Chapter

COVID-19 Transmission in Children: Implications for Schools

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Abstract

The COVID-19 pandemic poses multiple issues of importance to child health including threats to physical health and disruption of in-school learning. This chapter reviews what is currently known about COVID-19 epidemiology, presentation, pathophysiology, case definitions, therapies, and in-school transmission in children. COVID-19 has some unique characteristics in children including the rare yet severe Multisystem Inflammatory Syndrome in Children (MIS-C) that may be related to acquired immune responses. There are limited studies to date to define therapeutic guidelines in children, however consensus recommendations from multiple organizations are summarized including the use of immunomodulatory therapies (intravenous immunoglobulin, steroids, anakinra and tocilizumab), antiplatelet (aspirin) and anti-coagulant (low molecular weight heparin) therapies. Finally, considerations for safe return to the classroom are discussed including strategies for optimized student to teacher ratios, hand washing, social distancing, sibling pairing and staged re-opening strategies.

Keywords: COVID-19, children, SARS-CoV-2, MIS-C, Kawasaki

1. Introduction

Coronavirus disease (COVID-19) is caused by a virus in the beta-coronavirus family, SARS-CoV-2. The specific characteristics of COVID-19 infection in children are of particular interest. Little is unknown about the epidemiology of SARS-CoV-2 transmission in children. The transmissibility of COVID-19 in general is greater than other coronaviruses [1]. COVID-19 is typically asymptomatic or presents with mild symptoms [1, 2]. Coronavirus causes up to 14% of respiratory infections in children however influenza virus infections remain the most common pediatric infections. Those most likely to be infected with SARS-CoV-2 are children under three years of age [1] and more specifically, children under one year of age. Furthermore, according to a metanalysis, 50% of children under the age of five infected with COVID-19 were infants under one year of age, male and were exposed to the infection via community transmission [3]. This highlights the importance of testing and disease monitoring in families with infants and young children.

COVID-19 disease is less common in children than adults [1, 2]. The lower incidence of COVID infection in children may be explained by the lower expression of Angiotensin Converting Enzyme 2 (ACE2) and TMORSS2 (protease) in alveolar epithelial cells in children in comparison to adults and decreased viral transmission [2–4]. The higher rates of infection seen in infants may be due to their immature immune system, which not only increases their risk of infection, but also makes vaccination less effective [1, 3]. Maternal immunization may provide maternal-fetal protection [1, 3, 4]. In addition, maternal immunization may protect young children as transmission from COVID-positive mothers to children has been documented [1, 4]. Therefore, targeted maternal vaccination may be an important tool to protect vulnerable infants and children.

2. SARS-CoV-2 overview

Since the discovery of SARS in 2002, including the recent detection of SARS-CoV-2, seven strains of human coronavirus have been identified, defined by the WHO as "A broad family of viruses that cause various conditions, from the common cold to more serious illnesses, such as the Middle East respiratory syndrome coronavirus and the one that causes severe acute respiratory syndrome." Among them, SARS-CoV-2, the virus responsible for the 2019 coronavirus disease, originated in Wuhan (Hubei, China) in December 2019, was declared a pandemic by the WHO in March 2020 and is defined as an "enveloped positive-sense single-stranded RNA virus 80-220 nm in diameter. The envelope has corona-shaped peaks 20 nm in length that resemble the corona of the sun under electron microscopy" [5].

The coronaviral genome encodes four major structural proteins, the spike protein (S), the nucleocapsid protein (N), the membrane protein (M), and the envelope protein (E), all of which are necessary to produce a structurally complete viral particle. Unlike the other major structural proteins, N is the only protein that functions primarily to bind to the CoV RNA genome, forming the nucleocapsid. Although N is largely involved in processes related to the viral genome, it is also involved in other aspects of the CoV replication cycle and the host's cellular response to viral infection [6]. Furthermore, protein S plays a crucial role in the entry of the virus into host cells and the structural capabilities of this newly discovered SARS-CoV-2 enhance its intended actions. Because these prominent peaks are the first point of contact with host receptors, therapeutic strategies can be applied to prevent their binding to target receptors and prevent viral entry into host cells [7].

The WHO reported that the most common symptoms of COVID-19 are fever, dry cough and tiredness. Other less frequent symptoms include nasal congestion, headache, conjunctivitis, sore throat, diarrhea, loss of taste or smell, skin rashes or changes in the color of the fingers or toes [8]. These symptoms are usually mild and begin gradually. Approximately 80% of people recover without the need for hospital care, while approximately 1 in 5 people who contract COVID-19 end up with severe symptoms and experience breathing difficulties. Elderly people with underlying diseases, such as high blood pressure, heart disease, lung problems, diabetes or cancer are more likely to suffer from an aggravated clinical stage [8].

The primary route of transmission to humans was zoonotic, via interaction with animals. A hypothesis that was later confirmed and defined by the WHO was that the virus was spread through droplets that are expelled from the nose or mouth of an infected person by coughing, sneezing, or talking, and even by touching infected objects and surfaces, such as tables, doorknobs, and railings, so that healthy people can become infected if they touch those objects or surfaces and then touch their eyes, nose, or mouth [9].

Kotfis & Skonieczna-Żydecka identified viral cells in gastrointestinal biopsy samples, including those that belonged to patients who had left the hospitals, which may partially explain gastrointestinal symptoms, potential recurrence, and transmission of SARS by persistent shedding in stool as well. Specifically, the virus is protein molecule covered by a protective lipid layer that is absorbed into ocular, nasal, oral and gastrointestinal mucosal epithelial cells and replicates there [10].

