove the safety, efficacy, and necessity of such treatment in the context of infection-triggered hyperinflammation. Yes, of course, randomized double-blind, controlled trials would have been ideal, but they were unavailable and would take much time to complete.In the meantime it seemed unacceptable to withhold treatments that were likely to be effective, safe, and necessary.

Our carefulboldness resulted in the eventual accumulation of increasingly justifying clinical evidence of the efficacy, safety, and necessity of such treatment — for both hyperinflammatory states associated with childhood rheumatic diseases and hyperinflammatory states associated with infection. Prior to onset of the COVID epidemic, ample ideal randomized controlled trials still had not been completed for treatment of viral-triggered hyperinflammatory states, but lessons from treatment of hyperinflammatory states associated with childhood rheumatic diseaseshadbecome well-established and were available for extremely valuable guidance. For several years now, such treatment has become the "standard of care" for cytokine storm/hyperinflammatory responses in children — both when it occurs in the context of a childhood rheumatic disease and in the context of infection. I will not speak for all pediatric rheumatologists, but many of us, particularly those of us who have seen the sad outcomes of untreated and under-treated children, would not automatically withhold corticosteroid and anakinra from a child suffering from life-threatening viral-triggered cytokine storm/hyperinflammation, and, instead, just watch them suffer and die, un-treated, or only lamely treated, as if there was nothing more we could,or should do, or appropriately try.

Pediatric rheumatologists have also learned how to recognize and treat immune-mediated microvascular endotheliopathies (as occurs in juvenile dermatomyositis and in Susac syndrome) and other immune-mediated phenomena that damage our human cells/tissues/microvasculatures [47]. This is mentioned because it is possible that a proximal cause of the initial hypoxia in COVID is an immune-mediated, ischemia-producing, occlusive microvascular endotheliopathy within the pulmonary microvasculature — with subsequent, consequent ischemic injury to the alveoli (air sacs) [48–51]. If this hypothesis is true, the best treatment would be early, effective immunosuppression, not waiting until the damage has already been done and then putting the patient, fruitlessly and harmfully, on a ventilator.

So, if pediatric rheumatologists were taking care of severely ill COVID patients back in January and February of 2020, what would they have done? Again, I do not want to speak for all pediatric rheumatologists, but here is what many of us would have done:

In the case of each patient, wewould have immediately started (early in the hospital course) to compulsively and serially document (via serial lab testing): the extent of the patient's initial viral load and whether it was subsequently increasing or decreasing, and how fast; and, the extent to which cytokine storm, microvascular endotheliopathy, and inappropriate coagulopathy were developing. If evidence of immune over-reactions (hyperinflammation/cytokine storm)were found, and if this hyperinflammation were deemed to be a greater threat than less-than-desirable viral eradication, we would have been quick to carefully, but boldly treat with immunosuppressive/immunomodulatory medications (e.g. corticosteroid and anakinra), while continuing to compulsively monitor the viral load and being prepared to augment viral eradication. This would have been our routine approach.

Yes, we would have worried about the possibility that treating a person with a viral infection with immunosuppressive treatments might adversely interfere with viral eradication and promote viral replication. But, we would have monitored for this and made necessary adjustments.We would have worriedthat under-treatment (or no treatment) of a viral-triggered immune over-reaction (e.g. cytokine storm/hyperinflammation) would lead to regrettable (and preventable) organ failure and death and represented a considerably greater threat than the virus becoming overwhelming.We would have suspected that in most patients with severe COVID illness the main problem is not the virus infection, itself, but the excessive immune reaction the virus had provoked in that particular patient. We would have concluded that failure to suppress that immune over-reaction would result in high likelihood of death or regrettable organ damage. We would have concluded that the potential benefits of treating such a patient with immunosuppres-

sive medications far outweighed the potential risks of adversely affecting viral eradication. We would have concluded that, for most patients with severe COVID illness, much greater harm is likely to occur without immunosuppressive treatment than with immunosuppressive treatment. We would have applied what we had individually and collectively learned (over the course of 40 years) by treating hyperinflammation/cytokine storm in children.

As mentioned earlier, to be careful, we would have serially and quantitatively tested the patient's viral load before and during any aggressive immunosuppressive treatment — to serially determine the viral load and whether immunosuppressive treatment was interfering with viral clearance to any clinically significant degree; to determine whether certain concomitantly administered anti-viral therapies (e.g. interferon, remdesivir, or convalescent plasma, given in combination with the immunosuppression) was wise and (if used) was providing additional benefits; and to make careful adjustments.

