Early ambulatory outpatient sequenced antiviral multidrug COVID-19 treatment (including for Delta or similar variants) for high-risk children and adolescents

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Abstract

During the past 19 months the global spread of the Severe Acute Respiratory Syndrome, Coronavirus-2 (SARS-CoV-2 or COVID-19) has led to acute hospitalizations and death in primarily high-risk elderly and younger age groups who often present with comorbidities associated with increased risk. Otherwise, the virus is largely self-limiting in those infected outside of high-risk groups. Presently, the global community is confronting a predominant Delta variant of the virus, distinct from the initial variants, highly contagious and less virulent. The good news for high-risk populations is that early drug treatment (sequenced multi-drug treatment/SMDT) for all variants, has been shown to reduce the risk of hospitalization and death by as much as 85%. This paper is a combination of scientific research including clinical expert opinion of front-line doctors treating patients with COVID-19 and focuses on early treatments in children. The authors however, in support of the scientific literature recognize the risk of severe illness or death in the pediatric population is significantly low (statistical zero). Outlined are some of the key issues and pathophysiological principles that relate to the pediatric population with early infection. Therapeutic approaches based on these principles include 1) reduction of reinoculation, 2) combination antiviral anti-infective 'repurposed' therapy, 3) immunomodulation via oral/inhaled corticosteroids, 4) antiplatelet/antithrombotic/anticlotting therapy, and 5) administration of oxygen, monitoring, and telemedicine as needed. The key message is that as with adults, high-risk persons of any age, including the pediatric population, should not be left in a 'wait-and-see' mode whereby there is the potential for clinical decline; this, while effective, affordable, accessible, and safe treatments exist that could be administered in the pre-hospital phase. This paper should not in any way be taken as an indication or endorsement of elevated COVID-19 risk to pediatric populations, but rather as a proactive position in the rare instance a young child requires treatment. Future comparative effectiveness research comprised of high-quality and trustworthy observational study research and randomized controlled trials (especially study involving multiple therapeutic combinations/SMDT) will undoubtedly refine and clarify our clinical observations.

Keywords: COVID-19, pediatric, children, early treatment, SARS-CoV-2, ambulatory, Delta

Introduction

The authors have published multiple comprehensive treatment algorithms and protocols based on professional observations from clinical practice management of COVID-19 patients. These protocols advocate for early outpatient (ambulatory) treatment of infections with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the consequent disease COVID-19 (Figures 1 & 2).[1-6] The progression from the initial viral replication stage (spanning approximately two weeks from infection/initial symptom onset) to the subsequent hyperimmune, inflammatory, ARDS, florid pneumonia 'cytokine storm' stage (that occurs around seven/eight days to 14 days from symptom onset) presents a clear window of opportunity to arrest the disease progression and prevent hospitalization (and potential death). The initial two weeks are absolutely critical (and particularly the hyperinflammatory stage by day 8th or so from symptom onset) if we can get in there clinically and provide early treatment.

Previous guidance[1,2] was built on a repurposed antiviral framework focused on adults and older persons. Utilizing a sequenced multidrug treatment (SMDT) regimen including early application of antiviral drugs, combined with pleiotropic drugs including doxycycline and azithromycin, corticosteroids and anti-platelet/anti-thrombotic therapeutics, reduced the risk of hospitalization by as much as 85% to 90%, and eliminated the risk of death for high-risk patients.[1-6] With the evolving variants (in part due to the vaccine pressure placed on the pathogen particularly when a vaccination program is implemented during an ongoing epidemic/pandemic as this can drive antigenic, or immune, escape), it has been observed clinically that younger persons may be more susceptible to a SARS-CoV-2 infection. Therefore, the need for an early intervention protocol is prudent and necessary even for the more infectious but non-lethal predominant Delta variant for high-risk younger individuals with co-morbidities, which could increase their risk for severe symptoms. The authors have decided that a proactive approach for high-risk younger individuals is judicious at this time.

We also point out, with urgency, that there is a groundswell of worldwide data indicating that the current COVID-19 genetic therapies (vaccinations/injections) being touted for children and adults alike have been demonstrated to have markedly less efficacy than originally predicted.[7] Moreover, there are morbidities, particularly cardiomyopathies in children which are strongly associated with the COVID-19 vaccination: we see that these morbidities are temporally associated with administration of the vaccines, and we also see abundantly available biologically plausible probabilities. These vaccinal harms are far more prevalent than anticipated, and many of these injuries are life-altering. Of even greater concern, we point out that the post-vaccine injuries are so severe as to be lethal in some cases. The CDC alone showed that the risk of dying from or being hospitalized from the vaccines was greater than that from COVID. Currently as of this writing, the CDC reports on hospitalizations in children show no significant increase in numbers of hospitalizations from presumably the delta variants, for the 0-4 and the 5-17 age group, than they did in January of 2020, before Delta was the predominant strain in the US. They are also showing a downward trend as of September 4, 2021 reporting.

Secondary to the decreasing efficacy[7] of the current COVID-19 genetic therapies program (vaccination/injections) as well as observed increased observed post-vaccine injures and even death in children,[8] we cannot rely on the this EUA program to protect children from COVID-19. For example, US researchers say teenagers (boys 12 to 15 years old with no medical conditions) are more likely to get vaccine-related myocarditis than end up in hospital with COVID-19 (six times more

likely).[8] We feel strongly that children should not be vaccinated for COVID-19 given their low risk profile from the virus[9] and the lack of vaccine safety testing data,[10] particularly long-term data for this population, to exclude harms reliably. No healthy children, which comprises the overwhelmingly vast majority of children, are at risk and should be targeted for vaccination against COVID-19. In sum, we do not support these injections in children given their very low risk of COVID-19 infection, of spreading infection, or of getting severely ill. The COVID-19 vaccine offers no opportunity for benefit in children, just opportunity for potential harms.