2.1 ACE2: The door to SARS-CoV2

The renin angiotensin aldosterone system (RAAS) is the primary regulator of plasma volume, maintaining cardiovascular and fluid homeostasis. This system plays a protective and adaptive role against risk phenomena, such as hypotension, sodium or water deprivation, and in turn, its dysregulation has implications in the development of hypertension and other cardiovascular diseases [11].

Activation of the classic RAAS pathway begins in the juxtaglomerular apparatus with the release of preformed renin from its prorenin precursor, secondary to baroreflex, beta-adrenergic or molecular stimuli in the macula densa. Renin takes the hepatic precursor angiotensinogen and converts it into angiotensin I (Ang I) [11]. This decapeptide has no specific known physiological action and ends up being converted into octapeptide angiotensin II (Ang II) by angiotensin converting enzyme (ACE), which is located primarily in cells of the pulmonary endothelium, as well as other tissues [11].

Ang II acts on AT1 receptors and exerts powerful vasoconstrictive, profibrotic and proinflammatory effects [6]. The action of Ang II on the AT2 receptor generates the opposite vasodilator and antiproliferative effect [11].

ACE is an essential component of the renin angiotensin aldosterone system, functioning as a transmembrane protein with two N- and C-terminal active catalytic domains. The C-terminal domain generates the soluble carboxypeptidase that removes the carboxy-terminal dipeptide of Ang I, generating Ang II, while hydrolysis of the vasodilator peptides, called bradykinins, occurs by the enzymatic action of both domains. ACE2 is a monocarboxypeptidase homologous to ACE but has only one transmembrane helix, an intracellular segment, and N- and C-terminal domains with a single enzymatic active site, endowing ACE with distinct characteristics [11].

ACE2 is also homologous to ACE, which plays a role in the cleavage of angiotensin I into angiotensin-(1–9) and the vasoconstrictor peptide angiotensin II in the vasodilator angiotensin-(1–7). Consequently, ACE2 acts as the entry point into cells for various coronaviruses [12]. By cleaving angiotensin II and increasing vasodilator angiotensin-(1–7), it can act as an important regulator of cardiac function and plays a protective role in acute lung injury.

Possible antitumor effects of ACE2 and future therapeutic prospects for cancers have been reported for ACE2. Unfortunately, ACE2 has a high affinity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7], which may explain its manifestations at the respiratory level.

2.2 SARS-CoV-2 and ACE2

Viral infections bind their viral structures with receptors on the host cell surface. Although it has been shown that there are several coronaviruses that cause human diseases, only three of them bind ACE2: SARS-CoV, SARS-CoV-2 and HCoV-NL63, with SARS-CoV being responsible for a health emergency known as severe acute respiratory syndrome (SARS) in 2003 in China. Curiously, glycoprotein S is characterized as the critical determinant for viral entry into host cells, consisting

of two functional subunits, S1 and S2. The S1 subunit recognizes and binds to the host receptor through the receptor-binding domain (RBD), while S2 is responsible for fusion with the host cell membrane. MERS-CoV uses dipeptidyl peptidase-4 (DPP4) as an entry receptor, while SARS-CoV and SARS-CoV-2 use ACE2, which is abundantly expressed in pulmonary alveolar epithelial cells and enterocytes, suggesting glycoprotein S as a potential drug target to stop SARS-CoV-2 entry [13].

However, SARS-CoV infection downregulates surface expression of the binding protein (ACE2), a fundamental component for the entry of the host cell. Low ACE2 expression is associated with a greater severity of the infection in epithelial cells of the human respiratory tract [14].

3. Presentation of COVID-19 in children

The presentation of COVID-19 in children differs somewhat from the presentation seen in adults. COVID-19 in children most commonly present with fever and cough [15] and gastrointestinal symptoms such as diarrhea and vomiting. Gastrointestinal symptoms are reported in a considerable portion of cases [1, 3, 15] which is less characteristic of adult cases. While some patients develop respiratory distress syndrome, the severe form of COVID-19 is less common in children as compared to adults [15] and the mortality rate of COVID-19 in children is <0.1%. COVID-19 infection in children may present with anemia, thrombocytopenia, hypoalbuminemia, and altered INR [12]. Other laboratory abnormalities may include leukopenia, lymphopenia, increased transaminases and inflammatory markers such as procalcitonin and C-reactive protein [1, 16]. While patchy lesions in pulmonary lobules of children are identified on chest computed tomographic scans with moderate infection, the ground-glass opacities which are a typical feature in adults are rare in pediatric patients [15]. The mechanisms underlying the unique presentation of COVID-19 in children are unknown and further study is required to understand why the presentation differs in children.

IgA antibodies have been found both in Kawasaki disease and in COVID-19 cases with vasculitis. This suggests that MIS-C could be triggered by a COVID-19 infection and that similar to Kawasaki disease, IgA antibodies are produced. These antibodies have receptors in endothelial, mucosal, and cardiac cells [1]. This hypothesis that the vasculitis is mediated by IgA antibodies may explain the similarities between the two pathologies and the potential post-infectious origin [1].

Another common pathology associated with COVID-19 in children is "COVID toes", or chilblains. This primarily affects the toes but can also be seen in the heels and fingers, presenting as red-purple, tender, or itchy bumps [17]. The cause appears to be the result of vascular damage through the impact of the SARS-CoV-2 virus on endothelial cells as well as T-cells CD4, CD8, and B-cells [1].