We would have placed great emphasis on the timing, tailoring, and adjustment of treatment; on knowing exactly where the patient stood and how matters were trending, regarding the extent of viral load and the extent of excessive inflammation; and on tailoring treatment to the changing specifics of the individual patient — always balancing concerns about benefits versus risks. Several possible patient characteristics/profileswould have been imagined whena given patientwas admitted to the hospital:

1. In some patients the main problem might be hyperinflammation, with little or no problem with ongoing viral infection. That is, the patient's innate immune system(and subsequent adaptive immune system) hadadequatelysubdued the viral infection, but an excessive immune reaction had become the main problem. At least, the threat posed by the hyperinflammation was greater than the threat posed by the viral load at the time. In such a patient, immunosuppression would be appropriate — greater immunosuppression if the viral infection had already been fully eradicated; lesser, more careful immunosuppression if viral eradication had been less complete.
2. In other patients (a minority, probably), inadequate eradication of the virus might be the main problem, without an excessive immune reaction being present. This would result in potentially overwhelming viral infection that needed immune help(interferon, and/or convalescent plasma) and anti-viral therapies (like remdesivir), not immunosuppression. One would want to be careful, however, if type 1 interferon is given (to boost viral eradication), lest it unwittingly create an excessive downstream immunologic reaction (hyperinflammation).
3. In other patients, the problem might be both an inability to eradicate the virus (resulting in varying degrees ofworrisome ongoing viral infection) and an inability to control the immune reaction to the virus (resulting in varying degrees of a hyperinflammatory state). Such patients would benefit from both anti-viral therapies (e.g. remdesivir, interferon, and/or convalescent plasma) and immunosuppressive therapies — with the anti-viral therapies being given first, followed by immunosuppressive treatment as soon as it was deemed relatively safe. Serial monitoring would guide the making of adjustments along the way.

Timing, compulsive serial monitoring, tailoring, attention to trends, and prompt informed adjustments would have been of great importance: If a patient in a threatening hyperinflammatory state was found to have a viral load that had become low, or is waning, more aggressive immunosuppression could be promptly given. If a patient in a hyperinflammatory state was found to have a viral load that was still very high, less aggressive immunosuppression might be given, until the viral load lowers, and anti-viral therapies might be initiated, first, to accelerate viral eradication. Compulsive monitoring, compulsive caring, careful timing, tailoring, constant prompt adjustments, andnuanced clinical judgment are the keys.

To maximally learn from the COVID experience, pediatric rheumatologists, starting at the beginning of the epidemic, would have made certain that **all** patients with severe COVID illness were promptly placed on some sort of an appropriately aggressive protocol — consisting of immunosuppressive treatment for those with hyperinflammation, anti-viral treatments for those with poorly controlled viral infection, or both — so that various treatment approachescould ultimately (at least retrospectively) be compared for efficacy, safety, and necessity. For example, please see the Treatment Proposal provided at the end of this article (Addendum).Pediatric rheumatologists would have made certain that no patient with threatening cytokine storm/hyperinflammatory reaction was left untreated — i.e. not given at least some corticosteroid, as early as conditions (benefit/risk ratios) would permit.

Also, it goes without saying that one of the first things pediatric rheumatologists would have done at the start of the epidemic is establish strict, accurate, uniform criteria for what constitutes a "definite COVID death" vs a "probable COVID death" vs a "possible COVID death" vs a "death occurring in the context of either a positive COVID test or exposure to COVID, but not due to COVID." This is a basic, fundamental principle of scientifically sound clinical research. These categories would not have been lumped together and all counted as "COVID deaths," which is what has been done (by the Fauci Task force, the CDC, WHO, and Johns Hopkins) and is still being done, to the astonishment of careful scientists.

Furthermore, pediatric rheumatologists would have developed strict criteria to define gradations of the disease severity of patients upon entry to the hospital and ICU — including characterizing and stratifying (both initially and serially) patients according to the severity of their viral load and the severity of any hyperinflammatory reaction.

Finally, pediatric rheumatologists would have emphasized the importance of thorough patient and family education (and Public education), including detailed discussion of the pros and cons (benefits versus risks) of all treatment options. And, family concerns would be honored. Advocacy is an important component of comprehensive pediatric care.

