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COVID-19 in Pediatric patients: Clinical presentations, Diagnosis and treatment

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Abstract

Coronavirus Disease 2019 (COVID-19) is an infectious condition caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Unlike adults, children are less frequently affected by SARSCoV-2, with milder symptoms and a lower mortality rate. Conversely, as individuals age, the severity of COVID-19 tends to increase for both genders. This escalation can be attributed to various factors such as immune response dysregulation, diminishing sex hormones between males and females with age, and imbalance in the coagulation/fibrinolytic system, along with endothelial dysfunction associated with aging. In the pediatric population, COVID-19 exhibits unique epidemiological characteristics. It is more prevalent in male children and infants. Furthermore, pediatric COVID-19 patients manifest distinct clinical features when compared to their adult counterparts. Symptoms are like other viral respiratory tract infections, including fever, cough, shortness of breath, sore throat, diarrhea, nausea, vomiting, anorexia, and myalgia. Notably, several studies have reported that many confirmed cases of COVID-19 in children present as asymptomatic. Fever and cough are the most observed symptoms in children infected with SARS-CoV-2. The excessive production of inflammatory cytokines plays a crucial role in the pathogenesis of the disease, with pro-inflammatory cytokines like TNF and ACE2 being key contributors. However, it is worth noting that no single symptom, sign, laboratory test, or radiological finding can reliably predict a COVID-19 diagnosis, although some data can help assess the severity of the disease. These indicators should be incorporated into clinical practice to identify high-risk children and provide prompt management to reduce the risk of complications and mortality. Overall, the prognosis for pediatric patients with COVID-19 is generally favorable, with spontaneous recovery in most cases. As of now, there is no standardized approach for the management or prevention of the disease in pediatrics. Vaccination programs for children have been introduced later than for adults, primarily due to limited early safety and effectiveness data and the relatively mild nature of the disease in pediatric populations. Further research is essential to better understand the age-related differences in clinical presentation of COVID-19, assess the role of children in community transmission, and develop effective treatments and vaccines tailored to the pediatric population.

Keywords: Clinical, Management, Pediatric, COVID-19

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1. Introduction

1.1. Epidemiology of COVID-19 in Children

- ***General epidemiological features***

Children represent a minority of SARS-CoV-2 infections, often acquiring the virus through contact with adults. While there have been sporadic cases of transmission from symptomatic children to household members involving the original 19A/19B strain of SARS-CoV-2, their impact on the broader pandemic has been minimal. The continual evaluation of the significance of these discoveries is important, particularly in consideration of developing variations, such as Delta (B.1.617.2) variation [1]. Initial investigations conducted in Australia pertaining to the Delta variation have indicated elevated rates of transmission, particularly within domestic settings. Nevertheless, the spread of the virus is generally more evident when originating from adult individuals as opposed to youngsters. Future variations of concern may provide unique difficulties, requiring continuous assessment of current paradigms based on variant-specific information [2]. The predominant means by which SARS-CoV-2 is transmitted is through direct proximity between individuals, notably through the dissemination of respiratory droplets. Modifications in guidelines from the World Health Organization (WHO) and local infection control measures have been prompted by the acknowledgment of possible aerosol transmission, particularly in the context of highly infectious varieties such as Delta. The augmented transmissibility of the Delta variant is apparent through notable increases in household attack rates and basic reproduction numbers (R0) (refer to Table 1). Moreover, Delta variant demonstrates a comparatively reduced average incubation period. This characteristic presents further complexities for public health agencies in their endeavors to conduct effective testing, contact tracing, and isolation measures [3].

Within familial clusters, parents have been identified as the primary source of infection in most cases, accounting for 56% of instances. In contrast, the study found that a mere 4% of instances identified a sibling as the most probable index case [4]. In recent months, there have been the emergence of novel variations of SARS-CoV-2, which have shown an increased reproduction number of up to 90% and a more significant effect on morbidity and death, as indicated by model forecasts. The involvement of children in the transmission dynamics of these variations is currently being actively investigated [5]. Although children have constituted a minority of SARS-CoV-2 cases in many places, the prevalence of infections has shifted towards younger age groups due to the combination of high household attack rates linked to the Delta variant and the increasing vaccination rates among older individuals. However, it is commonly observed that the disease's impact on youngsters is often moderate. The prevailing epidemiological patterns suggest that in nations such as Australia, the United States, and the United Kingdom, young adults are emerging as the predominant demographic group, as opposed to children. The observed change can be ascribed to the increased transmissibility among adults and the comparatively lower rates of immunization among young individuals [6].

- ***The Role of Schools***

The occurrence of SARS-CoV-2 transmission has been recorded in educational environments, leading some nations to enforce nationwide closures of schools as a strategy to mitigate the dissemination of the virus. Nevertheless, epidemiological studies have demonstrated that in the majority of nations, particularly when stringent infection control measures are implemented, the transmission of SARS-CoV-2 within schools accounts for a fraction of the total COVID-19 cases. A pertinent illustration may be found in Sweden, where educational institutions, including schools and preschools, choose to continue their operations during the epidemic. Notably, these establishments observed a relatively low prevalence of severe COVID-19 cases among the kid population. The findings of a prospective cohort research done in Australia, which incorporated case-contact testing, indicated that the role of children and teachers in facilitating COVID-19 transmission within educational contexts was minimal [7]. Likewise, research conducted in Ireland has investigated the occurrence of pediatric COVID-19 cases in school environments, revealing no evidence of subsequent transmission to either fellow children or adults, across both primary and secondary educational settings. A comprehensive nationwide monitoring initiative was carried out in England after the reopening of schools following the first lockdown that aimed to assess the level of risk associated with SARS-CoV-2 infection among both educational personnel and pupils. The findings revealed a relatively low overall risk of infection in educational settings [8]. In the context of Germany, the implementation of infection control measures in schools and childcare facilities resulted in a low incidence of child-to-child transmission of SARS-CoV-2.

Although transmission was observed among high school students in northern Italy, no secondary cases were identified among pre-school children, except for a single case reported in a primary school. Moreover, there were no additional instances of transmission documented among the teaching staff. A separate cross-sectional and prospective cohort research done in Italy yielded findings that did not substantiate the notion that the reopening of schools played a significant role in the resurgence of the SARS-CoV-2 outbreak during its second wave [9].

A systematic review of 16 articles incorporated modeling studies to examine the effects of school closures and other school-based social distancing measures in the context of coronavirus outbreaks, specifically focusing on COVID-19. The findings of this review indicate that the implementation of school closures would have a limited impact on reducing mortality rates, particularly when compared to the effectiveness of alternative social distancing interventions. Moreover, the dissemination of transmission inside educational institutions may be effectively reduced by the rigorous enforcement of several mitigation strategies. The procedures encompass the regular cleaning of surfaces that are often touched, ensuring proper ventilation in rooms, practicing good hand hygiene, implementing the use of face masks both within and outside of the classroom, promoting physical distancing among children, and temporarily isolating children who are unwell [10].

In relation to distinct age cohorts, the distribution of data pertaining to SARS-CoV-2 infections in the United States between March and December 2020 found that almost 1.2 million individuals below the age of 18 [11].

- The percentage of children enrolled in preschool (aged 0 to 4 years), is 7.4%.
- The percentage of children enrolled in elementary school (aged 5 to 10 years), is 10.9%.
- The percentage of children enrolled in middle school (aged 11 to 13 years), is 7.9%.
- The percentage of children enrolled in high school (aged 14 to 17 years), is 16.3%.

2. Diagnosis

The determination of a COVID-19 diagnosis will be contingent upon the establishment of a case definition encompassing both suspected and confirmed cases (Figure (1)). The implementation of case definition is contingent upon the clinical presentation of the case, as well as the results of laboratory tests and radiographic findings. The cases will be categorized based on this aggregated data into various levels of severity [12]. Mild instances are distinguished by either being asymptomatic or exhibiting symptoms such as Leucopenia and/or lymphopenia, without any radiological indications of pneumonia. The symptoms often observed encompass upper respiratory tract sickness, maybe accompanied by one or more of the subsequent manifestations: temperature below 38°C, cough, gastrointestinal symptoms, myalgia, and/or arthralgia [12]. In contrast, moderate instances refer to individuals who have both leucopenia and/or lymphopenia, as well as clinical and radiographic evidence of pneumonia. These individuals commonly exhibit a body temperature above 38°C, accompanied by symptoms such as coughing and rapid breathing. The specific respiratory rates associated with tachypnea vary depending on the age group: infants under 2 months have a respiratory rate exceeding 60 breaths per minute, infants aged 2 to 12 months have a rate of more than 50 breaths per minute, children aged 1 to 4 years have a rate above 40 breaths per minute, and children older than 5 years have a rate beyond 30 breaths per minute. Furthermore, it has been shown that cases of mild to severe dehydration may exhibit an association with the aforementioned factors [12].