3.1 Multisystem inflammatory syndrome in children (MIS-C)

While most cases of COVID-19 in children range from asymptomatic to mild/moderate disease, severe disease has been documented in children. Some countries have documented cases of COVID-19 in children under the age of five [1, 18] with an acute inflammatory syndrome called Multisystem Inflammatory Syndrome in Children (MIS-C) [1, 3] that is similar to Kawasaki disease [1, 3, 19] that is a medium-vessel vasculitis [1, 18] and typically presents 2 weeks after initial infection. The most commonly affected vessels in MIS-C are the coronary arteries [20].

Most infants (more than 80%) infected with SARS-CoV-2 develop mild COVID-19 with a natural history similar to other self-limited respiratory viruses,

without complications [21]. But in the case of children who develop MIS-C, severe systemic inflammation occurs with elevated pro-inflammatory cytokines and acute phase reactants, affecting multiple organ systems including the gastrointestinal, respiratory, cardiovascular, renal, hepatic, hematological and nervous systems among others [22, 23]. The most comprised organ systems include the gastrointestinal, dermatologic and cardiovascular organ systems.

MIS-C typically presents with fever lasting more than 4 days [1, 12, 16] as the universal characteristic. Gastrointestinal symptoms [1, 3, 12] may also present as the first symptoms [24]. These include abdominal pain, vomiting [1, 3, 12], and diarrhea [24]. Neurological symptoms such as headache, sensory disturbances, and meningeal signs [1, 24] can also be present. Hemodynamic instability can be present as well as cardiovascular complications including heart failure, myocarditis and pericarditis. Laboratory values may demonstrate elevations in troponin, proBNP, ferritin, C-reactive protein, and D-dimer with neutrophilia and lymphopenia [1, 12, 16]. Patients may also develop shock [1, 16] with single or multi-organ dysfunction requiring intensive care, mechanical ventilation [1, 12] and/or extracorporeal membrane oxygenation (ECMO) [3, 12]. Cytokine storm and ferritin counts >1400 μg/L may present in older patients [1]. In summary, MIS-C presents as a hyperinflammatory syndrome with gastrointestinal, neurologic and cardiac manifestations.

3.2 Epidemiology of MIS-C

In April 2020, the United Kingdom reported a series of cases with clinical presentation similar to Kawasaki disease (KD), toxic shock syndrome (TSS) and hyper-inflammatory state that had an epidemiological link with SARS-CoV-2 [25]; since that event, clinically similar cases have been reported in other parts of the world, including France, Switzerland, the United States, Canada, Norway, among others [18, 26–28]. After the notification of these cases, an expert consensus among critical care, infectiology, rheumatology and hematology pediatric subspecialists named this new clinical condition "Multisystemic inflammatory syndrome in children".

The worldwide incidence of SARS-CoV-2 in children under 18 years of age is 322 cases per 100,000 inhabitants and the incidence of MIS-C is 2 per 100,000 inhabitants [29]. The first cases were reported in the United Kingdom, as well as in other places in Europe (France, Germany, Greece, Italy, Luxembourg, Portugal, Spain, Switzerland, Sweden), later in Canada and the United States [30]. Most cases of MIS-C occur in previously healthy children older than 8 years and adolescents. Children of African-American and Latino ancestry are the most affected, in contrast to classic KD, which typically affects children under 5 years of age and has a higher incidence in East Asia and in children of Asian descent [31].

The first report of MIS-C was a series of 8 cases receiving medical assistance in southeast England [25]. Subsequently, 3 series of cases were reported in England (n = 58), France and Switzerland (n = 35) and New York (n = 33). In most cases, the children were previously healthy, that is, without underlying comorbidities (88% in the United Kingdom, 89% in France, and 79% in the New York series) [12, 18]. In those with comorbidities, obesity and asthma were the most frequent. The average age was 10 years with an age range of 1 to 17 years [32].

To date, the prognostic factors of severe disease in children are not known, however, a French prospective study that took data from 397 children admitted for COVID-19 in 60 hospitals identified three factors that were independently associated with severe evolution of the disease in the univariate analysis: age ≥ 10 years (OR: 3.4; p = 0.034), hypoxemia (OR: 8.9; p = 0.0004) and C-reactive protein ≥80 mg / L (OR: 6; p = 0.012) [33]. Meanwhile, research presented at the 2021

ENDO Virtual Congress revealed that children with type 1 diabetes whose glycated hemoglobin (A1c) is greater than 9% have a higher risk of severe forms of COVID-19 [34]. At the moment many efforts are being carried out in order to better characterize the pediatric population at risk, with the aim of identifying susceptible populations early and preventing life-threatening events in infants.

3.3 The epidemiology of MIS-C in the Americas

As of January 14, 2021, a total of 17 countries in the Region of the Americas have officially notified PAHO / WHO or have published information through an official website a total of 2,737 cumulative confirmed cases of MIS-C that coincide chronologically with COVID-19, including 78 deaths [18]. Of the total reported cases, 66% were between 0 and 9 years old at the time of illness and only 10% were in the age group between 15 and 19 years. Regarding the outcome of these cases, the highest proportion of deaths is observed in the age group of 15 to 19 years. Regarding the distribution by sex, 56% of the cases are male [35].