With a brief focus on the emerging variants, the concept of '*Muller's ratchet*'[11] may help explain (at least partially) the development of various variants/mutations including that of the SARS-CoV-2 Delta variant which, as per Muller's concept, is generally more contagious but less deadly than the original version of SARS-CoV-2 that originated from Wuhan. The Delta variant poses even less risk to the health of our children than previous iterations of this virus. There are some however, who speculate that the Delta variant may be more pathological than initial variants. Although all the data we have seen thus far suggests otherwise, we must remain open to the possibility and be alert to this should future evidence show this. At this time, it does not.

It is also entirely possible that the early treatment window for the Delta variant may be shorter than the four-to-five day window of previous variants, if the Delta variant is more efficient at entering the cells and replicating. It also may be that the substantially higher viral load observed in the nares of the fully vaccinated, may be transmitting a higher load of infectious viral particles to start with which ramps up the infection sooner.[12] In addition, it may be that Muller's ratchet does not apply to Delta specifically, but the applicable principle remains sound: vaccinating during a pandemic with a non-sterilizing and imperfect vaccine will drive the creation of mutant variants some of which could be more dangerous versions of the pathogen. It is generally accepted and well-known that as time goes by and viruses evolve in an unvaccinated population, they will mutate into attenuated or weaker forms that no longer cause major illness in people. However, in this case we would expect a drive toward the opposite due to immune escape in the vaccinated and an evolutionary pressure to avoid the narrowly targeted antibodies, such as is seen with Marek's disease in chickens.

We strongly believe this is the case with Delta variant, and this consideration alone underscores why, at this time in history, children should not participate in the current COVID-19 vaccination program—especially considering the lack of long-term safety data in the pediatric population. Notwithstanding the fact that should a child become infected with the extant viral variants, the child will develop durable, long lasting, and robust immunity resulting from natural exposure; immunity that is far more vigorous than any immunity that could possibly be conferred by any vaccine; even more so for the very narrow 'spike-specific' vaccine-induced immunity that is provided by the current mRNA and DNA based injections. Moreover, currently available data show that the current mRNA/DNA injections put our children at risk for the development of potentially dangerous side effects in the short term and unknown side effects in the long term.[8]

The combination of absolute risk reduction (ARR) of <1.0% in children and the high risk of adverse events, especially antibody-dependent enhancement (ADE) and emerging cardiac events in this population (pericarditis and myocarditis[8]) leads many (including those in this research group) to contend vehemently that the vaccine should not be given under any circumstances, even to children who have risk factors e.g. are obese, have diabetes, or are immunocompromised. The <1.0% ARR and the non-theoretical and compelling ADE risk with the vaccine safety risks make compelling arguments for contraindication in children.

Discussion

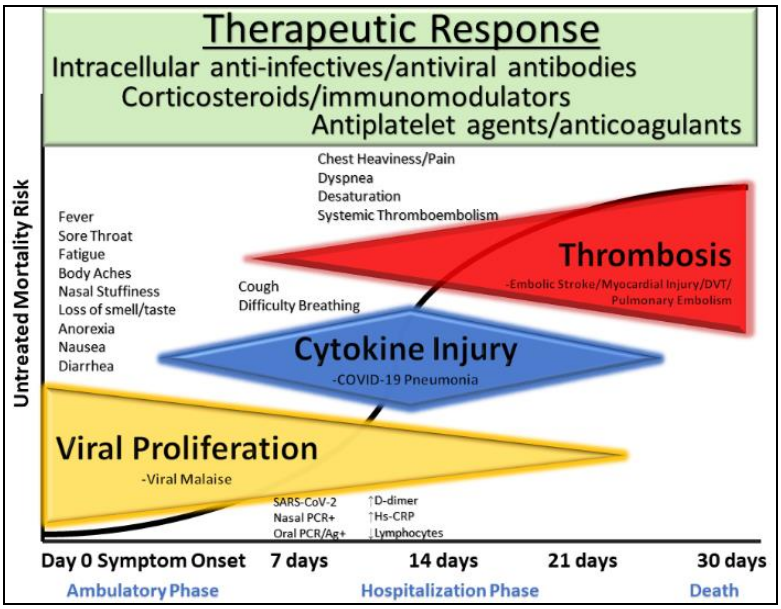
Therefore, we present here much more viable and effective treatment options in the form of SMDT which are highly safe and effective for the prevention and treatment of COVID-19. As noted above, healthy children and young adults have little to no risk (statistical zero, almost zero) for death from COVID-19. If they do develop COVID-19, the presentation is usually mild. Although more severe disease can develop, especially in those with comorbidities, the treatments proposed hereunder (i.e., SMDT) should reduce the risk for serious disease and death by potentially the same 80-90% as seen in adults, if not more.

COVID-19 is known generally as a disease of the respiratory system, but as increasingly more evidence emerges, it has become clear that it is also, if not principally a disease of the vasculature,[13-15] with accumulating evidence indicating that SARS-CoV-2-mediated endothelial injury is a central effector of viral disease, injury and death.[13-15] The spike glycoprotein on the viral ball appears to be a key player in pathogenicity and dysfunction to the vascular endothelium (and endothelial glycocalyx). The spike glycoprotein activates many inflammatory mechanisms of the immune system. Although these features are observed in acute respiratory distress syndrome (ARDS), researchers have reported that "endothelial dysfunction is the common denominator of multiple clinical aspects of severe COVID-19 infection that have been problematic for treating physicians" and could be more severe than similar symptoms observed with ARDS.[15]

COVID-19 presents as either a mild flu-like condition (asymptomatic or mild symptoms) or more serious illness in those at high risk. A very small fraction of persons infected with the COVID-19-causing virus, progress to serious illness (increased age, obesity, renal disease, cardiovascular disease, COPD etc. are typical risk factors). Evidence indicates that younger persons manifest similar risk factors whereby Kompaniyets[16] (June 2021) reported in a cross-sectional study of 43, 465 patients aged 18 years or younger with COVID-19, that more than one-quarter had one or more underlying medical condition. The cross-sectional study found "a higher risk of severe COVID-19 illness among children with medical complexity and certain underlying conditions, such as type 1 diabetes, cardiac and circulatory congenital anomalies, and obesity".