THE APPROACH TAKEN BY THE FAUCI-LED COVID TASK FORCE

Since the beginning of the COVID epidemic in the USA (January-February 2020), have patients with severe COVID illness been approached and treated in the compulsive, caring, anticipatory, ap-

propriately bold, tailored, and scientific way that many (most)pediatric rheumatologists would have treated them? It does not appear so.

In the beginning (or since), were strict, accurate, uniform criteria established to identify true COVID deaths? For example, has the Task Force made it abundantly clear what percentage of the reported 170,000 "COVID deaths" (as of this writing) have truly been due to COVID? No. They have lumped "definite," "probable," "possible," "conceivable-but-not likely," and "not at all likely, but there has been definite or possible COVID exposure" all together. That is not scientific or helpful.

In the beginning (or since), were strict, accurate, uniform criteria established to define gradations of disease severity and gradations of viral load and hyperinflammation (in each patient)? It appears not.

In the beginning (or since), were all patients immediately, anticipatorily, and serially evaluated for viral load and extent of immune hyperreactivity? It appears not.

In the beginning (or since), were **all** patients placed on one of several appropriate immunosuppressive/anti-viral treatment protocols, stratified according to severity and characteristics, to optimally treat and maximally learn from each and every clinical experience? Did patients and families receive adequate advocacy and education about options? Was the Public informed that treatments (like corticosteroid and anakinra) were available that, if used carefully, could likely save many patients with severe COVID illness. It appears not.

On the contrary, from the beginning, the NIH (the National Institutes of Health, both in the USA and other countries), the CDC, the WHO, the Infection Disease Society of America, and the Fauci-led COVID Task force specifically and strongly discouraged use of corticosteroid and anti-cytokine therapies for COVID [52–55]. Specifically, their guidelines stated that "corticosteroid therapy and specific anti-cytokine therapies are not recommended, unless as part of a clinical trial." Only a small percentage of patients have had realistic access to a clinical trial. Furthermore, this policyhad the effect of making clinicians fearful of using these treatments — because if clinicians used them, they would be going against "accepted expert guidelines" and would, thereby, worry about being liable if a patient's outcome became poor (regardless of whether it was due to their treatment decisions).

During the early months of the COVID epidemic, clinical trials were rare, especially in non-academic medical centers. It took months before some clinical trials were started, and now (6–7 months later) there are many in progress (though not completed). To date, most patients with severe COVID have not had access to a clinical trial and have not been treated with corticosteroid or any anti-cytokine therapy. For example, in one of the most widely cited retrospective studies of treatment of severe COVID, only 7.7% of 1806 hospitalized patients had received corticosteroid, while 92.3% had not [56]. In that study, those who had elevated inflammatory markers and were treated with corticosteroid had a better outcome.

Apparently, throughout the bulk of the COVID epidemic, the majority ofpatients with COVID-related cytokine storm/hyperinflammatory reaction have not been treated with corticosteroid or anti-cytokine therapy, and many of those who eventually received anti-cytokine treatment (e. g. tocilizumab, an anti-IL-6 therapy) as part of a clinical trial, received it after their cytokine storm/hyperinflammatory reaction was far advanced and had already caused severe damage — i.e. they were treated too late.It is unclear how many of the randomized clinical trials have paid adequate attention to issues of timing, stratification, tailoring, adjustment, and compulsive monitoring (of both viral load and extent of hyperinflammation).

The approach taken by the NIH, CDC, WHO, Infectious Disease Society of America, and the Fauci Task Forcehas seemed to ignore the extensive earlier-mentioned 40-year experience of pediatric rheumatologists. It has been as if that extensive and well-conductedbody of medical knowledge and experience did not exist, or was irrelevant to treatment of COVID — neither of which is true. Instead, the Fauci Task Force and the conventional media have promoted the impression that "we have never seen anything like this before; this is all new; we are constantly being surprised; we must await the results of randomized clinical trials and a vaccine."

Have the eventual, belatedly-conducted clinical trials on immunosuppressive treatment of severe COVID illness supported the pediatric rheumatology approach described above? Yes [57–73]. Corticosteroid treatment and anti-cytokine therapies (anakinra and tocilizumab) have, belatedly (6–7 months too late for thousands of patients), been found to be beneficial, particularly when given in a timely, careful, tailored fashion — just as the many years of pediatric rheumatology experience would have predicted. Granted, the level of ferritin and cytokine elevation in severe COVID illness has, often, not been as dramatic as in other cytokine storm situations, but this does not mean that COVID-related hyperinflammation is not harmful and does not need to be treated with early and appropriately aggressive immunosuppression.

