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Review Article

The Impact of COVID-19 Pandemic on Children: Evidence, Underlying Mechanisms and Interventions

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Abstract

The ongoing COVID-19 crisis around the world has put children at much greater risk of compromising their health, arising in part from strained healthcare systems and disruptions to many critical childcare amenities, resulting in excess mortality among children of all age groups. COVID-19-related school closures, worldwide, impacted children multidimensional. About 3.5 million COVID-19 deaths reported in MPIDR COVerAGE database, of which 0.4 percent (over 12,300) occurred in children and adolescents below 20 years of age; 58 percent occurred in adolescents ages 10-19, and 42 percent among children ages 0-9. Therefore, it is critical to understand the underlying mechanisms of COVID-19 disease transmission and severity and its potential interventional approaches to protect children from further damages. This article is based on a thorough and careful review of relevant literature on epidemiological analyses of childhood COVID-19 cases and information from government websites across the world, etc., which captures the epidemiological evidence of childhood COVID-19 cases, together with identification of underlying mechanisms, affecting child health directly or indirectly such as impairment of cognitive development, aggravation of neurological disorders etc., and their consequences. A comprehensive update on the potential intervention approaches to mitigate COVID-19 disease in children e.g. vaccines, therapeutic monoclonal antibodies, cell-based therapies, antiviral and immunomodulatory drugs etc., is included in the article, which provides a useful informational platform on which improved intervention approaches and innovative pandemic preparedness can be constructed by the public health experts around the world, to prevent children from deleterious consequences of COVID-19 pandemic.

INTRODUCTION

The ongoing worldwide COVID-19 crisis not only affects the adult population, but has also put children at much greater risk of endangering their lives. Although, the direct effects of COVID-19 infection on children in terms of hospitalizations, case fatalities, and deaths are less severe with relatively smaller number of children experiencing severity of the COVID-19 disease1, emerging data suggest that children and adolescents' health may be profoundly impacted by the pandemic than originally thought in the initial phase of the pandemic. A noticeable emerging COVID-19-related health hazards, such as impairment of cognitive development2 and other neurological disorders in children, have gained immense importance over the long pandemic. Moreover, the public health restriction during COVID-19 pandemic has adversely affected children's health, and psycho-social well being as a result of difficulty in accessing primary and community services3. COVID-19-related school closures, worldwide, have impacted children multidimensional, ranging from education and social interaction to equity, food security, and mental health4.

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Overall, the article captures the worldwide evidence of SARS-CoV-2 infection in children, and the underlying mechanisms of the pathophysiology of SARS-CoV-2 infections that are critical in disease transmission and severity among children, together with potential disease interventional modalities to improve upon on COVID-19 pandemic preparedness.

METHODS

The present article is based on a thorough and careful review of relevant literature on epidemiological analyses of childhood COVID-19 cases derived from reliable sources, such as government (state and federal) websites, public databases such as Global Health 50/50, COVerAGE, MPIDR/INED, and in peer-reviewed publications and/or preprints.

RESULTS & DISCUSSION

Worldwide Epidemiological Analyses of COVID-19 Disease in Children

Pediatric infectious diseases are often considered as major causes of childhood morbidity and mortality worldwide. In the early phase of COVID-19 disease outbreak, cases were predominantly more prevalent among adults as opposed to younger children and adolescents5. Since then, massive COVID-19 detection drives have launched in many parts of the world, which has resulted in a gradual surge of COVID-19 cases, determined by large-scale, high-throughput genomic surveillance of SARS-CoV-2 infections among children. About 3.5 million COVID-19 deaths reported in MPIDR COVerAGE database6, of which 0.4 percent (over 12,300) occurred in children and adolescents below 20 years of age; 58 percent occurred in adolescents ages 10-19, and 42 percent among children ages 0-9. During the first wave of COVID-19 pandemic, People's Republic of China (PRC) identified immaturity7 of the immune system in children as the leading cause of a child's susceptibility towards SARS-CoV-2, since novel coronavirus infection in hospitalized infants was observed even under 1 year of age. A systematic review and meta-analysis of epidemiological and clinical characteristics of SARS-CoV-2 infection in children less than five years was performed8 following the Preferred Reporting Items for Systematic Reviews and Meta-analysis. The authors in this study, searched electronic databases, such as PubMed, EMBASE, Web of Science, and Scopus for studies reporting laboratory-confirmed COVID-19 cases in children under five years until June 4, 2020. The pooled estimates indicated that 50 percent cases were in infants (95% CI: 36%-63%, 27 studies); 53 percent were male (95% CI: 41%-65%, 24 studies), 43 percent were asymptomatic (95% CI: 15%-73%, 9 studies), and 7% (95% CI: 0%-30%, 5 studies) exhibited severe disease that required intensive-care-unit (ICU) admission. Moreover, Kotlyar and colleagues9, studied vertical transmission of SARS-CoV-2 in a systematic review, and meta-analysis using studies published until May 28, 2020 that included cohort studies, case series, and case reports of pregnant women who were diagnosed SARS-CoV-2 positive, and their neonates; immediately after birth and within 48 hours of birth. The study revealed that 27 neonates were positive for SARS-CoV-2 RNA among 936 neonates from mothers contracted with SARS-CoV-2, indicating a pooled proportion of 3.2 percent that accounted for (95% confidence interval, 2.2-4.3) vertical transmission.