The complex and multidimensional pathophysiology of life-threatening COVID-19 including viral-mediated organ damage, cytokine storm (as with ARDS), and thrombosis warrants early interventions to address all components of the illness. The multi-dimensions of COVID-19 infection and disease sequelae are shown in Figure 1, underscoring the rationality of a multi-drug approach to treatment in the early period of illness (presented without any adaptations and with permission from the original publication).[1,2] A key feature is the overlapping pathology that clinicians must be aware of and treat accordingly in terms of timing of therapeutics in order to obtain optimal clinical outcomes. While this figure[1,2] demonstrates the general pathophysiological course of COVID-19 in adults, it is highly relevant for high-risk children as well.

Figure 1: Major dimensions of COVID-19 infection that call for a multi-drug strategy in the early ambulatory period with available medications[1-6]



The illness can be divided into three phases:[1,2]

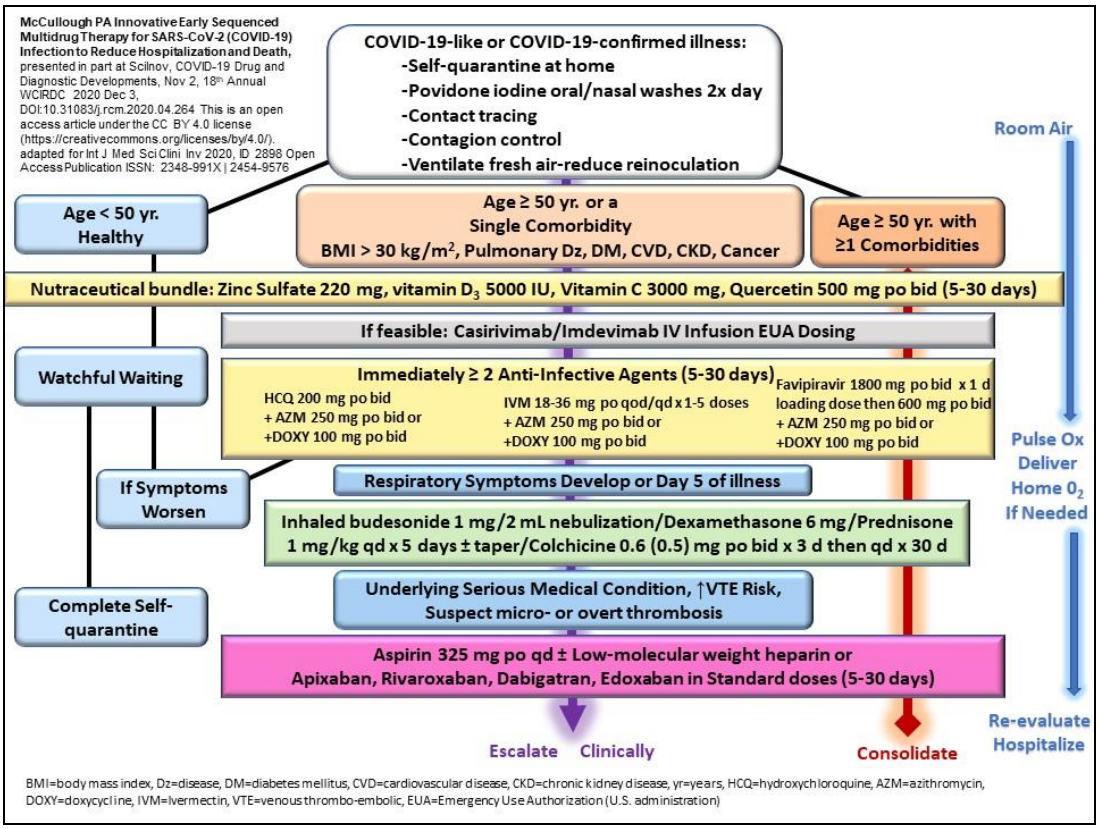
1) An initial viral replication phase whereby the virus *hijacks* the metabolic machinery of the host cells which then begin to synthesize new viral particles,[2]

2) A more advanced inflammatory hyper-dysregulated immune-modulatory florid pneumonia phase (acute inflammatory response) characterized by the cytokine storm and impaired gas exchange with breathing problems, this being representative of or at the least highly similar to ARDS, and which is generally what causes most deaths attributed to COVID-19,[2] and

3) A thromboembolic 'blood-clotting' phase whereby microthrombi develop within the lungs (causing hypoxemia) and in the vasculature,[2] leading to disastrous tertiary complications including cerebrovascular and myocardial ischemia, although notably, such infarcts can occur in any organ or tissue, causing unique symptoms relevant to the function of the organ or tissue.

An ideal 'early treatment' regimen in adults will arrest the virus in the initial phase (during the days immediately post-infection when symptoms initially emerge) while the patient is still within the private home setting or extended care setting (nursing home, long-term care facility, assisted-living facility, care-home etc.). The goal is to prevent hospitalization and death. The risk of death escalates rapidly with time elapsed following the development of symptoms (the risk of death is approximately 38 to 40% at 28 days in-hospital); hence the need for early intervention is critically important. The progression in high-risk children is likely comparable if they are not treated early based on extrapolation of clinical data. Figure 2 presented with permission and with updates by Dr. Peter McCullough (August 27th 2021),[1,2] outlines early repurposed treatment (for early COVID-19 infection) for the adult population but can be adopted easily for high-risk children, adjusted by the treating physician.