So, what are the answers to the three questions asked at the beginning of this article?

1. What percentage of the patients who have died of COVID could have been saved if they had received prompt, careful, timely, nuanced, appropriately aggressive immunosuppression/immunomodulation for the immune-mediated aspects of their disease, with or without initial anti-viral therapies? Unfortunately, this important question has not been systematically investigated, so we do not know. My educated guess, based on experience with treated versus untreated cytokine storm in pediatric rheumatology, is that perhaps as many as 80% of COVID deaths (particularly among patients younger than 80 years of age) could have been prevented if their cytokine storm and other immune-mediated aspects of their COVID had been detected early and promptly treated with appropriately aggressive immunosuppression/immunomodulation. That is my hypothesis. It willrequire, and it warrants, thorough investigation to see if it is true.
2. What percentage of patients who have survived severe COVID, but are now dealing with potentially irreversible organ damage could have been spared that damage, if the immune-mediated aspects of their disease had been detected early and treated carefully and promptly with appropriately aggressive immuno-

suppression/immunomodulation? Unfortunately, this important question has not been investigated, so we do not know? My educated guess is that possibly as much as 80% of this damage could have been prevented with early appropriate immunosuppressive/immunomodulatory treatment.

3. What percentage of the 170,000 reported "COVID deaths" have truly been definite or probable COVID deaths? Unfortunately, this important question has not been adequately investigated, so we do not know? Unfortunately, the Fauci-led Task force did not promptly or adequately establish the criteria necessary to answer this question — and still has not. We do not even know how many of the "positive COVID tests" are accurate, because many of these lab tests have been developed by for-profit lab companies and rushed into use without proper quality control. My guess is that the true number of definite or probable COVID deaths is probably around 60,000 and that the other 110,000 "COVID deaths" havenot truly been due to COVID. Whether this guess is true will require and warrant thorough re-examination of all 170,000 "COVID deaths." Such re-examination is imperative and must be done promptly.

If there have truly been only about 60,000 true COVID deaths and 80% of these deaths could have been prevented by a pediatric rheumatologist's approach to care, this would mean that 12,000 COVID deaths would have occurred in the USA — not 170,000. This is in comparison to an average of 41,000 deaths from seasonal influenza in a typical year in the USA and 61,000 seasonal influenza flu deaths during 2017–18, in the USA, according to the CDC [74]. (The possibility that severe influenza illness has also been undertreated, historically, also needs to be evaluated.)

For further perspective, the CDC reported that, during the 2017–18 seasonal influenza epidemic, in the USA, 11 million children developed symptomatic influenza infection and 643 children died. In contrast, during the current much longer COVID epidemic, in the USA,442,785 cases of COVID positivity have been reported in children, and 92 children have died from (or with) COVID (as of 8/20/20) [75]. Despite this contrast, most people in the USA do not even remember the 2017–18 seasonal flu epidemic, while the COVID epidemic has provoked a prolonged and dreadfully harmful global lockdown. Why did 11 million children with symptomatic influenza illness, including 643 deaths, not provoke a memorable response; while 442,785 childhood COVID cases and92 deaths has provoked an extreme response that will be among the most memorable events in Human history? The number of children suffering from influenza illness in 2017–18 was more than 20 times the number of children who have been COVID positive in 2020, and the number of children who died from influenza in 2017–18 is more than 6 times the number of children who have died from/with COVID. And, yet, this COVID epidemic is being portrayed as the worst, most lethal epidemic since the 1918 influenza pandemic, and we are all being asked (soon forced?) to view ourselves and others as if we might be carriers of a virus as lethal as smallpox — despite the fact that the infection fatality rate (IFR) for smallpox is 1 in 3, while the IFR of COVID appears to be somewhere between 1 in 5000–10,000, amongst people under age 60 [76–77]. Why?

Incidentally, the most likely reason for the incidence of COVID illness in children being so much less than the incidence of childhood influenza in 2017–18 is that frequent and repeated past childhood exposure to the 4 common coronaviruses has probably conferred children with considerable cross-reactive immunity to COVID (either antibody mediated, memory T-cell mediated, or both). The same could be said about children's teachers, children's parents, and all those in the general population who have had considerable exposure to ordinary coronaviruses. This also is the probable reason for such a high percentage (41%) of COVID positive people being asymptomatic — because they have partial cross-reactive immunity. This, in turn, argues against the initial claims that the novel COVID virus was "so new" that people would have "no immunity to it" and would be quite defenseless against it. It also argues against the initial claim that COVID is extraordinarily contagious — because widespread partial immunity would be expected to at least partially reduce the spread of infection. In short, the above observations argue against the claim that the COVID virus is extraordinarily novel, extraordinarily lethal, and extraordinarily contagious.