The countries with the highest number of confirmed cases are the United States with 1,659 cases, Brazil with 631 cases, Chile with 151 cases, the Dominican Republic with 102 cases, and Argentina with 65 cases [36]. So far in Colombia, 3 cases of MIS-C have been identified in the district of Cartagena. These cases were detected through media monitoring. The incidence rate of COVID-19 in people under 18 years of age per 100,000 inhabitants in Colombia by department, shows us that the departments and districts above the 75th percentile are: Amazonas, Barranquilla, Atlántico, Bogotá, Cartagena, Chocó, Cesar and Nariño; Between the 50 to 75 percentiles are the departments of Valle del Cauca, Cundinamarca, Santa Marta, Sucre, Tolima, Bolívar, Magdalena, Antioquia. At the 25th percentile are Risaralda, Arauca, Cauca, Santander, Córdoba, Quindío, Caldas and Norte de Santander and below the 25th percentile are Boyacá, Guajira, Meta and Huila [37].

3.4 Pathophysiology of MIS-C

MIS-C is a clinically severe event that mimics other pathologies that present with hyper-inflammatory status in the pediatric population, in mention: KD, SST, Hemophagocytic Lymphohistocytosis (HHL), Macrophage Activation Syndrome (SAM), among others [38]. It is characterized by persistent fever (≥38°C) for more than 24 hours, with involvement of vital organs and consequent cardiological, renal, gastrointestinal, respiratory and / or hematological affection. Patients may present with maculopapular rash, arthritis, and aseptic bilateral conjunctivitis, similar to KD [39].

Symptoms begin 2 to 6 weeks after the resolution of COVID-19 symptoms (in those symptomatic), so it is suggested that it is not due to an effect of the acute event, but to an event mediated by the mechanisms of acquired immunity (cellular and / or humoral) [40]. In the initial stage, fever is usually documented, accompanied by constitutional symptoms, intense headache, general malaise, irritability, GI manifestations such as abdominal pain, vomiting or diarrhea, palmar and / or plantar erythema, mucosal edema, among others less frequent [41].

A range of cardiac dysfunctions are commonly seen with MIS-C, including but not limited to, myocarditis, pericarditis, aneurysms or dilatation of the coronary arteries, valvular insufficiency [1, 16], heart failure [16, 24] and electrocardiographic abnormalities. Other common findings include elevation of troponin, proBNP, C-reactive protein, ferritin, IL-6, D-dimer and need for intensive care [12, 16]. The presence of pericarditis, coronary aneurysms and myocarditis suggest that patients with COVID-19 could have an incomplete form of the Kawasaki disease.

Immunomodulators used in treatment have yielded positive results restoring normal left ventricular function [1] in echocardiographic reports after six weeks of treatment.

Subsequently, the patient presents a hyper-inflammatory state, characterized by an increase in pro-inflammatory cytokines such as: Interleukin 1 (IL-1), Tumor Necrosis Factor alpha (TNF-α), Interleukin 11 (IL-11), Interleukin 12 (IL-12), and especially, Interleukin 6 (IL-6) [42]. Proinflammatory cytokines exert a pleiotropic and redundant effect, which favors the elevation of acute phase reactants and products of the coagulation system, processes termed "immunothrombosis and thromboinflammation" [43]. Lactate Dehydrogenase (LDH), Procalcitonin (PCT), Globular Sedimentation Rate (ESR), C-Reactive Protein (CRP), Serum Ferritin, Serum Amyloid A, Fibrinogen, and D-dimer among other biomarkers may elevated. This state can produce functional alterations at the endothelial level, generating an imbalance between the homeostatic mechanisms of vasoactive control, leading to a state of severe hypotension and the consequent cardiogenic shock. These conditions may lead to multiple organ failure and death in some cases [44].

Immunologically, the mechanisms underlying the hyperinflammation state are not known; however, there are some findings that suggest certain molecular and cellular mechanisms. Regarding immunogenetics (Major Histocompatibility Complex, MHC, and HLA molecules), Nguyen and Cols, by immunoinformatic analysis, examined how HLA variation could affect the cellular immune response against coronavirus peptides that infect humans [45]. The researchers found that the HLA-B * 46: 01 allele has few SARS-CoV-2 peptide binding sites, while the HLA-B * 15: 03 allele showed greater ability to recognize and display highly conserved peptides in SARS-CoV-2, which suggests that host genetic factors may play a role in cellular immune response and clinical presentation in response to SARS-CoV-2 infection [46].

The superantigen hypothesis has also been proposed to understand and clarify the immunological events that support MIS-C [47]. This hypothesis suggests that the SARS-CoV-2 virus produces super antigens that activate the immune system. A superantigen refers to peptides (sometimes motifs and / or proteins) that bind to T lymphocytes of an individual, expressing a particular group or family of genes on the β chain of the variable region (Vβ) of the T-cell receptor (TCR) [48]. The binding of the superantigen with the Vβ domains of the TCR leads to their polyclonal activation, leading to the production of large amounts of cytokines and a clinical syndrome similar to septic shock, similar to what occurs in MIS-C. Superantigens are presented to T-cells through binding to non-polymorphic regions of HLA-II molecules located on antigen presenting cells (APC) and interact with conserved regions of the Vβ domains of the TCR. For example, several staphylococcal enterotoxins are SAg [49].