Figure 2: Sequential multidrug treatment algorithm for ambulatory acute COVID-19 like and confirmed COVID-19 illness in patients[1-6]



Fortunately, prompt and early initiation of SMDT remains a widely and currently available solution to stem the tide of hospitalizations and death. The repurposed drugs already have regulatory approval, are safe, effective, accessible, and economical. Physicians globally must embrace both the science and the art of medicine when they consider the needs of each of their patients.
There is no reason for physicians globally not to stand against these sanction threats and to exercise their best clinical judgement to save their patients.

Viral illnesses like COVID-19, with their complex pathophysiological features, do not respond to single drug treatment but more often require a multi-drug approach. Knowing this elementary science regarding the virus, is critical to evaluating emerging treatments and optimal strategies. The fact that many non-clinical physicians and scientists failed to understand the complexity of COVID-19 illness led to a stunning failure in developing early clinical trials. Many tested only a single drug at a time (sometimes in lethal doses) and often failed to intervene upon first detection of infection, which was an approach almost guaranteed to fail.

Randomized trials of *individual*, novel oral medications have not delivered effective information. *Single* therapeutic treatments have been inadequate for treatment of COVID-19 while *combinations* of the medications described here have been employed very successfully. There is, unquestionably an urgent need for the medical profession to apply the SMDT approach universally to benefit large numbers of patients (including younger persons) with acute COVID-19 thereby reducing the intensity and duration of symptoms while, most importantly, preventing hospitalization and death.

As is seen in the protocols illustrated above,[1-6] the multipronged 'combination' therapeutic approach, SMDT, includes

1) Adjuvant nutraceuticals;

2) Combination intracellular anti-infective therapy (antivirals and antibiotics, the latter having pleiotropic and beneficial effects on downregulation of viral replication, protease activity and oxidative stress which are critical components of ARDS);

3) Inhaled/oral corticosteroids and colchicine;

4) Antiplatelet agents/anticoagulants; and

5) Supportive care including supplemental oxygen, and monitoring often requiring only telemedicine.

The authors have called for the routine use of EUA monoclonal antibodies since their inception (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19) especially in high-risk persons as it could cut the risk of hospitalization and death (by as much as 85%). We continue to call for the use of these antibody therapeutics as part of the curative armamentarium, and stress intravenous infusion application very early on in the development of COVID-19.

This brief update thus describes the use of early SMDT regimens specifically in high-risk children (which also can be applied to adolescents, and young adults of child-bearing age) if infected with SARS-CoV-2 in any of its variant forms including the current predominant Delta form. Our proposed treatment protocols are likely to be effective for respiratory syncytial virus (RSV) and influenza in children too and thus, the initiation of early treatment regardless of COVID diagnosis can be an optimal approach.

Are children at risk for severe COVID-19 and death? Based on 18 to 19 months of data, children are at near zero risk for the development of severe COVID-19 and thus it is appropriate to ask why we would propose a treatment paradigm for them. This is because while it is clear that children are at low risk of spreading infection to other children, to adults, or of taking it home or becoming ill, there is still a small subset of children, particularly those with notable comorbidities, who might develop more serious disease; disease that can be prevented with SMDT.[17,18] This knowledge has been available for over one year now.

We understand that children and younger people who have comorbidities including obesity can *still* be at risk for the development of severe COVID-19, and we concluded that it was necessary to focus on this very small portion of children for their protection. In this regard, reports suggest that children with major excess body weight often present with more advanced COVID-19 symptoms which underscores the need to focus on these children if infected. Clinical experience suggests the only time children get hospitalized occurs if early treatment is not offered when presenting with severe symptoms.

Several factors may account for such a low risk of infection and transmission in children, also underscoring why current COVID vaccines offer no opportunity for benefit yet only opportunity for potential harms in children. We must also be on guard for the possible development of more virulent mutations in the future, particularly given the use of what are now known to be rather 'leaky' vaccines.[19] Children seem to have the capability to evade SARS-CoV-2 naturally due to a lack of angiotensin-converting enzyme 2 (ACE-2) receptors in their oral cavity and upper respiratory tract, which SARS CoV-2 needs to bind to in order to infect cells.[20,21] Children also bring prior cross-reactive cross-protective immunity from common cold exposures.[22]

Research evidence by Yang et al.[22] showed that blood retrieved from children prior to the COVID-19 pandemic contains memory B cells that produce antibodies that can bind to SARS-CoV-2, indicating the potent role of early childhood exposure to common cold coronaviruses. This underscores the importance of early childhood B cell clonal expansions and cross-reactivity/cross-protection, in subsequent exposures and responses to novel pathogens e.g. SARS-COV-2. Researchers reported that "Consistent with reported serology, pre-pandemic children had class-switched convergent clones to severe acute respiratory syndrome coronavirus 2 with weak cross-reactivity to other coronaviruses…these results highlight the prominence of early childhood B cell clonal expansions and cross-reactivity for future responses to novel pathogens". These two points[20-22] may help explain why children are not candidates for the COVID-vaccines and may well be (are) immune and can be considered "vaccinated."

Building the case against COVID-19 vaccination in children, ongoing research and discussion suggests that children are less likely to suffer widespread infection throughout the body and that their immune systems appear capable of eradicating SARS-CoV-2 before it can reproduce in high numbers.[23] Weisberg and Farber et al. suggest that the reason children can more easily neutralize the virus is that their T cells are relatively naïve and thus since children's T cells are mostly untrained, they might have a better capacity to respond to novel viruses. This builds on the research by Kumar et al.[24] and enticing research by Mateus et al.[25] who reported on T cell memory to prior coronaviruses that cause the common cold.