COVID-19 disease is classified as severe pr critical if any of the following conditions are seen [12]:

- Oxygen saturation levels equal to or less than 92%, or a Pa O2/FiO2 ratio below 200, even after increasing oxygen treatment to the maximum allowable flow rate of 6 L/min.
- Oxygen saturation levels equal to or less than 90%, or a Pa O2/FiO2 ratio below 300, when breathing room air.
- If the patient is experiencing septic shock, confusion, or hemodynamic instability despite undergoing fluid resuscitation,
- If respiratory symptoms are accompanied by other forms of organ failure.
- Chest radiography showing pulmonary lesions accounting for more than 50% of the chest or if the lesion is showing signs of progression within a 24 to 48-hour period.

2.1. Clinical diagnosis

2.1.1. COVID-19 manifestations in children

It has been observed during the early stages of the epidemic, children tend to display less severe symptoms compared to adults. To validate this finding, an extensive case series was undertaken in China, comprising a cohort of pediatrics who were diagnosed with COVID-19. The results of the study indicated that around 55% of the patients either presented with no symptoms or displayed just mild symptoms. However, it is important to highlight that 6% of pediatric cases were categorized as severe or critical demonstrating a notable decline when compared to the prevalence of severe and critical cases seen in the adult population, which was around 18.5%. According to research published by the US Centers for Disease Control and Prevention (CDC), a significant proportion of pediatric COVID-19 cases, around 73%, had symptoms like fever, cough, or dyspnea. The current proportion exhibits a significant decrease in comparison to the previous reporting period, whereby 93% of individuals between the ages of 18 and 64 displayed comparable symptoms. Moreover, 6% of pediatric cases needed hospitalization [13].

2.1.1.1. Theories for the milder symptoms and lower prevalence in children

Several explanations have been proposed to provide an explanation for the very low prevalence of reported COVID-19 cases among children and the comparatively milder clinical manifestations observed in this population as compared to adults. A comprehensive examination and synthesis of 32 research revealed that individuals in the age group of children and adolescents, below 20 years old, had a 44% reduced probability of acquiring SARS-CoV-2 in comparison to people aged 20 years and older. The observed discrepancy was particularly notable among those falling within the age bracket of 10 to 14 years [15]. Davies et al. conducted a study to examine the correlation between susceptibility to infection in children and adults and the emergence of clinical symptoms. The results of their study revealed the presence of an "age gradient," wherein the likelihood of experiencing serious illness escalated in tandem with advancing age. In their study, it was shown that a significant proportion of pediatric patients, namely 79% of those aged 10 to 19 years, had no symptoms of COVID-19. Furthermore, the susceptibility to the virus was seen to be twice as high in individuals aged 20 years and above compared to those under the age of 20 [16]. Numerous reasons have been posited to elucidate the age-related distribution of COVID-19 cases. The presence of milder symptoms or asymptomatic instances among pediatrics may introduce a reporting bias. Individuals who exhibit milder symptoms are less inclined to actively pursue medical assistance, thereby diminishing the probability of obtaining official confirmation and subsequent reporting [13]. An alternative hypothesis is that the regular exposure of children to several coronaviruses, known to cause common colds, could provide a certain level of protection against SARS-CoV-2. This phenomenon of immunity can be ascribed to either cross-protection resulting from prior infections caused by coronaviruses or non-specific protection conferred by other respiratory viruses. The presence of a concurrent viral infection might possibly have a competitive effect on SARS-CoV-2, resulting in a diminished replication capacity and potentially mitigating the severity of the associated disease [17]. Furthermore, the SARS-CoV-2 virus utilizes its spike protein to attach itself to the human angiotensin-converting enzyme 2 (ACE-2) receptor, therefore facilitating its entrance into host cells. A study conducted on a cohort ranging from 4 to 60 years of age discovered that the expression of the ACE-2 gene in the nasal epithelium was found to be at its lowest in those under the age of 10, with a subsequent increase observed as age advanced. The downregulation of ACE-2 expression may potentially restrict the cellular entrance of SARS-CoV-2, hence playing a role in reducing the susceptibility to infection and attenuating the severity of clinical manifestations in pediatric populations. Furthermore, it is worth noting that the relatively lower incidence of comorbidities, such as diabetes, chronic lung disease, and cardiovascular disease, among children, may contribute to the less severe progression of the illness when compared to adults [18]. A significant number of juvenile COVID-19 cases have been associated with familial transmission. In a research investigation encompassing 34 verified pediatric instances, it was observed that 38% of the patients had encountered exposure to COVID-19 through familial contact. There has been a proposition positing that in cases when an adult passes on the SARS-CoV-2 virus to a child, the subsequent infection in the child may include a subsequent generation of the virus, perhaps leading to a less severe disease because of reduced pathogenicity. A retrospective analysis was conducted on data pertaining to 9 pediatric individuals and 14 adult family members. The findings revealed that 44% of the children had symptoms such as fever or cough, while 6 children remained asymptomatic. In contrast, the study revealed that 71% of the adult participants exhibited abnormal radiograph results, but just 44% of the pediatrics demonstrated such abnormalities. The inclusion of family clusters as a factor may provide more insight into the less severe manifestation reported in young patients [19].

The most common symptoms in pediatrics include fever, upper respiratory symptoms, and gastrointestinal problems. A comprehensive examination of a cohort of 333 pediatric patients revealed that the prevailing symptoms seen were cough (48%), fever (42%), and sore throat (42%). Moreover, a significant percentage of individuals, namely 35%, were identified as being asymptomatic. Other symptoms that have been recorded encompass rhinorrhea, nasal congestion, myalgia, fatigue, dyspnea, abdominal pain, diarrhea, emesis, nausea, cephalalgia, disorientation, decreased oral intake, and cutaneous eruption (Figure (2)). In a study including 26 investigations and included a total of 1793 children who were diagnosed with COVID-19, the most common symptoms were fever and cough (Figure (3)). The healing process often occurred within a duration of 1 to 2 weeks subsequent to the onset of symptoms [18]. Anosmia and ageusia have been often seen symptoms in adult COVID-19 cases. In the context of pediatric patients, there has been a comparatively lower frequency of recorded occurrences of these symptoms. It is worth mentioning that coronaviruses, belonging to the viral family, can infiltrate the olfactory bulb, resulting in anosmia, or the loss of the sense of smell. Parisi et al. have emphasized the importance of undertaking additional examinations in pediatric patients with COVID-19 who present with complaints of anosmia. The evaluation included nasal endoscopy and the utilization of olfactory tests, such as the Pediatric Smell Wheel, to ascertain the degree of olfactory impairment [26].