By structure-based computational modeling Rivas and Cols discovered that the SARS-CoV-2 Spike (S) protein possesses a high affinity motif located close to the S1 / S2 cleavage site with a highly conserved sequence to superantigens [50]. The region containing this motif exhibits a high binding affinity to the complementarity determining regions (CDRs) present in the variable domains of the α and β chain of the TCR. This region is highly similar to the primary sequence and three-dimensional structure of a superantigen fragment corresponding to staphylococcal enterotoxin B (SEB), which interacts with the TCR and CD28 of T cells [51].

Next-generation immuno-sequencing of the TCR repertoire of COVID-19 patients indicated that the severity of the infection may be associated with some genes that encode the Vβ region of the TCR [52]. Using structure-based computational modeling, Cheng and cols. Demonstrated that the SARS-CoV-2 protein S exhibits a high-affinity TCR-binding motif, being able to form a complex with

HLA-II molecules. The researchers argue that this interaction between the virus and human T cells could be enhanced by a rare mutation (D839Y / N / E) from a European strain of SARS-CoV-2 [52]. The studies also found that the SARS-CoV-2 protein S possesses a neurotoxin-like sequence motif in the receptor-binding domain, which exhibits a high tendency to bind to TCR. These findings are consistent with the clinical presentation of patients with MIS-C, who exhibit hyperinflammation and neurological symptoms suggestive of neurotoxicity [53, 54].

3.5 Cases definition

Most children with Covid-19 infection are asymptomatic or present mild symptoms, however, children who may develop a significant systemic inflammatory response have been identified, which may require hospitalization, ICU admission and even management for different medical specialties [55]. This syndrome, although it is a rare complication, can be fatal in children and adolescents. Due to the risk to the health of this population, it is necessary to characterize this disease and its risk factors, as well as to initiate immediate epidemiological surveillance. WHO has developed a preliminary case definition and case report form for MIS-C in children and adolescents. The preliminary case definition reflects the clinical and laboratory features observed in children reported to date and are used to identify suspected or confirmed cases (**Figure 1**) [56]. The National Institute of Health of Colombia, in its technical document of January 21, 2021, defines the operational concepts of cases as follows (**Table 1**; **Figures 2** and **3**) [57].

3.6 MIS-C treatment

Currently, studies comparing clinical efficacy of various treatment options are lacking. According to the United States Center for Disease Control, Colombian Association of Infectious Disease and American College of Rheumatology treatments have consisted primarily of supportive care and directed care against the underlying inflammatory process. Supportive care may include that may include fluid resuscitation, inotropic support; respiratory support and in rare cases, ECMO [58, 59].

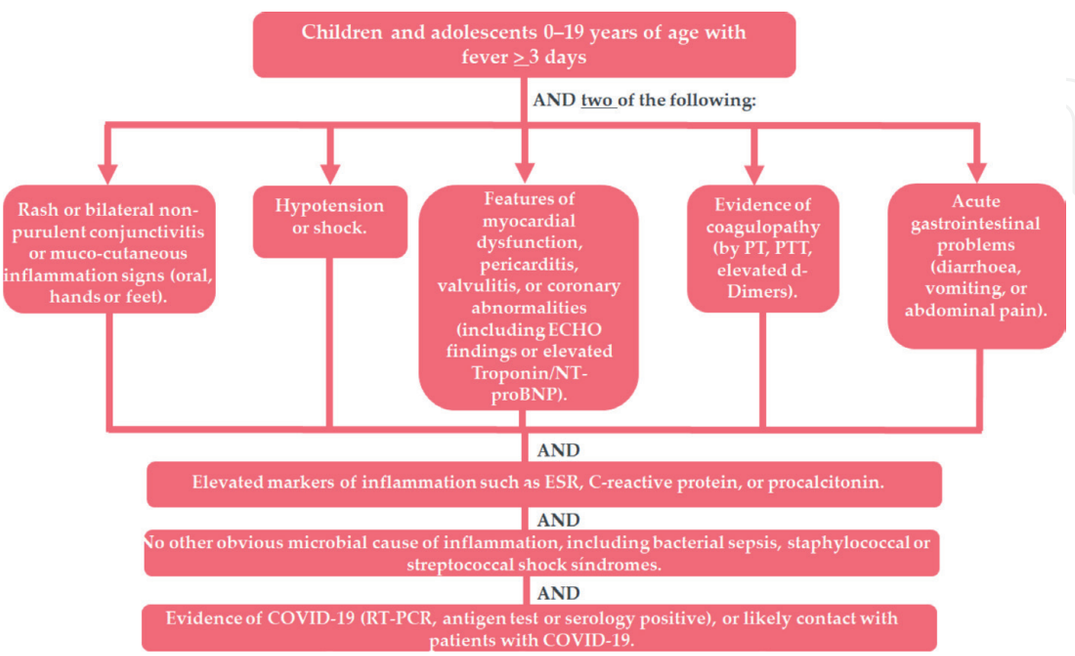

Figure 1.
Preliminary case definition according to the World Health Organization.