Adding to this, we have very recent research by Loske et al.[26] that deepens our understanding even further by showing that pre-activated antiviral innate immunity in the upper airways of children works to control early SARS-CoV-2 infection. The study provides evidence that "the airway immune cells of children are primed for virus sensing, resulting in a stronger early innate antiviral response to SARS-CoV-2 infection than in adults".[26] Pulling these emerging research findings together strengthens our case that children are not candidates for the COVID-vaccines and are to be considered already "vaccinated."

To underscore the vast publicly available medical evidence that children do not transmit the virus, very recent research by Galow et al.[27] was based on examining household transmission rates in children and adults. They reported that there was "no transmission from an index-person < 18 years to a household contact < 18 years (0/7), but 26 transmissions from adult index-cases to household contacts < 18 years (26/71, SAR 0=37)". These findings (no child-to-child transmission but adult to child transmission) are in line with evidence that children are less at risk of developing severe illness courses, and also are far less susceptible and likely to spread and drive[17,18] SARS-CoV-2. These findings, again, run counter to the notion that children need a vaccine for COVID-19.

While the risk for infection in children is very low, parents and societies are being pressured to participate in vaccination programs which have been largely untested and are void of long-term follow up. This greatly concerns us and it is the lack of 'exclusion of harms' short, medium, and long-term study data in children, that is very worrisome. Parents and physicians should be aware of alternate successful treatment options in the rare instance of severe illness in their child.

Any medical intervention should be based on informed consent which the Joint Commission suggests should include 1) the nature of the intervention/procedure, 2) the risks and benefits, 3) reasonable alternatives, 4) risks and benefits of alternatives, and 5) assessment of patient/guardian understanding.[28] Parents will be less likely to chose COVID-19 vaccination if they are educated on the first 4 points. Informed consent results in parents participating in joint decision-making with the healthcare team. We therefore urge the consideration and application of early SMDT as described below on a case-by-case basis. It is critically important to understand for children who get sick, a "wait-and-see" approach while symptoms progress is contraindicated. As soon as the child's condition worsens, early treatment should begin.

Our position has been clear from the outset and we continue to hold that children should be left alone given how well they do when dealing with SARS-CoV-2/COVID-19. Low-risk children should be allowed to live largely unrestricted lives with natural and harmless exposure and infection 'if' it occurs, as part of daily life (regular day-to-day living), so that they can develop very broad, durable, robust, and long-lasting naturally acquired immunity. We will *never* support the concept of "deliberate" infection or unnecessary risk, and importantly, the high-risk persons (elderly etc.) in a society must be firstly properly and strongly protected as a basis. Importantly, natural exposure immunity for children is equal and in truth superior to any immunity the existing vaccine can confer. Low-risk persons (young) are very well able to confront the virus (this virus, based on all we have learnt across the prior 19 months) and contribute to population immunity once the high-risk (elderly etc.) are properly secured.

Obesity is the number one risk factor (along with elevated age and co-morbidities) for severe outcomes such as death in COVID-19.[16,29] Addressing obesity in both children and adults should be the number one public health priority for prevention of not only COVID-19 but a multitude of non-communicable diseases, where many of those have additionally been observed as comorbid risk factors for COVID-19 (Type 2-diabetes, coronary heart disease, stroke, asthma and several cancers).[30] Prevention regarding overweight and obese children is thus germane to this paper and is very important since about 19.3% of US children are obese and about one third are classified as overweight. Obesity can harm nearly every system in a child's body-heart and lungs, muscles and bones, kidneys, and digestive tract. If it is not addressed, it may interfere with the effectiveness of treatment. For both adults and children, obesity (excessive body weight) remains one area needing urgent 'acute' focus and management given the potential for a more severe outcome if infected.

Evidence-based medicine (EBM) involves finding evidence and utilizing evidence to drive clinical decisions. The hierarchical system of classifying evidence includes randomized controlled trials (RCTs), Level I evidence, at the top and expert opinion (Level V) at the bottom. Whenever possible, RCTs should be embraced, however these studies especially when performed well take time; time which unfortunately is not available during a global pandemic. Therefore, science and society can not exclude the value of observations made during clinical practice by physicians who treat patients with COVID-19. During times like this where the science of the disease is evolving on a daily basis, we cannot discredit the value of the "n of one" to drive scientific inquiry. The

following paragraphs will take into consideration a combination of clinical observations from physicians who treat patients with COVID-19 as well as supporting evidence for the theoretical application of repurposed medications and nutraceuticals for the prevention and early treatment of COVID-19 not only in adults but children.

Dr. Peter McCullough who has pioneered and championed early therapeutic treatment for COVID-19,[1-6] has indicated through personal communications, in e-mail communications, and in presentations that "...it depends how children present. When children are going to get sick, they present with severe symptoms early.... The expert doctors treating patients recognize that. If you have a child with the sniffles and they go for three or four or five days, they're going to be fine. But if a child presents early, with high fever and pulmonary symptoms, that's the type of child you're concerned about. That's the child that in my view needs to be treated....school aged kids, problems breathing, severe symptoms, fever that will not come down, fever over 40°C, then you make a call to the doctor…outside of that it comes down to underlying medical conditions…Type I diabetic, cystic fibrosis, let's get going on treatment early…the hospital is too late to begin to treat the high-risk ill child, so we have to activate the pediatricians and doctors early to play their part…".[31] Dr. McCullough further states (electronic communication September 4th 2021) that "No child should need admission with Delta if properly managed early…the only children we hear about getting hospitalized, are those who are denied any early treatment, or those who have underlying lung disease, like cystic fibrosis or other problems. Of all the deaths that occurred with COVID-19, there are very few, fortunately, with children. We know that the majority had underlying heart or lung disease or cancer, and there were far more children, unfortunately, who died of accidental injuries, or even strangling, than COVID-19 last year, so COVID-19 is not a major threat to children".