However, many indirect, long-term effects of a pandemic event are difficult to measure quantitatively, by merely looking at the numbers of infection caseloads, and associated deaths. Thus, comprehensive studies of underlying causes that contribute directly or indirectly to the overall COVID-19 causalities in children and adolescents will provide key insights on potential opportunities to disease interventions.

COVID-19 Pandemic Affects Child Health, and Exacerbates Disease Severity by Various Mechanisms

Since the onset of the ongoing COVID-19 pandemic, the clinical presentations of the COVID-19 disease in children have shown different behaviors10 compared to adults. Additionally, COVID-19 pandemic has brought a complex spectrum of additional societal challenges that have serious mental and cognitive health consequences for children and adolescents. The wasting, stunting and being underweight and/or overweight are among the worst consequences of malnutrition, which are leading causes of weak immune health11 among children, can potentially increase their vulnerability to COVID-19 disease. Malnutrition augments the systemic proinflammatory mediator levels, resulting in chronic inflammation12 that can aggravate the fatal cytokine storm in COVID-19-infected children. Malnutrition13 further impairs immune priming by the immune cells; dendritic cells and monocytes, and by reducing effector memory T cells function. The cumulative immune dysfunction in malnourished children can drive pathological processes, such as malabsorption, increased metabolic demand, dysregulation of growth hormones and HPA14 (Hypothalamus-Pituitary-Adrenal) axes, causing increased susceptibility to SARS-CoV-2 infections. Malnutrition is also one of the leading causes of obesity and the obesity-related comorbidities15 in children, which augment the risk of COVID-19 disease severity in obese children. Several common neurological problems in children like autism, ADHD (attention deficit hyperactivity disorder), dyspraxia, epilepsy, headaches, dyslexia, and cerebral palsy are also affected by the COVID-19 pandemic16-18. Additionally, the ongoing COVID-19 pandemic severely affected psychological and emotional health of the children19-21. In a survey

studies22 with 65,508 participants, ranging from 4 to 19 years of age, anxiety (28%), depression (23%), loneliness (5%), stress (5%), fear (5%), tension (3%), anger (3%), fatigue (3%), confusion (3%) and worry (3%), were found to be the most common mental health issues reported.

The underlying mechanisms of these diverse manifestations remain elusive, to date. However, one potential mechanism that takes precedence over others is the microglial activation in the brain leading to neuroinflmmation23, 24. The systemic cytokine storm associated with SARS-CoV-2 infections can penetrate blood-brain barrier to activate brain microglia25, 26. Importantly, SARS-CoV-2 CNS (central nervous system) invasion is supported extensively by its detection in both the cerebrospinal fluid, and autopsied brain tissue from COVID-19 patients27-29. Also, bone marrow-derived peripheral immune cells; T lymphocytes and macrophages can enter the CNS through bloodstream, activating microglia, leading to increased neuroinflammation in COVID-19-infected children, which can potential cause several neurodisorders, such as aggressiveness, psychosis, depression, and anxiety disorders30, 31. Psychosocial stressors that arise during the pandemic can drive the production and release of cortisol-stress hormone, catecholamines, and proinflammatory cytokines into the blood stream, causing activation of microglia, resulting in dysfunctional synaptic remodeling32, leading to neurodevelopmental disorders, among others33-35. .