2.1.1.2. Severe and Critical Disease in Children

While most pediatric children infected with COVID-19 display moderate symptoms or remain asymptomatic, there have been documented cases of severe disease and, if seldom, fatalities. Symptoms frequently noticed in cases of the condition that are severe and serious encompass hypoxia, which is distinguished by oxygen saturation levels that fall below 92%. Furthermore, it is worth noting that patients may have acute respiratory distress syndrome, shock, and organ failure, which can present as encephalopathy, heart failure, abnormal coagulation, and severe kidney damage. In Zimmerman et al. study, it was shown that within a sample of 333 children, a proportion of 3% required admission to pediatric critical care units with two of these children had pre-existing medical conditions, including leukemia and hydronephrosis [18]. The incidence of COVID-19-related mortality has been notably greater among the adult and older demographics in contrast to the pediatric group. The heightened occurrence of deaths among adults has been linked to the coexistence of comorbidities such as cancer, diabetes, cardiovascular disease, chronic lung disease, and impaired immune systems. An investigation including a sample size of 44,672 individuals diagnosed with COVID-19 revealed that 26% of the patients had comorbidities. Among the total of 965 fatalities examined in this study, there was only 1 pediatric case. However, it is important to highlight that no precise information was provided on the characteristics or circumstances surrounding the 14-year-old case. As of March 2020, this instance constituted one of the two recorded fatalities among pediatric patients diagnosed with COVID-19. The second kid was a female infant aged 10 months, who presented with a range of medical problems including intussusception, encephalopathy, septic shock, and multiorgan failure [21]. In a comprehensive evaluation of 29 studies spanning a total of 4,300 children, it was shown that 19% of the cases were characterized by the absence of symptoms, while 37% had no detectable abnormalities in radiographic imaging. A minute proportion, estimated at roughly 0.1%, need admission to critical care units, and the analysis documented four fatalities. In a study conducted by the US COVID-19-Associated Hospitalization Surveillance Network, a total of 208 hospitalized children were included for comprehensive medical chart reviews. The findings revealed that 33% of these children were admitted to intensive care units, while 6% required invasive mechanical ventilation with one child (0.5%) did not survive. The group under study had comorbidities such as obesity (38%), chronic pulmonary disease (18%), and preterm (15%). Typically, pediatric patients diagnosed with COVID-19 have a positive prognosis. Nevertheless, it is crucial to acknowledge that there have been documented instances of a significant post-infectious hyperinflammatory disease referred to as multisystemic inflammatory syndrome in children [22].

2.1.1.3. The clinical manifestations include

- ***Respiratory Manifestations***

Respiratory symptoms frequently exhibit similarities to symptoms associated with upper respiratory tract infections or influenza, perhaps accompanied by various levels of pyrexia. Anosmia and loss of taste are prominent in older children. Apnea may be observed in infants. When symptoms exhibit a significant elevation in body temperature and involve several bodily systems, it may indicate a potential correlation with Multisystem Inflammatory Syndrome in Children (MIS-C), whereby respiratory symptoms are less pronounced. Around 30% of individuals who necessitate hospitalization in critical care exhibit indications of acute respiratory distress syndrome. The disease is differentiated by elevated levels of inflammatory markers, radiographic abnormalities [23], and histological findings that indicate anomalies in type 2 pneumocytes, pulmonary micro-thrombosis, and exudative widespread alveolar damage. Uncommon manifestations such as viral bronchiolitis or exacerbations of asthma, which saw a decline in prevalence during the initial phases of the COVID-19 pandemic, may elicit suspicions regarding potential viral co-infections [24].

- ***Gastrointestinal and Hepatic Manifestations***

The incidence of gastrointestinal symptoms as the major manifestation in pediatric patients with COVID-19 has exhibited variability across several case groups. Nevertheless, gastrointestinal symptoms are more common in Multisystem Inflammatory Syndrome Children (MIS-C), and there is evidence linking the persistence of antigens from a gastrointestinal origin to the development of this condition. The symptoms include nausea, vomiting, and diarrhea. In more severe cases, the phenotypic presentation may resemble that of acute appendicitis or intussusception. In instances of heightened severity, the radiography observations may be like those in patients of inflammatory bowel disease [25].

- ***Cardiac Manifestations***

The cardiac symptoms of SARS-CoV-2 are predominantly found in severe instances of Multisystem Inflammatory Syndrome in Children (MIS-C), typically accompanied by inflammatory response, necrosis, and direct invasion of the virus into the myocardium. In the series of cases pertaining to Multisystem Inflammatory Syndrome in Children (MIS-C), it has been shown that over 50% of the patients exhibit a decrease in the left ventricular ejection fraction. Furthermore, a significant majority of children with cardiac involvement demonstrate higher levels of cardiac troponin. A comprehensive case series of 1,733 patients documented a range of cardiac conditions, such as cardiac dysfunction (31.0%), pericardial effusion (23.4%), myocarditis (17.3%), and coronary artery dilatation or aneurysms (16.5%) [26].

- ***Neurologic Manifestations***

Approximately 20% of pediatric COVID-19 cases exhibit neurologic symptoms. Infants may show neurologic signs, such as the occurrence of new seizures or episodes of apnea. Adolescents may suffer from severe headaches, which can occasionally coincide with the manifestation of pseudotumor cerebri syndrome. After infection with SARS-CoV-2, individuals have reported experiencing postinfectious sequelae, such as peripheral neuropathy, demyelination, transverse myelitis, and Guillain-Barre syndrome. These conditions have been shown to emerge, in some cases, even without any further systemic signs [27].

- ***Dermatologic Manifestations***

Transient maculopapular rashes have been observed in both acute and late stages of COVID-19 infection. The infection caused by the ability of SARS-CoV-2 to induce cutaneous vasculitis, which may lead to the development of disorders such as perniosis (often referred to as "COVID toes") or acral gangrene. Petechiae have been shown to be linked with disorders related to thrombocytopenia, such as Henoch-Schoenlein purpura. The mucocutaneous signs observed in MIS-C bear resemblance to those observed in Kawasaki disease (KD), including a diverse rash and the engagement of the oral mucosa [28].

- ***Other Systemic Manifestations***

The incidence of clinical thrombotic events in pediatric patients with COVID-19 is lower in comparison to the adult population. The prevalence of MIS-C is higher in older children, particularly those with pre-existing risk factors for thrombosis such as malignancy or the utilization of a central line. Thrombotic events include deep vein thrombosis, pulmonary embolism, and strokes. The occurrence of diabetic ketoacidosis was found in children admitted to the hospital with multisystem inflammatory syndrome in children (MIS-C), and as a complication in children who already have a diagnosis of diabetes. Acute renal failure is a prevalent occurrence, affecting around 25% of children admitted to intensive care units with Multisystem Inflammatory Syndrome in Children (MIS-C), as reported in a study [29].

2.1.2. COVID-19 manifestations in Newborns and Infants

The presence of COVID-19 has also been seen in newborns. In a Chinese study including a total of nine newborns, ranging in age from one to eleven months, who were admitted to hospitals in China, four had symptoms of fever, two experienced moderate upper respiratory tract infections, one remained asymptomatic, and data on the health status of two newborns was not provided [30]. An additional review provided an account of three cases involving neonates. The first case was a neonate who exhibited symptoms of fever and cough, while the second case involved a neonate with symptoms of rhinorrhea and vomiting. The third case involved a neonate experiencing respiratory distress. Complications have been documented in neonates who are delivered to moms who had experienced COVID-19 throughout their pregnancy. In a study involving 65 mothers with a documented history of COVID-19 during pregnancy, a total of 67 neonates were observed. Out of these neonates, 12 (18%) exhibited symptoms of respiratory distress or pneumonia, nine (13%) were born with low birth weight, two (3%) developed a rash, two (3%) experienced disseminated intravascular coagulation, one (2%) suffered from asphyxia, and unfortunately, two (3%) did not survive the illness [18].

2.1.3. Inverse Relationship between Severity and Age in Pediatrics

Age is commonly associated with a heightened severity of COVID-19 symptoms among the general population. However, Dong et al.'s found that newborns demonstrate a heightened vulnerability to severe sickness, as indicated by the fact that 10.6% of infants under the age of one exhibit symptoms of severe or critical disease. Nevertheless, with the progression of age, there is an observable decline in the occurrence of severity. The prevalence of severe disease varies across different age groups of children, with rates of 7.3% in the 1- to 5-year-old age group, 4.2% in the 6- to 10-year-old age group, 4.1% in the 11- to 15-year-old age group, and 3.0% in the 16 and older age group. Within the United States, newborns who are under the age of one year have been identified as the demographic group with the highest proportion of hospitalizations among pediatric patients diagnosed with COVID-19. The estimated range for this percentage is between 15% and 62% [13].

2.2. Methods for Laboratory Diagnosis

2.2.1. Verification of SARS-CoV-2 Infection via Laboratory Testing

The most often utilized approach for the diagnosis of COVID-19 is the detection of SARS-CoV-2 genetic material by the application of real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The virus may be identified in several physiological fluids, including samples collected from the upper airway (nasopharynx swab), lower airway secretions (tracheal aspirates, bronchoalveolar lavage), blood, urine, and stool [31].