Case	Case characteristics
Probable MIS-C Covid-19 Case	• Under 18 years of age with fever for >24 hours, current or recent infection for SARS-CoV-2 evidenced by RT-PCR or IgM / IgG antibody serology or close contact with a COVID-19 confirmed case in the prior 4 weeks. • Also presenting with any of the following symptoms: abdominal pain, vomiting, diarrhea, skin rash, non-purulent bilateral conjunctivitis, erythema on the soles or palms or mucosal edema, headache or altered state of consciousness. • Without alternative diagnosis or other possible causes that explain this clinical picture.
Confirmed MIS-C Covid-19 case	• Probable case with clinical findings in at least 2 organ systems (Gastrointestinal symptoms: abdominal pain, vomiting, diarrhea or Mucocutaneous; skin rash, non-purulent bilateral conjunctivitis, erythema on soles or palms or mucosal edema or Neurological symptoms such as headache or conscious state alteration or Cardiological symptoms: myocardial dysfunction, pericarditis, abnormalities in the coronary arteries or Hematological: evidence of renal or respiratory coagulopathy). • At least one of these altered laboratory findings: Neutrophilia, thrombocytopenia or lymphopenia or elevation of ESR, Fibrinogen, C-reactive protein, Ferritin, lactate, D-Dimer, interleukin-6 orThrombocytopenia.
Dismissed MIS-C Covid-19 case	None of the conditions listed in the probable or confirmed case definitions are met

Table 1.
Case definition according to National Institute of health of Colombia.

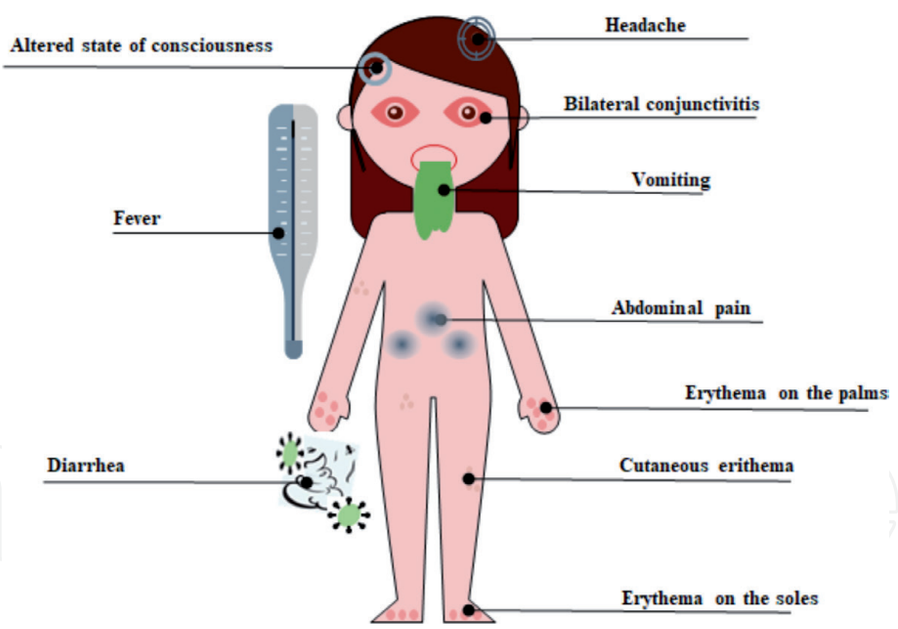

Figure 2.
Probable MIS-C COVID-19 case.

Anti-inflammatory measures may include the use of intravenous IgG (IVIG) and steroids. Aspirin may be used due to concerns for coronary artery involvement and antibiotics are sometimes used to treat potential sepsis while awaiting bacterial cultures. Thrombotic prophylaxis is often used to treat the hypercoagulable state typically associated with MIS-C.

The Colombian Association of Infectious Diseases (CAID) [60] and the American College of Rheumatology (ACR) (cite website shown above) have provided consensus statements for the management of MIS-C related to the immunomodulatory, antiplatelet and anticoagulation that are summarized below:

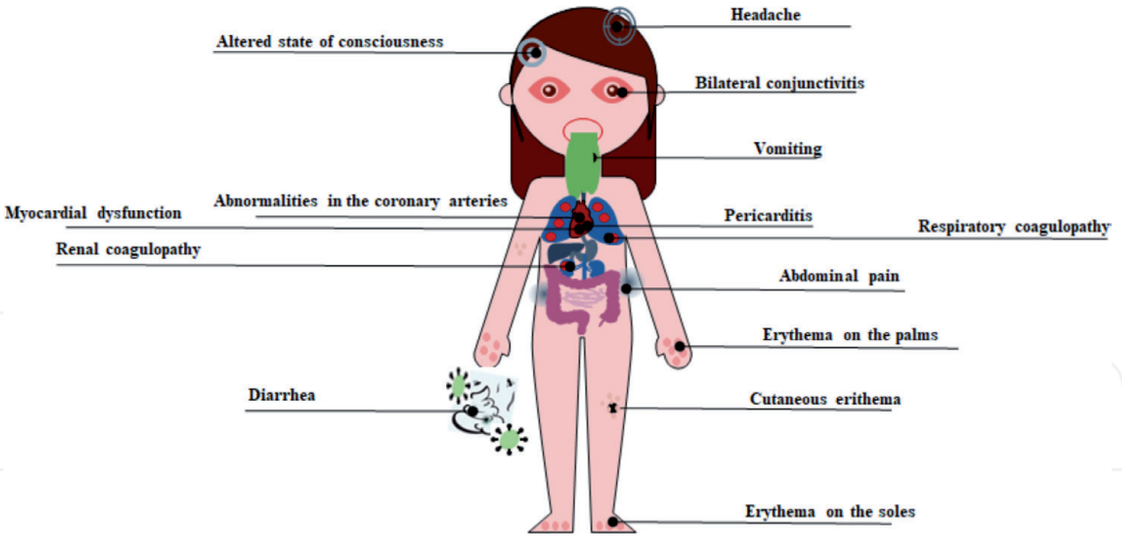

Figure 3.
Confirmed MIS-C COVID-19 case.