The Multifaceted Interventional Approaches in Combating COVID-19 Disease in Children

The subtlety of the child COVID-19 disease, lacking any disease-specific clinical symptoms that distinguish COVID-19 disease from other common childhood infections, such as influenza, streptococcal pharyngtitis, and allergic rhinitis, together with significant proportion of asymptomatic infections in children, which make symptom-based screening for identifying SARS-CoV-2 carriers often challenging for the clinicians36-38. Thus, a comprehensive update about the current knowledge on the potential approaches in the prevention of COVID-19 disease in children will help public health professionals to effectively utilize the appropriate interventional modalities, to mitigate prevalence, and severity of the COVID-19 disease in children.

Vaccines

As of now, two vaccines, Pfizer-BioNTech and Moderna are authorized for childhood vaccination against COVID-19 in the U.S.39, 40. In one of the recent clinical studies41, a case-control, test-negative design that includes a group of people who present them with similar clinical sign and symptoms of COVID-19 disease, vaccine effectiveness against COVID-19 in adolescents between 12 and 18 years of age was measured. The overall effectiveness of the BNT162b2 vaccine against hospitalization for COVID-19 was 94 percent (95% CI, 90-96); the effectiveness was 95 percent (95% CI, 91 to 97) among test-negative controls and 94 percent (95% CI, 89-96) among syndrome-negative control patients. Also, new bivalent COVID-19 vaccines42 have been approved by FDA, which include an mRNA component of the original strain of SARS-CoV-2 to generate neutralizing antibodies, broadly protective against COVID-19 disease, along with an mRNA component corresponding to omicron variant BA.4 and BA.5 lineages, to provide better protection against COVID-19 disease caused by the omicron variant. They are authorized as single booster dose in younger age groups down to 5-6 years of old43. Also, at the time of writing this article, Pfizer and BioNTech are beginning the process of submission for the Emergency Use Authorization (EUA) of their COVID-19 vaccine for children aged 6 months to 4 years old. In this study44, pediatric data were compared to the data collected for 16-25-years-old, called a “bridging study” to compare the difference in immunogenicity induced by vaccines between two cohorts. The initial results suggest a strong association with the non-inferiority criteria of the vaccines, tested using 3□g pediatric dose, compared to 30□g dose for 16-25-years-old.

Monoclonal Antibodies

Monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 in infected patients are new anti-viral biologics in the form of passive immunotherapy45. The use of tocilizumab for severe cases of acute COVID-19 disease was described in pediatric patients46. Tocilizumab is a mAb which blocks IL-6 receptor functions, inhibits the IL-6 signaling pathway, causing amelioration of cytokine storm in COVID-19-infected patients47. Also, EUAs have been issued for bamlanivimab plus etesevimab-neutralizing mAbs48 that bound to different, but overlapping, epitopes in the spike protein RBD (receptor binding domain) of SARS-CoV-2, and also for casirivimab together with imdevimab; mAbs specifically directed against the spike protein of SARS-CoV-2, known as REGN-COV249, to treat non-hospitalized, high-risk COVID-19 patients aged 12 and higher with mild to moderate COVID-19. Despite the promising results on the use of mAbs for the treatment of COVID-19 disease, administration of mAbs to children and adolescents needs careful evaluation in terms of risk-to-benefit ratio, as majority of the child COVID-19 cases are not severe, and the role of a chronic underlying disease as a potential risk factor of severe COVID-19 disease development in children, is not entirely clear184.

Stem Cells

Mesenchymal stem cells (MSCs) are investigational

biologics that have been extensively studied in recent years for broad clinical applications in regenerative medicine, primarily due to their immunomodulatory properties50-52. The current hypothesis states that MSCs can potentially reduce the acute lung injury due to severe COVID-19 disease through tissue regeneration and inhibit the cell-mediated inflammatory response induced by SARS-CoV-2. MSCs lack the ACE2 receptor, which favors the use of MSCs for therapeutic purpose53, 54 due to their inherent resistance to SARS-CoV-2 infections. MSCs express very low levels of major histocompatibility complex, which makes these stem cells non-immunogenic in allogenic recipients to avoid rejection55 by the recipients. Also, pro-inflammatory mediators released by M1 macrophages at the site of viral-mediated tissue injury, activate resting MSCs with immunosuppressive properties through induction of regulatory T cells (T-regs), which in turn, lower the overall inflammation56, 57. There are several clinical trials58-60 evaluating MSCs for the treatment of COVID-19, COVID-19-related ARDS (acute respiratory distress syndrome) (E.g., NCT04333368) and COVID-19-associated MIS-C (multisystem inflammatory syndrome in children) (E.g., NCT04549285), etc., in children. That said, the potential risk of using MSCs, include differentiation of stem cells into inappropriate cell types, product contamination during large-scale expansion, and administration site reaction61.