2.2.2. Laboratory examinations for the detection of alternative diagnoses

When managing young children who are very ill and have a low absolute risk of hospitalization because of acute COVID-19, it is crucial to conduct a thorough assessment to investigate potential underlying reasons. There have been cases in which both prevalent illnesses, such as bacterial enteritis, and atypical ailments, such as primary immunodeficiency syndromes, have been identified. Therefore, a comprehensive diagnostic approach that includes the involvement of subspecialists is required when assessing pediatric patients who exhibit a variety of symptoms and yield positive results for SARS-CoV-2. It is important to highlight that cases of co-infections have been recorded in both acute COVID-19 and MIS-C cases. These co-infections involve bacterial pathogens like Staphylococcus aureus and group A Streptococcus, as well as viral pathogens such as Epstein–Bar virus, parvovirus, herpes viruses, and other respiratory viruses [33].

2.2.3. Supplementary Laboratory Testing for the Purpose of Risk Stratification and Disease Classification

Hematological studies found a relation between COVID-19 and various blood abnormalities, encompassing leukocytosis or leukopenia, lymphocytosis, or lymphopenia, as well as heightened concentrations of C-reactive protein (CRP), serum ferritin, lactate dehydrogenase (LDH), D-dimers, procalcitonin, erythrocyte sedimentation rate (ESR), serum aminotransferases, and creatine kinase-myocardial bands (CK-MB) [31]. In pediatric patients necessitating admission to the Pediatric Intensive Care Unit (PICU), it has been noted that they exhibit heightened levels of C-reactive protein (CRP), procalcitonin, pro–B-type natriuretic peptide (BNP), and platelet count in comparison to children admitted to alternative hospital units. A correlation has been seen between organ failure and certain physiological markers, including heightened levels of C-reactive protein (CRP), an enhanced white blood cell count, and thrombocytopenia [34]. It has been shown that adult individuals diagnosed with COVID-19 who exhibit hyperinflammation, as indicated by elevated levels of LDH, D-dimer, IL-6, CRP, and ferritin, along with reduced lymphocyte count, platelet count, and albumin level, tend to suffer more worse clinical outcomes [35].

Other risk factor include.

- Several chronic illnesses, including diabetes, renal disease necessitating dialysis, moderate to severe asthma, substantial cardiac disorders, liver disease, and extreme obesity (characterized by a body mass index surpassing), have been identified [40].
- Immunocompromised states including malignancies, patients undergoing cancer therapies, bone marrow or organ transplants, uncontrolled HIV or AIDS, and prolonged use of corticosteroids and other immunosuppressive medicines [36].

2.3. Radiological diagnosis

Chest radiography is a customary procedure employed in the management of pediatric patients who have been admitted to the hospital because of severe respiratory failure stemming from COVID-19. Although chest radiographs may not provide the highest accuracy in diagnosing COVID-19, they are regarded as important instruments for monitoring the advancement of the illness. Typical observations in COVID-19 pneumonia or acute respiratory distress syndrome (ARDS) include bilateral distribution with peripheral or subpleural ground-glass opacifications and consolidation (Figure 4). In contrast to the customary characteristics observed in viral respiratory infections in children, such as enhanced perihilar markings and hyperinflation, these manifestations were not frequently documented in pediatric cases of COVID-19 [37]. Computed tomography (CT) scans are well recognized as the predominant imaging modality utilized for the evaluation of pulmonary manifestations associated with COVID-19. Computed tomography (CT) scans demonstrate remarkable sensitivity and specificity, enabling the identification of infection even prior to the onset of clinical signs. Three unique stages of evolution have been found in pediatric patients affected with COVID-19. The stages of this phenomenon include: first sage presented as "halo sign," which is distinguished by the presence of nodules or masses encircled by ground-glass opacifications. Subsequently, the progressive phase is defined by the widespread occurrence of ground-glass opacifications, while the last stage, referred to as the developed phase, exhibits consolidative opacities [38]. In comparison to adults, children frequently have a higher incidence of peri-bronchial thickening and inflammation along the broncho-vascular bundle. Furthermore, there have been reports of tiny mesh reticulations and a phenomenon referred to as the "crazy-paving sign." Pleural effusion and lymphadenopathy are infrequently found in pediatric populations. In contrast to adults, children have a reduced prevalence of positive CT findings, less pulmonary lobe involvement, and a lower semiquantitative lung score, which serves as a measure of the level of lung impairment [39].

Based on the observations and taking into account the potential risks associated with radiation exposure, logistical challenges related to the transportation of critically ill patients to CT suites, and the need of infection control, it is not advisable to prioritize chest CT as the primary diagnostic modality for pediatric individuals suspected of being afflicted with COVID-19. However, CT might be suitable for some clinical investigations, such as the evaluation of pulmonary embolism, the assessment of unresponsive patients, and the monitoring of fibrotic disease advancement. Lung ultrasonography is an additional imaging technique that has significant value, especially due to its shown correlation between semiquantitative scores in lung ultrasonography and lung CT scans in critically sick adults with COVID-19 [40].

3. Treatment guidelines

During the time of acute infection, the primary goal is to eradicate the virus using antiviral drugs. During the post-infectious period, there is a change in attention towards the regulation of the immune response. The selection of the therapeutic strategy is dependent on the level of illness severity, as indicated (Table (1)). In the case of children exhibiting a modest phenotype, it is typically unnecessary to pursue therapeutic interventions. Nevertheless, in situations when the body temperature surpasses 38.5°C, antipyretic medications such as oral ibuprofen at a dose of 5–10 mg/kg or oral paracetamol at 10–15 mg/kg may be used. Despite initial reports, there is currently no definitive data to substantiate the notion that ibuprofen has a harmful impact on individuals with COVID-19 [41].

It is important to offer supportive care for children exhibiting mild phenotypes. Potential interventions for the management of the condition may include intravenous (IV) administration of fluids for rehydration purposes, as well as providing respiratory support if needed. In instances when individuals exhibit severe or critical phenotypes, it becomes imperative to adopt a tailored treatment strategy that incorporates the administration of second-line drugs such as antivirals, immunomodulators, and enhanced respiratory support. Like other viral respiratory infections, the use of bronchodilators and/or inhaled steroids is necessary in the event of bronchospasm [43].