Although the above questions and issues remain to be more completely investigated and definitively answered, my concern, as a pediatric rheumatologist, a scientist, and a caring human being, is the very real possibility that massive, widespread undertreatmentof severe COVID illness has occurred throughout most of the US health care system, since January 2020 — starting from the top, down (the Fauci-led COVID Task Force, the NIH, the CDC, the Infectious Disease Association of America, and the WHO). If such practice has, indeed, occurred, those responsible must be held accountable and we must never make such a huge mistake again.

I would like to close by emphasizing the conclusion stated in the next paragraph, about the COVID situation in general. This conclusion is more fully explained in a companion article recently published in a peer-reviewed pediatrics journal [77]. That conclusion:

COVID is a serious, potentially life-threatening viral infection, primarily in the elderly and frail, and is quite communicable; BUT, patients with severe COVID illness can be treated far more successfully than has been realized to date. Overall, there is insufficient scientific evidence to conclude that COVID represents a threat that is "far greater" than the worst seasonal flu epidemics we have experienced over the past 10 years (e.g. the 2017–18 seasonal flu). Instead, the most scientifically sound data suggest that the intrinsic deadliness of the COVID virus is comparable to that of the 2017–18 seasonal flu, possibly even less severe. Furthermore, many COVID deaths (and non-COVID deaths associated with this epidemic) could have been prevented by correcting the intrinsic deadliness of the health care system, nursing home model, general housing model, economic system, social system, and culture. Finally, the prolonged lockdown/re-lockdown approach appears to be mis-guided, unnecessary, and extremely harmful. It is dehumanizing and is not "following the science (i.e. good science)." The Swedish approach has been far more scientific, far more responsible, and far more humane. The en-

tire approach to the COVID epidemic in the USA needs thorough, honest, and immediate re-examination — preferably by a new, independent commission of unbiased, impeccably scientific, altruistic individuals (including virologists, epidemiologists, immunologists, rheumatologists, pediatricians, public health specialists, statisticians, nurses, and hospital administrators, as well as social philosophers, economists, political scientists, patients, and community representatives).

APPENDIX

Treatment Proposal for Severe COVID Illness:

This proposal begins with the understanding that patients with severe COVID illnessmay be severely ill because of one or more of the following reasons:

- Unusual difficulty eradicating the COVID virus:
- Sluggishly produced, or dysfunctional type 1 interferon.
- Sluggishly activated, or dysfunctional NK T-cells (Natural Killer T-cells).
- An unusually large viral load in the first place.
- Unusually low level of cross-reactive coronavirus antibodies or memory T-Cells (that are often provided by past exposure to ordinary non-COVID coronaviruses).
- Combinations of the above.
- Excessive immunologic reactions to the COVID virus — e.g. hyperinflammation/cytokine storm.
- A combination of unusual difficulty eradicating the COVID virus AND excessive immunologic reactions to the COVID virus.
- In addition, illness in some patients is complicated by microvascular and macrovascular thrombosis, triggered by the hyperinflammation/cytokine storm.

This proposal encourages an understanding that, statistically, most patients who become severely ill with COVID primarily do so because of hyperinflammation/cytokine storm, and they may or may not also be dealing with a worrisome, ongoing viral load.

A principle of this proposal is that it is incumbent upon the physician to thoroughly study the patient — both upon entry to the hospital and serially thereafter — to document which of the above factors are responsible for the patient's severe illness. For example, serial testing of viral load and serial testing for evidence of hyperinflamation/cytokine storm are essential aspects of excellent care.

Options for suppression of viral replication (augmentation of viral eradication):

- Remdesivir (possibly in combination with other anti-viral medications) — to interfere with viral replication [67].
- Interferon alpha 2b (possibly in combination with anti-viral medications) — to induce an anti-viral state and further inhibit viral replication [67–69].
- Convalescent plasma (possibly in combination with anti-viral medications and interferon alpha 2b) — to immediately provide high levels of antibody against the COVID virus.
- Specific monoclonal neutralizing antibody(ies) against the COVID-19 virus [78].
- IVIG [65, 70] — to possibly block attachment of virus to receptors on human cells (?); to possibly provide cross-reactive anti-coronavirus antibodies; [70] and to also helpsubdue an excessive immune response to the virus (which possibly includes an immune-mediated occlusive microvascular endotheliopathy in the pulmonary microvasculature) [47–51].