In this regard, emergency physician Dr. Mark Trozzi (personal communication to the research group) emphasizes para "that most children will have mild symptoms if any, and require no medication. However, physicians could be guided by various criteria for pharmaceutical treatment such as shortness of breath, decreased O2 saturation, signs of sepsis, or a clinical impression of serious illness".

Issues with availability of early treatment therapeutics may arise, but the key backbone antivirals such as hydroxychloroquine and ivermectin have regulatory approval and have been and continue to be used safely by billions of people yearly across the world. Similarly, corticosteroids and acetylsalicylic acid (ASA/aspirin) are readily available core medicines. Zinc supplementation[32] cannot be overlooked in its potential prophylaxis and treatment role for COVID-19 because it plays a part in mechanisms of viral attachment and thus invasion of host cells, infection, uncoating, blocking of the virus entry into the cell, and altering RNA-dependent RNA polymerase (RdRp).[32]

Zinc inhibits RdRp, the common path of replication for all the variants. Therefore, the zinc/zinc ionophore mechanism forms the basis of a broad, efficacious treatment approach that is efficacious for all the variants if used in the right time frame. Vitamin D[33-37] is also critical for immune system function (T-cell immunity) and deficiency has been shown to predict the development of severe COVID-19. Vitamin D deficiency has been reported in 9% of children 1-21 years surveyed in the 2001-2004 National Health and Nutrition Examination Survey (NHANES) and 61% were considered vitamin D insufficient.[38] Documented deficiencies and efficacy in treatment necessitated highlighting these two nutraceuticals.

Dr. George Fareed and Dr. Craig Wax recommend "that the most symptomatic 'severe' children receive both [Hydroxychloroquine] HCQ and [Ivermectin] IVM at the outset along with [Azithromycin] AZM, zinc and Vitamin D". Dr. Wax indicates that he treats patients with COVID-19 for 10 days, pediatric, adult, and geriatric alike.

Next, a brief focus on younger children/babies, with Dr. Ira Bernstein indicating that supportive care (Table 1) is all that is needed. Dr. Billy Davis echoes this treatment strategy by reminding that as far as children are concerned, caution is a key component, stressing that no one wants a single severe issue with dosing of any drug in children. Dr. Davis leaves treatment to the respective physician suggests a single antiviral dose in children either at the first sign of symptoms or immediately after confirmation. If the physician decides to use ivermectin, then treating them prophylactically "for suspected COVID" with a single dose should be completely benign. The suggested dosing level for children is 0.2 mg per kg of body weight. This is the same dose used for FDA approved indication. Generally, this medication is not recommended for children weighing under 15 kg. However, in a 2020 study[39] of ivermectin treatment for scabies in pediatric populations Levy reported, "of 170 infants and children weighing < 15 kg who were treated for scabies with oral ivermectin, there were only seven reported mild adverse events and no serious ones". [39] Levy's results suggest children weighing, 15 kg can be treated using ivermectin without serious risk of adverse events.

Dr. Lionel Lee advises "for children with a body weight of 50 to 99 pounds, 6 mg ivermectin for only 2 days is reasonable". If the child is above 100 pounds, "then 3 tablets of IVM for 2 days is also reasonable and has worked well". Dr. Lee also suggests the use of Zofran or Phenergan to better treat severely ill children who experience episodes of vomiting.

Based on extensive clinical experience with Vitamin D, Dr. Richard Urso has specified "that 1000 IU Vitamin D3 be added for every 30-35 pounds or every 15 kilos body weight". In his personal communications to the research group, he has explained children under his care "never experienced [Upper Respiratory Infections] URIs, asthma and other childhood illnesses to any significant degree after beginning the D3" and with acute COVID-19, "it helps with thrombosis".

Pediatricians desiring to immediately correct vitamin D deficiency should consider the evidence for the use of calcifediol[40,41] as a viable over the counter alternative to vitamin D3 for those presenting with COVID19 and other severe respiratory illnesses. Calcifediol raises vitamin D levels within four hours, as it does not require liver metabolism. Vitamin D replete human beings can induce cathelicidin, an anti-microbial peptide; shown to both block viral S1 and cloak the ACE 2 receptors; a powerful, yet little recognized host defense mechanism.[40,41]

Anticoagulation is a central principle for SMDT and can be accomplished with ASA (low or high-dose). However, we recognize and appreciate potential concerns of the medical community regarding the use of ASA in children because of the association between ASA use and the development of the encephalopathy, Reye's syndrome. Anticoagulation is important to protect from the thromboembolic effects of COVID-19 but the use of antithrombotic drugs is problematic for outpatient treatment of children. Full-dose ASA, 325 mg/day works well for ambulatory outpatient adults with COVID-19, but ASA is contraindicated for children for reasons alluded to above. Coumadin/warfarin (vitamin K antagonist)[42] can be prescribed for children but requires titrating and monitoring, making it unsuitable as a pragmatic therapeutic choice. Other antithrombotic drugs (e.g., low molecular weight heparin[42]) might be suitable in hospital settings but not for home treatment.

"Curcumin, the main ingredient of Curcuma longa L., has been used as a spice and as an herbal medicine with different therapeutic characteristics for centuries in Asian countries. This phytochemical has been shown to possess beneficial antiplatelet activity that has introduced it as a promising candidate for the treatment of thromboembolism, atherothrombosis, and inflammatory diseases. Platelet dysfunction under different circumstances may lead to cardiovascular disease, and curcumin has been shown to have beneficial effects on platelet dysfunction in several studies".[43] This is untested, but it can only help, and it would be imprudent to provide no anticoagulant at all. There is also some consensus that ASA use be reserved for children over twelve years per the concerns previously discussed; therefore, using natural supplements such as fish oils or turmeric for antiplatelet activity in younger children is a strong consideration.