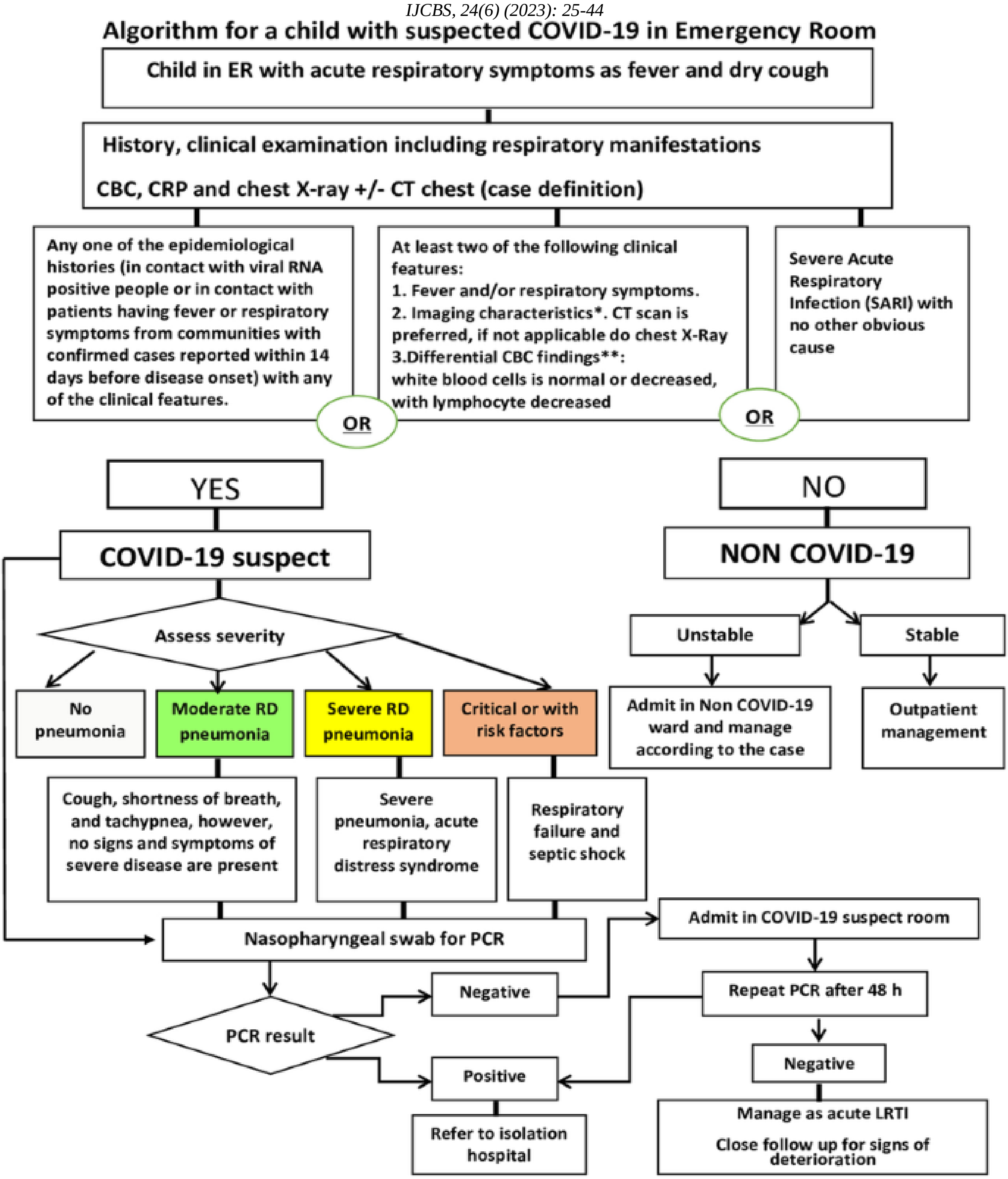

Fig.1. This paper aims to provide a comprehensive overview of the guidelines for evaluating a pediatric patient who is suspected of having COVID-19 in the emergency department. The abbreviations used in this discussion are as follows: RD, which stands for Signs of Respiratory Distress; PCR, which stands for Polymerase Chain Reaction; and LRTI, which stands for Lower Respiratory Tract Infection [12].

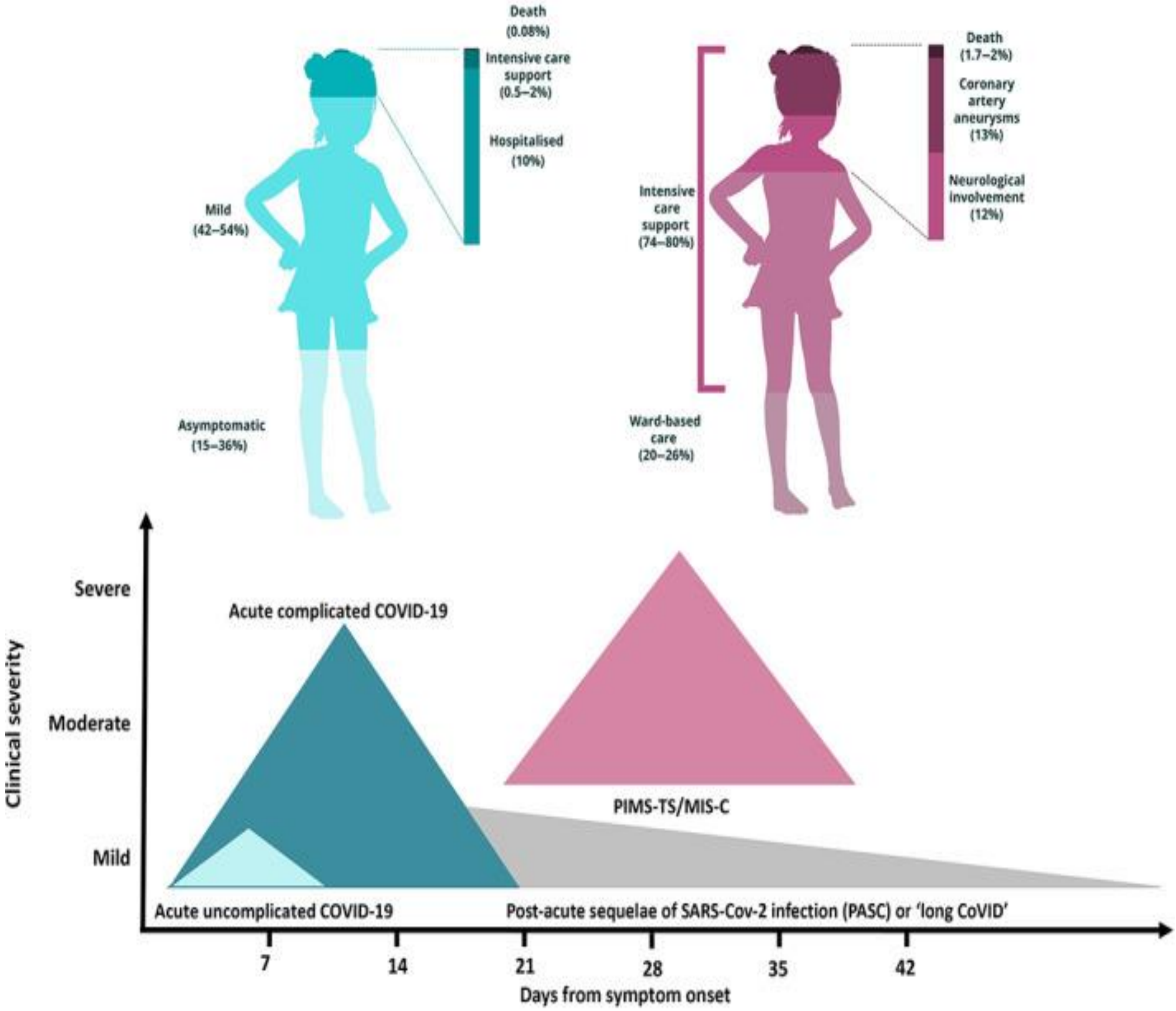

Fig.2. The collective impact of COVID-19 on children's health: The left-hand section illustrates results stemming from acute COVID-19 infection, while the right-hand section illustrates results linked to Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 **(PIMS-TS)** in children. The figures provided here, indicating the proportion of children requiring hospitalization and intensive care, are notably higher than what has been observed in Australia in 2021. Based on unpublished data by PN Britton, hospitalization rates for medical reasons were approximately 1% of cases, and intensive care unit **(ICU)** admission was around 0.1% of symptomatic cases during this time [14].