Immunomodulatory management of MISC:

- A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG and/or glucocorticoids considered as first tier treatments (ACR)
  The use of human polyclonal IVIG at a dose of 2 g / kg is suggested for all patients who meet MIS-C diagnostic criteria (CAID) with stable cardiac function and fluid status (ACR).

- In patients that do not respond to IVIG the following approaches may be considered:

  ○ Low to moderate doses of glucocorticoids may also be considered (ACR) noting that in endemic countries antiparasitic management with albendazole or ivermectin is needed to avoid hyperinfestation syndromes of strongyloides (CAID).

  ○ The use of a second dose of IVIG at a dose of 2 g / kg in case of no response within 36 hours of the first dose, with or without steroid at a low dose (prednisolone orally at a maximum of 1 mg / kg / day or its intravenous equivalent if there is intolerance to the oral route, according to response) may be applied (CAID).

  ○ High dose intravenous pulse glucocorticoids may be considered in shock (ACR) such as the administration of pulses of methylprednisolone at 30 mg / kg / day for 3 days (CAID).

  ○ Children with severe respiratory symptoms due to COVID-19 should be considered for immunomodulatory therapy if any of the following are present: ARDS, shock/cardiac dysfunction, substantially elevated LDH, d-dimer, IL-6, IL-2R, CRP, and/or ferritin levels, and depressed lymphocyte count, albumin levels, and/or platelet count (ACR). Risks and benefits suggest that anakinra (intravenously or subcutaneously) be used as first-line immunomodulatory treatment of children with COVID-19 and hyperinflammation (ACR).

- Tocilizumab may be effective in reducing mortality and intensive care admission in patients with severe COVID-19 pneumonia and signs of the hyperinflammation while causing higher risk for bacterial and fungal infections (ACR). When tocilizumab is used to treat children with COVID-19, weight-based dosing should be employed (body weight < 30 kg, 12 mg/kg IV; body weight ≥ 30 kg, 8 mg/kg IV, maximum 800 mg) (ACR). Currently there is no evidence to support the benefits of tocilizumab in the pediatric population, even in special populations such as cancer patients and patients with primary or secondary immunodeficiencies. Current evidence is based on adult patients with a therapeutic dose of 8 mg / kg of body weight (requiring a second dose 8–24 hours after the first), however, the results have also demonstrated adverse events such as gastrointestinal perforation and greater susceptibility to secondary infections when used concomitantly with dexamethasone 6 mg IV every 24 hours or equivalent corticosteroid dose [58].

- Taper of immunomodulatory medications is recommended in 2–3 weeks after recovery (ACR and CAID).

Antiplatelet and Anticoagulation management of MISC:

The use of aspirin at anti-inflammatory doses (3–5 mg / kg / day maximum 81 mg/day) is recommended in MIS-C (CAID and ACR) in the event of thrombocytosis (≥450,000 / μL) or dilatation of the coronary arteries until resolution and if there is no thrombocytopenia (≤80,000/μl), gastrointestinal bleeding, abnormal liver function tests (up to 5 times normal values of transaminases), uncontrolled asthma, oral intolerance, or influenza A or B virus infection (CAID). In cases of thrombocytosis (platelet count ≥450,000/μl), aspirin should be continued until the platelet count normalizes (ACR). Furthermore, patients with MIS-C and documented thrombosis or an ejection fraction <35% should receive therapeutic anticoagulation with enoxaparin until at least 2 weeks after discharge from the hospital (ACR).

4. Back to school

School re-opening is critical to support academic progress, mental health and access to essential services. Considerations of transmission and case severity in children may guide childcare and school policies. Many countries have reported that children under the age of ten have the lowest population based COVID infection rates [2]. Furthermore, while serious infections in children under the age of two are known to occur [2], studies have shown low infection in schools and low probability of transmission between children and teachers suggesting that safe school re-opening may be possible [60].

Despite uncertainties regarding the safety of returning to the classroom, some data collected suggests a partial or total return to face-to-face classes by taking measures to reduce community transmission may be possible. Schools in multiple countries have already reopened their classrooms with little published evidence that schools implementing COVID-19 control policies contribute significantly to COVID-19 transmission [61].

Some studies of COVID-19 transmission demonstrate that school-acquired infections are limited in comparison to community-acquired infections [62]. For example, a case–control study from Mississippi, USA carried out in children over 18 years of age described a total of 154 with SARS-CoV-2 infections and 243 without infection. In this group having attended social gatherings outside the home and

receiving visitors was associated with a greater risk of infection, while attending school in person was not associated with a greater risk [62].

Despite this promising data, there have been school-related outbreaks. For example, in Israel 2 weeks after the reopening of the schools in mid-May 2020 there was a large outbreak in a high school when 2 students attended school with mild symptoms. Students (n = 1,161) and the school staff (n = 151) were tested and infection was confirmed in students (n = 153) and staff (n = 25). However, some factors reported that may have contributed to this massive outbreak were full classrooms with insufficient physical distancing, the lack of mask use in some people and the continuous air conditioning that allowed recycle indoor air in closed classrooms. Therefore, perhaps implementation of these preventative measures may mitigate school transmission [61, 62].