Therefore, despite the medical profession's traditional avoidance of ASA for children due to the risk of Reye's syndrome, we questioned whether the risks of thromboembolic disease might outweigh the risks for development of Reye's. Altered to the stated issues and hesitance surrounding use of ASA, we engaged in greater reflection and deeper study before concluding the risks of severe and potentially life-threatening blood clots outweighed the risk for Reye's syndrome. Thus, we support the use of ASA in the treatment of children with COVID-19 but understand it should be the treating physician's choice as to whether inclusion of ASA is appropriate for treatment of COVID-19. The severity of COVID-19 in the child would most likely be the determining factor. We expect short-term, lower dose use of ASA should pose a low risk for the development of Reye's syndrome. Given the thrombotic and carditis risks to children (teenagers) with severe symptoms, the analogy to acute rheumatic fever should be taken and here, the benefits of ASA outweigh the risks for empirical treatment. The key in any ASA discussion in children relates to a child adjusted dose.

Today, our recommended treatment for COVID-19 includes the use of ASA out of grave concern for the seriousness of the thromboembolic complications of COVID-19 in a very small subset of children. Our decision, based on risk-benefit discussions, was not taken lightly and ultimately the same process must be engaged in by each physician treating a child with COVID-19. The risk of potentially damaging and long-term neurological complications of blood clots or even death from blood clots requires urgent intervention, and must be weighed against the risk of Reye's, which can be argued to be less severe. The risk of Reye's may be less risky than developing blood clots and physicians must appropriately apply their best clinical judgement to determine appropriate treatment for children with COVID-19. Clinical judgment and risk-benefit analysis are paramount to our early treatment model and should take precedence over traditional 'rules' as a physician makes decisions regarding the treatment of a very sick patient.

We also note ASA is considered as the standard of care for treatment of acute rheumatic fever and Kawasaki disease in children.[44, 45] Physicians unwilling to prescribe ASA (and this paper is not "carte blanche" recommending the use of ASA), even short term under these special circumstances, may choose to resort to such natural anticoagulants as curcumin which may provide a measure of protection. These are untested in COVID-19, whereas ASA has been used successfully in hundreds of thousands of adult cases, and its effectiveness has been documented.[46] Again, physicians can make the decision based on their autonomy and clinical discretion, on whether to include or not include ASA in their treatment plan.

In the authors' opinion, with acute moderate to severe COVID-19 disease, the risk of thrombotic complications (micro-thrombosis) is so high and the consequences so potentially devastating, it

would be irresponsible to not provide some form of anticoagulant protection as part of routine treatment. Balancing the risks by the physician based on their case-by-case judgement is critical. Dr. Peter McCullough stated further that in terms of adults (in personal communication) "the mode of death is micro-thrombosis. It has been shown in all the autopsies. The UCLA data show marked upregulation of TXA2. ASA is critical and other options much less viable. Observational data in adults all show benefit with ASA…ASA is recommended for acute rheumatic fever and Kawasaki disease in weight adjusted dosage…by extension to children with severe disease is very reasonable". On the basis of specific mechanisms of action, ASA is preferable to other anti-thrombotics such as curcumin but this is not a recommendation for the unconstrained use of ASA for all patients but rather raising it as an option for severe pediatric COVID-19.

Many natural supplements and foods are known to have anticoagulant effects (turmeric/curcumin, ginger, cayenne pepper, vitamin E, garlic, etc.) and may help circumvent the concerns over childhood ASA use. Of these and as mentioned, curcumin,[43] the concentrated extract of turmeric, may be best suited to help provide anticoagulant support for children with COVID-19. However, this is completely untested.

Another modality, ozone therapy, has been used successfully for viral diseases, including Ebola, and bears consideration.[47] The mechanism of action directly impacts the severity of the cytokine storm. The therapy improves blood rheology, oxygen delivery and utilization, modulates inflammation, and cytokines, including suppressing tumor necrosis factor alpha; just as well as dexamethasone. [48,49] It has already been reported useful in COVID infection and may be useful in high-risk children, upon the clinician's consideration.

It is also noteworthy that two important pathophysiological mechanisms underlying Reye's or other virally mediated encephalopathy include upregulation of matrix metalloproteinase activity, and the development of oxidative stress.[46-53] Importantly, the other drugs being used for SMDT are pleiotropic in nature and provide for inhibition of both oxidative stress and matrix metalloproteinase activity which would be expected to reduce any risks for the development of Reye's syndrome.[46-54]

ASA is known to be protective against COVID thrombosis complications, but we again urge caution in ASA's use in children.[55,56] No drug treatment must ever be used without a physician's supervision, especially when it comes to children. Table 1 has been populated based on expert clinical opinion from front-line and emergency clinicians who have successfully treated thousands of patients diagnosed with COVID-19, at various stages of illness and in various age groups. Pediatric dosing guidance could be taken from The Harriet Lane Handbook and Nelson Textbook of Pediatrics; physicians are in the best position to make dosing decisions based on their best clinical judgements,[57,58] increasing frequency or dosage as needed dependent on severity.

Children with severe symptoms and/or may have asthma may benefit from a budesonide inhaler or a brief course of oral prednisone. [59] Generally, children do not need monoclonal antibodies or antivirals. Authors also advise against the use of antivirals (HCQ or IVM) in Table 1 as a form of prophylaxis in children, who do not need prophylaxis.