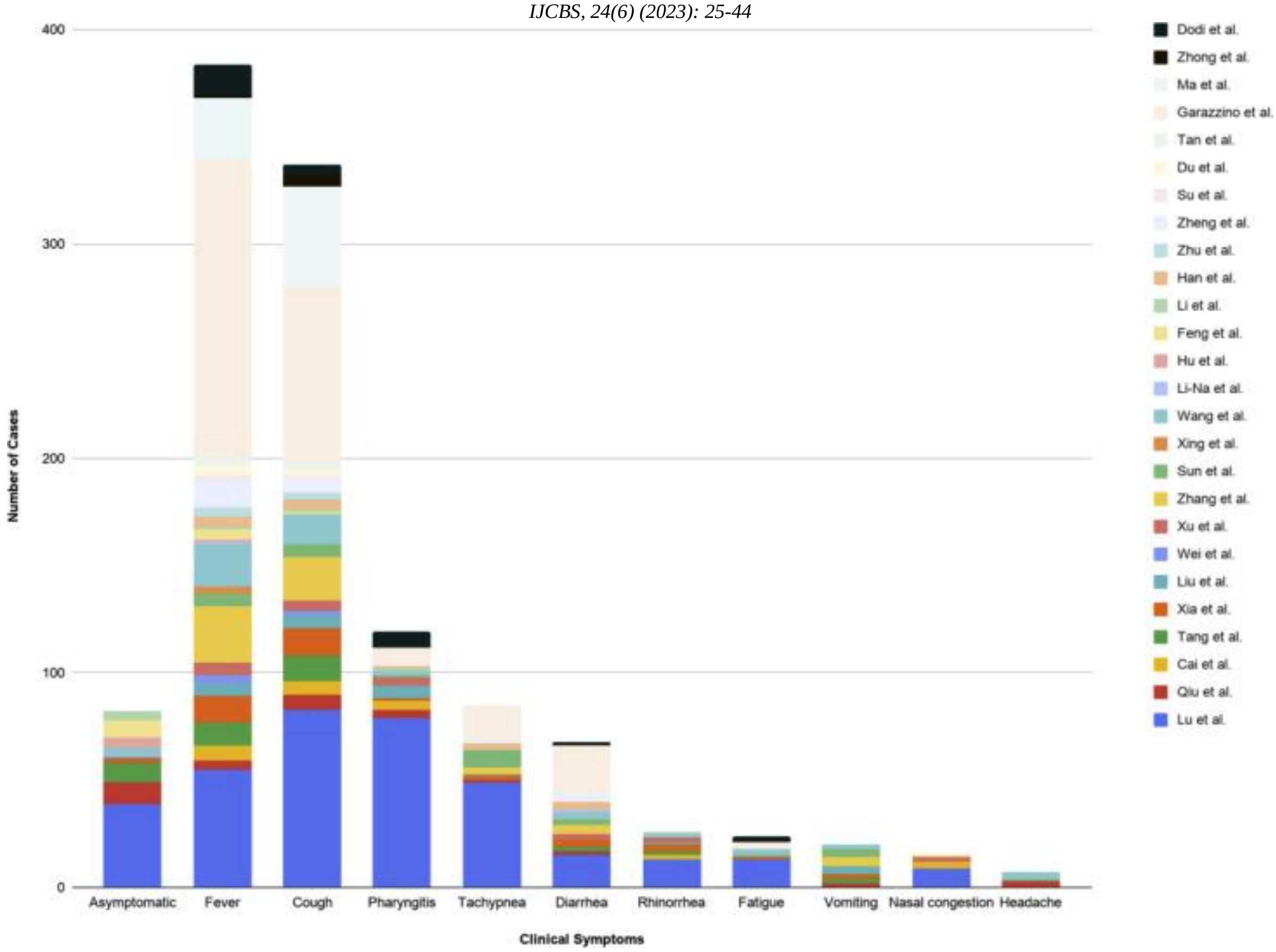

Fig.3. Summary of clinical manifestations in reported pediatric patients with COVID-19 [20]

Fig.4. The chest radiograph of a newborn diagnosed with bronchopulmonary dysplasia and subsequently developing COVID-19 acute respiratory distress syndrome **(ARDS)** reveals the presence of bilateral ground-glass opacities [38]

Table 1. Treatment of pediatric SARS-CoV-2 pulmonary disease [42]

Clinical phenotype	Antiviral therapy	Immunomodulatory therapy	Supportive therapy
Asymptomatic infection	-	-	-
Mild Fever, upper respiratory signs No respiratory distress	-	-	antipyretics
Moderate Fever, lower respiratory signs Mild respiratory distress	Remdisivir	-	If SaO2< 95%; low flow oxygen therapy
Severe Tachypnea Hypoxemia Feeding difficulties, lethargy severe respiratory distress	Remdisivir	Methylprednisolone IV/ oral dexamethazone	HFNC or NIV VTE Antibiotics
Critical PARDS **(**acute respiratory failure+ bilateral pulmonary opacities PaO2/ FO2 <300	Remdisivir Casirivimab/Imdevimab **(>12 years)**	Methylprednisolone IV Anakinra/ Oclizumab	NIV- invasive ventilation Prone positioning VTE Antibiotics

PARDS, pediatric acute respiratory syndrome; PaO2, arterial partial pressure of oxygen; FO2, fraction of inspired oxygen; HFNC, high flow nasal cannula; NIV, non-invasive ventilation.

Table 2. Risks factors for hospital VTE in children [42]

•The central venous catheter is a medical device used for many purposes, such as administering medications, fluids, or blood products, as well as monitoring central venous pressure.
•Factor V Leiden and factor II G29210A are genetic mutations associated with an increased risk of blood clot formation, which can lead to conditions such as deep vein thrombosis or pulmonary embolism.
•Extended duration of hospitalization
•Total lack of mobility
•Excessive body weight
•Presence of an active malignancy, nephrotic syndrome, cystic fibrosis, aggravation, sickle cell disease vaso-occlusive crises, or exacerbation of underlying inflammatory conditions **(e.g., lupus, juvenile idiopathic arthritis, inflammatory bowel disease)**
Congenital or acquired heart illness characterized by venous stasis or decreased venous return.
•Individuals with a prior occurrence of venous thromboembolism **(VTE)**, a familial history of VTE in first-degree relatives before the age of 40, or an unprovoked VTE incident.
•Individuals with a confirmed presence of thrombophilia, such as deficiencies in protein S, protein C, or antithrombin; the presence of Factor V Leiden or factor II G20210A mutations; or persistent antiphospholipid antibodies.
•Individuals who have reached puberty, post-puberty, or are older than 12 years of age
• Individuals who are already using oral contraceptive tablets that include estrogen. The patient's current condition is after undergoing a splenectomy procedure due to an underlying hemoglobinopathy.

The key goal concerning children with asthma is to provide appropriate management of their condition to protect them from experiencing a severe course of COVID-19. Hence, it is recommended that treatment modalities utilizing antihistamines, corticosteroids, leukotriene-receptor antagonists, and bronchodilators should not be prematurely terminated [43]. Nevertheless, individuals suffering from severe asthma who are undergoing biological therapies, such as omalizumab, mepolizumab, or dupilumab, must discontinue their medication in the event of acquiring an active SARS-CoV-2 infection. The unknown effects of discontinuing these drugs on acute treatment and the danger of losing illness control are attributed to their relatively lengthy half-life, which can last for several weeks. Furthermore, it is recommended to utilize a pressured metered-dose inhaler in conjunction with a spacer device as opposed to nebulizers, since the latter should be avoided due to the increased potential for viral transmission [44].

3.1. Antiviral Therapy

At now, there is a lack of established antiviral therapies that have been demonstrated to be both effective and safe for the treatment of pediatric patients diagnosed with COVID-19. During the earliest stages of the pandemic, patients were prescribed oseltamivir, a neuraminidase inhibitor, based on their initial diagnosis. However, it was observed that oseltamivir was unsuccessful in treating these patients, mostly because coronaviruses do not manufacture neuraminidase. In a similar vein, the utilization of ribavirin, a nucleotide analog renowned for its ability to impede viral RNA polymerase, was originally employed in pediatric patients afflicted with COVID-19; nonetheless, its efficacy was not substantiated. Interferons were suggested for use. However, the efficacy of inhaled interferon-alpha treatment has yet to be shown [45]. The antiviral and immunomodulatory properties of hydroxychloroquine led to its exploration as a possible therapeutic drug for the treatment of SARS-CoV-2 infection. Nevertheless, the recommendation for its use has been rescinded because of insufficient empirical support and the potential for adverse effects, including retinal toxicity and QT-interval prolongation. Various broad-spectrum antivirals, such as lopinavir/ritonavir (LPV/r) and remdesivir (RDV), have undergone clinical trials for the treatment of COVID-19. The data currently accessible predominantly originate from clinical studies conducted with adult participants or from isolated situations involving juvenile patients. The combination of lopinavir, a protease inhibitor, and ritonavir, which inhibits the metabolism of lopinavir through CYP-3A, was administered [46]. Since May 2020, the Food and Drug Administration (FDA) has granted approval for the utilization of RDV in hospitalized individuals, including children and adults, who exhibit symptoms or have received confirmation of severe or critical cases of COVID-19 by laboratory testing. Subsequently, the permission was expanded to encompass pediatric patients who are hospitalized and exhibit moderate illness. However, recent clinical trials have demonstrated that remdesivir (RDV) does not have any substantial effects on the treatment of COVID-19. Hence, it is advisable to contemplate the utilization of RDV as a potential intervention for children exhibiting elevated levels of care complexity and concurrent medical conditions, such as BDP. This consideration may extend to the early stages of the disease. The suggested dosage for pediatric patients weighing less than 40 kg is 5 mg per kilogram of body weight administered intravenously on the initial day, followed by a daily intravenous dose of 2.5 mg per kilogram. In severe situations, the period of treatment may be prolonged for up to 10 days [47]. The suggestions provided are derived from adult physiologically based pharmacokinetic modeling and are consistent with the protocols employed in the Ebola studies, as well as those endorsed by a "compassionate use" initiative. While it is anticipated that these dosages will yield comparable drug exposure to what has been found in individuals without health conditions, there is a lack of published pharmacokinetic studies [45]. RDV is offered in two different formulations: an injectable solution and lyophilized powder. The lyophilized powder is generally favored for use in children since it has a reduced risk of renal impairment. The use of RDV is not recommended in individuals with renal insufficiency and an estimated glomerular filtration rate (eGFR) below 30 mL/min. However, no dosage modification is necessary for those with an eGFR over 30 mL/min. Additionally, RDV should be avoided in individuals with elevated levels of liver enzymes, specifically alanine transaminase (ALT) levels equal to or greater than five times the upper limit of normal. Prior to commencing medication, it is imperative to do renal and liver function tests, as well as carefully evaluate potential drug interactions with hydroxychloroquine, azithromycin, or antiepileptic medicines, since they may increase the risk of hepatocellular damage. It is advisable to conduct regular monitoring of liver function tests on a daily basis over the course of therapy [45].