Options for suppression of COVID-induced "cytokine storm"/hyperinflammation:

- Corticosteroid (e.g. dexamethasone, methylprednisolone) — to comprehensively subdue immune over-reactivity [60, 71].
- IV Anakinra — to selectively block IL-1 and, thereby, shut down "cytokine storm" [40, 61–64, 66, 72].
- Tocilizumab, an anti-IL-6 agent, would be an alternative to anakinra, but anakinra provides more flexibility and has a better safety profile [57–59, 73].

Options for prevention/treatment of abnormal microvascular and macrovascular coagulation:

- Heparinzation [48].

The principle of this proposal is that treatment should be tailored and adjusted to the specific (often changing) characteristics of the individual patient. If the primary threat to the patient is hyperinflammation/cytokine storm, immunosuppressive treatment is the most urgent and the most important consideration. If excessive ongoing viral infection is the primary problem/threat, augmentation of viral eradication is the most urgent and important. If both problems are equally responsible/present, both need to be equally addressed, and done so in the most careful, timely, and sequenced fashion. If the primary problem is hyperinflammation/cytokine storm and there is little or no problem with ongoing viral infection, then immunosuppression can be provided more quickly, aggressively, and safely than if worrisome ongoing viral infection is also present. Furthermore, serial monitoring may reveal changes in status that permit or require nuanced adjustments.

Another principle of this proposal is that it is amenable to both tailored treatment and randomized treatment — i.e. parts of the treatment could be tailored to the specific characteristics of the patient, while other parts randomized for research purposes. For example, if a patient's primary problem is hyperinflammation/cytokine storm and that patient, at that time, has little or no problem with ongoing viral infection, then that patient could be randomized to receive either:

- High dose corticosteroid (IV pulses of mega-doses of methylprednisolone, which works faster and better than lower doses), alone
- Lower dose corticosteroid, alone
- Anakinra (or, alternatively, tocilizumab), alone
- Combinations of the above
- And, there would also be an option to randomize to also receive one or more of the treatments that would augment viral eradication.

A point of emphasis is that every patient, since the beginning of this epidemic, has deserved access to an approach like that described above. This pediatric rheumatology approach is not just some ideal, pie-in-the-sky approach that is "not possible in the

real world." The above immunosuppressive approach has been practiced for decades by pediatric rheumatologists. Pediatric rheumatologists have found this approach to not only be realistic, but to be necessary, if the goal is to save the patient.

Some further comments:

There seems to be some confusion regarding what Hippocrates meant when he said, "Do no harm." One aspect of this admonition is to avoid causing harm by the treatments/interventions you implement. But, another aspect is to avoid causing harm by your unwillingness to use a treatment/intervention that, yes, has risks, but can be life-saving or otherwise reduce suffering/damage. One aspect is "harm from actions taken;" the other is "harm from actions not taken." Some physicians seem to think that if harm occurs because of their actions, it is their fault; but, if harm occurs because of their inaction, it is the disease's fault. In my view, undertreatment of severe COVID illness results in "harm from actions not taken" and is the fault of the physician and/or the health care system, not just the disease.

It is also important to point out that randomized controlled trials (RCTs), though truly ideal, do not always represent the highest quality of evidence and data. It depends on the quality of the RCT. The assumption is that evidence from RCTs is always superior to carefully developed individual and collective experience. But, it should be realized that most RCTs are multi-center studies funded by private, for-profit pharmaceutical companies; not all studies are superbly designed; the physician-participants in RCTs are often enrolling patients and completing data record forms in a rushed fashion; and the final conclusions are typically drawn by a statistician who is being paid by the pharmaceutical company. It is a naïve assumption to believe that the data/evidence produced by all RCTs is always superior to the conclusions of thoughtful, careful, experienced, altruistically-motivated clinicians. Sometimes, carefully studied human experience contradicts the prevailing narrative (including the results of some RCTs) and is the better test of Truth.

Finally, it is important for the Public, particularly future patients, to know whether undertreatment of severe COVID illness occurs and has been widespread. (Hence, this article.) At the very least, for future patients, it is important that the pediatric rheumatology approach discussed in this article be considered for widespread implementation.If we want to save lives, perhaps the pediatric rheumatology approach should become the "standard of care," or at least be considered for such.

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