Regarding steroid inhaler dosage (Table 1): The Oxford STOIC and PRINCIPLE trials[60,61] of COVID-19 adult patients prescribed the highest recommended adult dosage of metered-dose budesonide (Pulmicort): 800 mcg bid. In the STOIC trial, treatment began on average 3 days after symptom onset and resulted in 91% reduction in urgent care visits including emergency room

evaluations and hospital admissions (p= 0.004). Standard textbook recommendations for steroid inhaler dosage for chronic asthma in children are based on long-term use. In pediatric COVID-19, typical length of treatment may be in the range of 5 – 7 days, which is a different consideration than with chronic asthma. It will be up to the clinician to determine starting dosage and make adjustments according to clinical response.

Age is always the first consideration with proposed treatment and starting dosage, however, a physician's clinical discretion and supervision is priority when considering each child on a case-by-case basis. As an example, physicians report that the children who have more advanced COVID-19 illness have excess body weight. Physicians will therefore need to consider this when dosing and not rely on age alone as a guide. Dr. Vladimir Zelenko advised that he would switch low risk patients in receipt of supportive care, to a high-risk care model if they developed shortness of breath.

Table 1: Suggested treatment protocol for children with age and weight appropriate dosing

TREATMENT	
Age range of children, young persons	**Suggested treatment protocol**
0-11 months	Supportive care
1 year to 48 months (1-4 years)	Supportive care
49 months to 120 months (5th year to 10 years)	HCQ or IVM or quercetin, AZM, Steroid Inhaler, low-dose limited ASA, Vitamin D
132 months to 180 months (11th year to 15 years)	HCQ or IVM or quercetin, AZM/doxycycline, Steroid Inhaler, Prednisone, ASA, Vitamin D
192 months to 228 months (16th year to 19 years)	HCQ or IVM or quercetin, AZM/doxycycline, Steroid Inhaler, Prednisone, Colchicine, ASA, Vitamin D

HCQ = hydroxychloroquine, IVM = ivermectin, AZM = azithromycin
NOTE: the use of doxycycline is restricted by age due to its ability to stain developing enamel during odontogenesis.

Table 2 outlines two suggested treatment approaches that act only as a guide:

Table 2: Examples if treatment algorithms treating physicians currently use for children

Treating physician	Example of treatment protocol
Dr. George Fareed, MD	Children with symptomatic COVID-19 Pediatric (weight-based) dosing: HCQ BID for 5 to 7 days AZM for 5 days Zinc elemental 50 mg daily for 10 days Vitamin D3 2000 to 4000 IU daily Dr. Fareed recommends for children 13 years and over with moderate to severe symptoms: Regeneron monoclonal antibodies infusion at the beginning of treatment
Dr. Kat Lindley, DO	Teens: Preventive nutraceuticals 5,000 IU of vitamin D, 1,000 mg of vitamin C Zinc 20 mg elderberry chewables, 450 mg Teens: Treatment

	Nutraceuticals, added: Steroids: Decadron 4 mg bid for 5 days (For kids who are asthmatic or have reactive airway disease, add: Budesonide 0.5mg/2ml via nebulizer bid for 5 days) HCQ 200 mg once daily N-acetylcysteine 500 mg Azithromycin – 10 mg/kg/day Black seed oil - 40-80 mg/kg Melatonin – 1-5 mg Young children, ages 1-12: Preventive nutraceuticals (gummies) 2,000 IU of vitamin D 1,000 mg of vitamin C Zinc 20 mg elderberry chewables, 100-150 mg Young children: Treatment Nutraceuticals, add: Steroids: Decadron 4mg bid for 5 days (For kids who are asthmatic or have reactive airway disease, add: Budesonide 0.5mg/2ml via nebulizer bid for 5 days) HCQ 100 mg once daily (break tablet in two) N-acetylcysteine 500 mg Azithromycin – 10 mg/kg/day Black seed oil - 40-80 mg/kg Melatonin – 1 mg

In the experience of the authors who are clinicians, the clinical responses to these early treatment modalities have been sustained, profound, and very positive in adults. That consistent, shared experience has led us to consensus in producing this paper update in high-risk children. We once again stress that the risk to children from COVID-19 is very small, and current preventative management should support a hands-off approach, including vaccinations. Our intent here was to address the rare high-risk child who may present with more serious symptoms and as for adults, the decision to 'wait-and-see' is not tenable. We also feel that this early treatment approach may be applicable to other similar infections/diseases that may emerge in the future and as such, may provide a framework to build upon and drive further scientific inquiry.

Conclusion

In summary, COVID-19 is a very mild illness for the vast number of children and young persons. It is self-limiting and typically presents with no symptoms or very mild, cold-like symptoms and

accumulated research offers an understanding of the biological factors that are likely working, at least in part, to confer that exceedingly low risk in children.[22-26, 62, 63] However, as with other similarly benign conditions, there may be children who progress to more serious illness or have superimposed infection with respiratory syncytial virus or atypical organisms (mycoplasma, chlamydia pneumoniae). These children should not forego intervention and be allowed to worsen. The great news is for even severe pediatric infections, safe and effective therapies are readily available and have been extensively proven in the adult population. This group stands committed to the investigation of safe treatments as alternatives to COVID vaccinations in children where, given their exceedingly low risk in the first place, we see no opportunity for benefit but only potential for acute and long-term harm. A recently published paper out of Israel by Gazit et al.[64] (pre-print) highlighted that natural immunity conferred longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity ("SARS-CoV-2-naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected").

We close by encouraging lifestyles in children that provide the real rock-bed of optimized immunity such as the NEWSTART paradigm: Nutrition, Exercise, Water (hydration), Sunshine, Temperance (hot and cold exposure), Air (fresh), Rest, and Trust in spiritual health.

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