Moreover, although the cardiovascular adverse effects of RDV have been documented in adults, a case involving a 13-year-old boy was described, whereby asymptomatic sinus bradycardia was seen. Nevertheless, there is a scarcity of evidence concerning the prevalence of arrhythmias in pediatric patients with COVID-19, and it is not possible to definitively establish a causal connection between remdesivir (RDV) and bradycardia. It is generally recommended to employ electrocardiographic monitoring for all pediatric patients hospitalized with COVID-19, particularly those on treatment with remdesivir (RDV). Finally, there have been documented instances of hypersensitive responses [48].

3.2. Immunomodulating Therapy

Severe COVID-19 in adults is characterized by the presence of immune-mediated lung damage and systemic hyperinflammation. In certain pediatric cases, it has been observed that SARS-CoV-2 can initiate an uncontrolled hyperinflammatory response, suggesting the potential for therapeutic intervention by immunomodulation. While there are currently several ongoing clinical trials investigating immunomodulatory therapy for adults with COVID-19, the enrollment of children in such trials is limited. As a result, it is difficult to offer precise recommendations in this regard. In the pediatric population, the utilization of immunomodulating therapy warrants careful consideration on a case-by-case basis, particularly in instances of severe pediatric acute respiratory distress syndrome (PARDS) or when there is a progressive decline in respiratory function or alterations in inflammatory markers such as IL-6, D-dimer, ferritin, and C-reactive protein [49].

Given the need of an early and strong immune response for efficient elimination of viruses, it is recommended that immunomodulating medicines be delivered no earlier than seven days following the manifestation of symptoms. This precaution is necessary as there is a risk of an excessive immunological response by the host during this period. Non-specific immunomodulators include corticosteroids and intravenous human immunoglobulin (IVIG). Systemic corticosteroids have demonstrated efficacy in several inflammatory disorders by suppressing the transcription of pro-inflammatory genes and inhibiting cytokine synthesis [50]. The study conducted by Liu et al. provided evidence that the use of low-dose corticosteroids (≤ 2 mg/kg/day) for a brief duration in adult patients with COVID-19 successfully suppressed the production of IL-6, leading to enhanced regulation of cytokine storm. The findings of a retrospective research conducted on Chinese patients diagnosed with acute respiratory distress syndrome (ARDS) indicated that the administration of methylprednisolone was correlated with a decrease in death rates [51]. Moreover, the multicenter Randomized Evaluation of COVID-19 Therapy (RECOVERY) experiment unveiled a decrease in 28-day mortality among adult individuals who necessitated respiratory assistance and were administered dexamethasone. Therefore, it is advisable to take into account the administration of corticosteroids in pediatric patients experiencing acute respiratory distress syndrome (ARDS) or deteriorating respiratory symptoms, especially after a minimum of seven days after the commencement of illness. This approach aims to mitigate the potential consequences of prolonged viral shedding and the development of secondary bacterial infections. In cases of severity, it is advised to administer intravenous methylprednisolone at a dose not surpassing 1-2 mg per kilogram per day, with a maximum daily dosage of 80 mg, for a duration of 3-5 days. Alternatively, a greater dose may be administered, consisting of a bolus of 30 mg per kilogram per day, in instances of severe conditions [52].

In an alternative approach, the administration of oral dexamethasone at a dosage of 0.2-0.4 mg per kilogram of body weight, with a maximum daily dose of 6 mg, for a duration of 10 days, might be taken into consideration. In contrast to corticosteroids, the use of intravenous immunoglobulin (IVIG) is not advised for the management of pulmonary illness in pediatric patients with COVID-19 since its effectiveness has not been shown. Nevertheless, in some clinical contexts, such as cases of severe thrombocytopenia linked to COVID-19, the use of intravenous immunoglobulin (IVIG) may be deemed appropriate [49]. The use of targeted immunomodulators that specifically address proinflammatory cytokines might be contemplated for pediatric patients with COVID-19 who are severely ill and exhibit heightened levels of IL-6, D-dimer, PCR, ferritin, and fibrinogen. The administration of these medications is recommended to occur at the appropriate timing, often towards the conclusion of the initial phase characterized by a substantial viral load of COVID-19. This is advised when the individual has been free from fever for a period exceeding 72 hours and/or at least seven days have passed from the beginning of symptoms, coinciding with the development of the cytokine storm. The utilization of Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has been suggested as a potential therapeutic intervention for individuals in critical condition due to its ability to counteract the deleterious effects of the COVID-19 "cytokine storm." This storm is characterized by an excessive release of cytokines, with IL-6 being a key player, and heightened levels of this particular cytokine have been identified as a prognostic indicator for an unfavorable result. The dosing regimen indicated for tocilizumab in pediatric patients is determined by their weight, with a dosage of 12 mg/kg administered intravenously for those weighing less than 30 kg, and a dosage of 8 mg/kg administered intravenously for those weighing more than 30 kg, with a maximum dose of 800 mg per administration. This dosing guideline is established based on the utilization of tocilizumab for the treatment of rheumatologic conditions. In situations where there is an absence of reaction, it may be deemed appropriate to provide a subsequent infusion after a period of 12 hours, and a third infusion after a span of 24 hours [49].

A further immunomodulatory agent, anakinra, a human IL-1 receptor antagonist, has demonstrated efficacy in reducing the requirement for invasive mechanical ventilation and mortality rate in several case studies involving adult patients. The utilization of these data, in conjunction with case studies involving pediatric patients, might potentially provide a rationale for employing it in children who exhibit severe pulmonary complications. Anakinra has the potential to be delivered by intravenous (off-label) or subcutaneous routes, with a recommended dose range of 8-10 mg/kg/day divided into 2-4 administrations (maximum of 100 mg each administration, up to 4 times per day) [54].

3.3. Passive Immunization: Convalescent Plasma Treatment

The use of hyperimmune SARS-CoV-2 convalescent plasma (CPT) has emerged as a viable therapeutic alternative in the absence of targeted antiviral interventions. The primary mode of action of CPT involves the neutralization of the virus. However, other mechanisms, such as the activation of antibody-dependent cellular cytotoxicity and the promotion of increased phagocytosis, have also been proposed. Nevertheless, recent randomized clinical trials done in adult populations have failed to demonstrate substantial enhancements in the clinical trajectory with the utilization of CPT. When considering children, the available data on the effectiveness of the intervention are restricted to case series that lack matched controls [55]. The results suggest that early administration of CPT may yield the greatest advantages, particularly prior to the development of endogenous antibodies or in individuals with weakened immune systems. Nevertheless, it is crucial to acknowledge that CPT also presents potential hazards, such as the possibility of allergic responses, transfusion-associated circulatory overload, infection, and antibody-dependent enhancement. A preliminary evaluation of CPT was conducted on a small sample of four pediatric patients diagnosed with acute respiratory distress syndrome (ARDS) at the Children's Hospital of Philadelphia. The findings indicated that CPT exhibited a satisfactory level of safety and showed promise in terms of its prospective effectiveness. At now, it is plausible to include CPT (with a dosage of 200-500 mL for children weighing above 40 kg and 10-15 mL/kg for children weighing less than 40 kg) as an intervention in a clinical study targeting severe instances of pediatric COVID-19. However, it is imperative to conduct worldwide clinical studies to determine the effectiveness of Cognitive Processing Therapy (CPT) in individuals of all age groups, including both adults and children [56].