Exosomes

In spite of early promise of MSCs in the management of many diseases, there are still concerns regarding their safety, durability, and scalability. Interestingly, many of the therapeutic effects are in part, mediated by secreted extracellular vesicles, known as exosomes or EVs (extracellular vesicles). MSC-derived exosomes62-64 contain bioactive molecules, such as lipids, proteins, mRNAs, long-noncoding RNAs, microRNAs, and mitochondrial DNA, through which paracrine immunomodulatory effects of exosomes are primarily mediated. Exosomes are nano-sized, lipid-bilayer-enclosed structures, secreted from all types of cells, including those lining the respiratory tract that are potential targets for SARS-CoV-2 pathogenesis. Exosomes released by the SARS-CoV-2-infected cells play critical roles in mediating communication between infected and uninfected cells, thereby regulating the infection transmission, and intracellular spread of the virus65. A non-randomized prospective clinical study66 assessed the safety and efficacy of a Bone-Marrow (BM)-MSC-derived exosomal product (ExoFlo) in 24 moderate-to-severe and severe COVID-19 patients. The majority of patients clinically recovered with improved blood oxygenation. That said, its efficacy in children with COVID-19 disease has not been tested yet.

Antiviral Drugs

Remdesivir is currently the only FDA-approved drug for treatment of COVID-19 in children. It is a phosphoramidate pro-drug metabolized in cells to produce an active nucleoside triphosphate (NTP) analog, known as remdesivir triphosphate (RTP) 67. Biochemical studies showed that RNA-dependent RNA polymerase (RdRp) that SARS-CoV-2 uses for its replication to augment viral loads in the host cells, can use RTP as a substrate, leading to the incorporation of remdesivir monophosphate (RMP) into the growing RNA chain68. After RMP incorporation, the RdRp extends RNA by three more nucleosides before it stalls. Remdesivir is currently approved for the treatment of COVID-19 in hospitalized pediatric patients who are 12 and older and weighing equal or more than 40 kg69.

Favipiravir (6-fluoro-3-hydroxy-2pyrazinecarboxamide) is an oral broad-spectrum inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA viruses70. It undergoes phosphoribosylation inside the cells to be an active form-favipiravir-RTP (favipiravir ribofuranosyl-5'-triphosphate), which is subsequently recognized as a substrate by RdRp, incorporated into the nascent viral RNA, resulting in chain termination. In vitro studies71 show favipiravir is effective in preventing SARS-CoV-2 infection, within a dose to be considered as safe therapeutic regimen in a clinical setting. Favipiravir-RTP exhibits no effects on DNA-dependent RNA or DNA polymerase that explains its specificity in targeting RNA viruses, and not the DNA viruses. Additionally being effective as an oral formulation, it is likely to reduce the viral load in COVID-19-infected patients, in outpatient settings, together with the reduction of the rate of hospitalizations of the patients. In a small clinical study72 that enrolled 11 pediatric patients under 18 years suffering from COVID-19 and MIS-C (multisystem inflammatory syndrome in children) with associated kidney injury, were treated with favipiravir at the time of hospital admission. The serum creatinine and GFR (glomerular filtration rate) levels were significantly decreased at discharge after treatment with favipiravir, indicating improvement in kidney function among pediatric patients infected with COVID-19. Importantly, recently, Paxlovid73, 74 was granted EUA for the treatment of mild to moderate COVID-19, based on the interim analysis of EPIC-HR trial (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) (NCT04960202)).

Immunomodulatory Drugs

In contrast to antiviral drugs that specifically target the initial phase of viral infection, such as viral entry into the cells and its intracellular replication, immunomodulatory drugs75, 76 intervene the subsequent inflammatory phase of the disease, to prevent the rapid deterioration and worsening respiratory symptoms, and minimize the risk of

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hospitalization of the patients.