Some measures implemented in schools and nurseries to mitigate the contagion are:

- Use of universal mask
- Adequate physical distancing
- Models of alternation classes (face-to-face-virtual)
- Avoid overcrowding
- Increase air ventilation in classrooms
- Increased coverage of rapid screening tests to quickly isolate asymptomatic infected
- Online education options for those who are at higher risk of serious illness or death if they contract COVID-19
- Limit groupings in classrooms to a maximum of 10 people
- Thorough cleaning of classrooms before and after activities
- Contingency plan in case someone is exposed to the virus
- Staged re-opening by year groups (eg, primary and secondary) or by geographic region to allow close monitoring and changes to the re-opening strategy as needed [63].

It is important to mention that athletic activities may increase the spread of SARS-CoV-2. For example, January 26 the CDC reported an outbreak associated with a wrestling tournament in a high school that occurred in December 2020 including 10 schools and 130 student-athletes, coaches and referees, of the students 38 (30%) contracted laboratory-confirmed SARS-CoV-2 infection [63]. Contact tracing identified 446 contacts of the positive cases that were considered to have had a high risk of transmission. One death of reported in one of the contacts of the students. However, limitations of the evaluation include that fewer than half of the participants were evaluated therefore some cases may have been unrecognized [64].

Simulation models have been used to determine how fast the virus spreads, how easily it is contained, effectiveness of containment strategies, social and economic impacts of closure, and the role of schools in transmission [63]. For example, some simulated transmission control strategies include placing siblings or children who

cohabit together in classrooms, assigning one group of children attends face-to-face one week while another group interacts online and then switching roles the following week, or school closure for 14 days if a symptomatic child attends school with those who are asymptomatic returning and symptomatic students staying at home. Another simulation evaluated the effect of child-educator ratios per classroom including 7: 3, 8: 2 and 15: 2. The most favorable transmission profile was shown with 7 students for every 3 educators and group assignment of siblings or students who cohabit together [65]. Whereas the worst transmission profile was shown with 15 students for 2 educators and the random assignment of students [64].

Virtual learning has been used to substitute for in-classroom experiences for many children globally. 143 countries had transitioned to online learning by August 2020, generating stress for both students and their families [66]. Virtual instruction has placed increased demands on family members in terms of time and other resources [67]. Fantini et al. suggests that we must take a deep look into the policies that have led to the necessary closure of the schools and the impacts they have [2]. The isolation school closures cause have great impacts on children, impacting not only their social life, but also their identity and personality development. Without proper social interaction, children may develop anger, guilt, and even depression in addition to anxiety and adjustment disorders. Another consideration is that in the setting of school closures students may spend a greater amount of time with their parents. While this phenomenon has certain benefits, without the support of schoolteachers, parents may become overwhelmed as the only caregivers, potentially exposing children to increased domestic violence, especially when parents have financial and mental health problems that may be exacerbated by the pandemic [2]. Virtual instruction also negatively impacts learning as children are taught best in hands-on learning, especially when learning to write [2]. Together, these factors illustrate some the hardships for children related to the pandemic and school closures.

For these reasons, it is important to implement in-person learning for children as part of early recovery. However, precautions should be effectively implemented and practiced, that may include social distancing, prevention of shared materials, ventilation of spaces, increased hand washing practices and sanitizing availability. Control measures include in-person learning could be started through alternating face-to-face and virtual learning scheduling to decrease density, the use of masks [2] and training of teachers in students in safety procedures [2].

5. The impact of the COVID-19 pandemic in children

The pandemic has affected children in great ways, impacting the way they grow, learn, play, and cope with their emotions [4, 60]. Younger children may be most at risk from the impacts of COVID-19, as lack of play, exercise, and interaction with peers [4, 60] can be affected. Additionally, other symptoms that affect brain development, such as stress, isolation, and depression [60], may develop if children witness friends and family members becoming infected or passing due to COVID-19. Children with psychiatric disorders face the greatest challenges, as 50% of psychiatric disorders [60] affect children by age 14. It is important to manage symptoms presented by these disorders as they may greatly affect child development.

Other symptoms children develop in this health crisis may include trouble sleeping and mental health problems. COVID-19 impacts the lives of children in various ways and include changing family-life circumstances. Parents might be working from home or become unemployed, increasing the risks for drug use and abuse in the home. These factors, as well as worries about their own physical health could cause children to have trouble sleeping. Additionally, if a child's mental

health is affected, they are at risk for post-traumatic stress [60], depression [60], and suicide [4, 60].

Important factors for mental health in children include good physical health and a good education system. Schools are a valuable resource to provide adequate information and help children understand COVID-19. Schools with trained professionals can also help identify children with problems and develop therapeutic approaches to support them. Teaching children how to cope with their emotions, generate healthy behaviors, and allowing children to participate in activities they enjoy are some of the benefits that schools can provide to try and counteract problems caused by the pandemic.

6. Conclusion

In conclusion, the COVID-19 pandemic poses some unique challenges for child health and learning. In relation to child health, Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but severe complication of COVID-19 related to acquired immune responses that requires further research. Despite limited studies to date to define therapeutic guidelines in children, consensus recommendations from multiple organizations recommend the use of immunomodulatory therapies, anti-platelet and anti-coagulant therapies. Furthermore, considerations for safe return to the classroom such as strategies for optimized student to teacher ratios, hand washing, social distancing, sibling pairing and staged re-opening strategies may facilitate child learning in the setting of this evolving pandemic. Further research into efficacy of these proposed interventions will be necessary to inform evidence based guidelines for the prevention and management of COVID-19 in children.

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