Corticosteroids are long been known to suppress inflammation in large varieties of inflammatory diseases by reducing the activation of several inflammatory mediators produced during infection, and subsequent inflammatory cascade events77, 78. Dexamethasone is a potent glucocorticoid with anti-inflammatory properties that works by suppressing the migration of neutrophils and decreasing lymphocyte colony formation by modulating the clonal expansion of lymphocytes. Cytokines, such as interleukin-1 (IL-1), interleukin-12 (IL-12), interleukin-18 (IL-18), tumor necrosis factor (TNF), interferon-gamma (IFN-□), and granulocyte-macrophage colony-stimulating factors (GCSF), which are markedly elevated in severe COVID-19 patients, can potentially be inhibited by dexamethasone79, 80. However, data on steroid use in children are very limited, to date.

Baricitnib is an oral Janus Kinase (JAK) 1/JAK2 inhibitor, originally used for the treatment of rheumatoid arthritis (RA), has been repurposed to treat COVID-19 disease81. Clinical evidence82 suggest that baricitnib is able to inhibit cytokine signaling implicated in COVID-19 infection, including IL-2, IL-6, IL-10, IFN-□ and G-CSF at lower than half maximum inhibitory concentration (IC50). A multicenter, open-label, pharmacokinetic and safety study of baricitnib in pediatric patients (n=24) from 1 year to less than 18 years old, hospitalized with COVID-19, is currently underway for therapeutic evaluation83.

Nutraceuticals

A wide range of different types of nutraceuticals come from dietary fiber, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, etc. A common feature of majority of the nutraceuticals is their ability to enhance the innate immune response against pathogens by regulating the cellular immunity and inducing key inflammatory mediators and antimicrobial peptides, affecting mucosal immunity in the body84. Among different neutraceuticals, probiotics regulate adaptive immune system through its effects on Th1, Th2, Th17, Treg cells, and B lymphocytes85, 86. They contain living microorganisms, which support the growth and activity of micro flora in the intestine, result in lowering of intestinal pH, causing pathogenic mircoorganism difficult to survive in the intestine. Prebiotics87 typically include fuctans, oligosaccharides, xylooligosaccharides, lactoglucose, polyphenols, etc. Although the potential use of probiotics and prebiotics looks promising against COVID-19 disease, a substantial amount of clinical data is needed on pediatric COVID-19 cases to conclusively determine their efficacy against childhood COVID-19 disease. Other neutraceuticals such as resveratrol (3,4,5-trihydroxy-trans-stibene) 88 is a polyphenolic compound present in various plant species like peanuts, grapes, etc. Recent studies have shown that resveratrol inhibits SARS-CoV-2 in vitro89, and molecular docking study shows its interaction with SARS-CoV-2 spike protein and ACE2 receptor complex90. Resveratrol mediates anti-inflammatory activities91 by activating Nrf2; a transcriptional repressor for inflammatory cytokines, such as IL-1□, IL-6, and TNF□. Hesperidin is a subclass of flavonoids present primarily in citrus fruits, such as oranges and lemons. The strong anti-inflammatory properties of hesperidin like inhibition of IFN□, IL-1□, IL-6, and TNF-□ are reported92, 93. Other nutraceuticals e.g., curcumin, omega-3 fatty acids, quercetin, and vitamins A, C, and D3, are being currently tested in clinical trials94.

CONCLUSION

Taken together, due to relatively underrated COVID-19 disease severity among children in the midst of substantially higher numbers of cases in adult population together with higher disease severity compared to child COVID-19 cases, compel healthcare professionals not focusing too much on child COVID-19 disease in the initial phase of the pandemic. As the pandemic situation has improved, the children of all age groups have started going to schools. Thus, it is important to protect them through prophylactics and other therapeutic interventions from getting COVID-19 disease. As we are beginning to understand more and more the childhood COVID-19 clinical presentations, its underlying pathological mechanisms, and the efficacy of wide variety of new medical interventions in controlled clinical studies, prevention of COVID-19 disease in children looks increasingly promising. Thus, this article will provide a useful informational platform on which improved intervention the public health experts around the world can effectively construct approaches and logistics.

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