3.4. Venous Thromboembolism Prophylaxis

Severe COVID-19 in adults is frequently correlated with an increased susceptibility to blood clot formation, which can be attributed to endothelial dysfunction generated by inflammation and a condition of hypercoagulability. A research study encompassing a cohort of 449 persons diagnosed with serious infections revealed a decreased death rate among individuals who had anticoagulant medication. As a result, guidelines for adult patients advocate the preventive administration of low molecular weight heparin (LMWH), especially in instances of acute respiratory distress syndrome (ARDS). It has been observed that pediatric patients infected with COVID-19 have a lower incidence of thrombotic problems in comparison to adult individuals. Research conducted in Italy examined a cohort of over 350 children COVID-19 patients who were hospitalized. The study found that just one instance of venous thromboembolism (VTE) was discovered in this group. In comparison, the estimated incidence of hospital acquired VTE in the general pediatric population is roughly 1 in 200 cases [57]. Moreover, a study conducted by Duarte-Salles et al. revealed a bleeding incidence ranging from 2% to 3% among pediatric patients hospitalized with COVID-19. Hence, in contradistinction to the recommendations for adults, it is not recommended to administer widespread anticoagulant prophylaxis to pediatric patients hospitalized with COVID-19. However, it is important to do a thorough assessment of the thrombotic and hemorrhagic risks for each individual kid. It is recommended that hospitalized children with COVID-19-related disorders, such as Multisystem Inflammatory Syndrome in Children (MIS-C), who possess additional risk factors for hospital-associated venous thromboembolism (VTE) (Table 3), should be given careful consideration for anticoagulant thromboprophylaxis [58]. In the case of pediatric patients who are clinically stable and do not have significant renal impairment, the recommended method involves the administration of low-dose subcutaneous LMWH twice daily. The objective is to get a post-dose anti-Xa activity level between 0.2 and less than 0.5 U/mL, within a 4-hour timeframe. It is recommended to administer continuous intravenous infusion of unfractionated heparin in situations involving children who are clinically unstable or have renal impairment. The objective is to achieve an anti-Xa activity level ranging from 0.1 to less than 0.35 U/mL [59].

3.5. Antibiotic Therapy

Langford et al. [60] discovered that three-quarters of COVID-19 patients take antibiotics, a percentage greater than the expected frequency of bacterial coinfection (8.6%). This has led to an increased risk of antimicrobial resistance owing to needless antibiotic treatment. Routine use of antibiotics and antifungal medications should be avoided and reserved for instances with proven or highly suspected co-infections or in individuals with underlying comorbidities such as bronchopulmonary dysplasia (BDP), cystic fibrosis (CF), immunodeficiency, or neuromuscular abnormalities. Some specialists propose considering azithromycin (15 mg/kg/day orally on the first day, followed by 7.5 mg/kg/day for 4 days) because to its in vitro anti-inflammatory and antiviral action against infections including Zika and Ebola. However, its usefulness and safety in severely sick children remain unclear, thus caution should be maintained, particularly in pediatric situations [43].

3.6. Supplemental Oxygen

Low-flow oxygen treatment is the initial choice for children with minor respiratory distress, normocapnia or hypocapnia, and peripheral oxygen saturation (SpO2) < 92%. Oxygen should be provided at the lowest flow rate necessary to achieve a goal SpO2 of 92–96%. Various delivery methods, such as nasal cannulas, face masks with or without reservoirs, or Venturi masks, can be utilized based on patient tolerance and the fraction of inspired oxygen (FiO2) required by each device [61]. In situations of mild-to-moderate hypoxemia and dyspnea resistant to low-flow oxygen, consider High Flow Nasal Cannula (HFNC) treatment, which combines improved alveolar gas exchange with reduced respiratory effort. A flow rate of 1.5–2 L/kg/min, as suggested in pediatric therapy, creates a positive end-expiratory pressure (PEEP) of roughly 4–6 cmH2O, reducing lung effort [62]. However, children on HFNC should be constantly observed, and if there is no improvement after 60 minutes, quick escalation to non-invasive respiratory support should be considered [61].

3.7. Respiratory Support

While SARS-CoV-2 infection in children can lead to serious respiratory difficulties, including pediatric acute respiratory distress syndrome (PARDS), respiratory failure is found in only a minority of infected children. In a meta-analysis with a sample size of 1,117 individuals who were below the age of 18, it was shown that 2.1% of the participants encountered significant respiratory complications. Furthermore, 1.2% of the individuals exhibited a serious development of the condition, necessitating the use of non-invasive ventilation in one instance and mechanical breathing in eight cases. In multicenter research conducted in Europe, a total of 582 children were examined. The study revealed that 13% of the infants required oxygen support, 5% got continuous positive airway pressure (CPAP), and 4% necessitated mechanical ventilation. Nevertheless, there is a scarcity of comprehensive data pertaining to the precise category, time, and characteristics of breathing assistance for pediatric patients with severe pulmonary complications due to COVID-19 [62].

Most data has been obtained from research conducted on adults, which may not be immediately applicable to the pediatric population. Children with SARS-CoV-2 pneumonia commonly exhibit type 1 or hypoxemic respiratory failure. This condition is characterized by intrapulmonary shunting, a decrease in ACE2 expression leading to an elevated release of pro-inflammatory cytokines and increased vascular permeability. Additionally, lung capillary endothelial injuries occur, resulting in the formation of intravascular microthrombi. As the illness advances, the basement membrane undergoes a process of fibrin deposition, accumulation of cellular debris, and activation of complement products, resulting in the impairment of lung diffusion capacity (DLCO). Therefore, it is crucial to conduct a precise evaluation of the extent of respiratory failure in conjunction with monitoring respiratory drive and effort to determine the necessary respiratory support for children affected by this condition [63].

3.8. Utilization of prone positioning

The utilization of prone posture has demonstrated advantages in enhancing oxygenation and maximizing positive end-expiratory pressure (PEEP) breathing among adult individuals afflicted with severe acute respiratory distress syndrome (ARDS). Prone posture in pediatric patients experiencing respiratory failure has been seen to result in enhanced alveolar recruitment homogeneity and increased positive end-expiratory pressure (PEEP). However, there is a scarcity of trials evaluating the efficacy of this approach in pediatric acute respiratory distress syndrome (ARDS), and the existing evidence does not consistently indicate long-lasting advantages. Furthermore, the utilization of extended prone posture, which is commonly employed in adults, might present difficulties when applied to awake and dyspneic juvenile patients. Hence, it is advisable to regard prone placement as a therapeutic alternative for intubated pediatric patients with acute respiratory failure [64].

3.9. Experimental Strategies

The elucidation of COVID-19 pathophysiology and the subsequent progress in the development of biological therapeutics have established a solid foundation for next investigations. The authorization by the Food and Drug Administration (FDA) in November 2020 pertained to the use of two monoclonal antibodies, namely casirivimab and imdevimab. These antibodies were specifically designed to target the protein S of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the objective of impeding its ability to penetrate host cells. The administration of these medications is presently limited to those who are 12 years of age or older, specifically targeting adults and adolescents who are at a heightened risk of experiencing serious illness. Nevertheless, there has been a change in emphasis towards the modulation of the cytokine storm rather than just the treatment of the original infection. The importance of IFN-γ signaling in the pathogenesis of COVID-19 has been shown [56]. Ongoing clinical trials with emapalumab, a monoclonal antibody targeting IFN-γ that has been licensed for use in pediatric and adult patients diagnosed with primary hemophagocytic lymphohistiocytosis, have the potential to information regarding its efficacy in treating severe pulmonary complications in children. Given the significance of complement activation in acute respiratory distress syndrome (ARDS), ongoing investigations are exploring the potential of complement inhibitors, such as the C5-specific antibody eculizumab, in clinical studies including adult patients with severe cases of COVID-19 [50]. Furthermore, some studies have suggested that the spike protein, in isolation from the coronavirus, may have the potential to harm endothelial cells and undermine the integrity of the blood-brain barrier. Nutraceuticals with antioxidant and antiviral characteristics, such as a liposomal combination of naturally occurring flavonoids luteolin and quercetin, exhibit promise in alleviating the adverse consequences associated with the spike protein. However, further case-control studies conducted in a pediatric environment are necessary to investigate the effectiveness of these interventions [65].

4. Preventive measures

The implementation of preventive strategies targeting pediatric populations is crucial in controlling the transmission of COVID-19 and safeguarding the well-being of children. The methods exhibit similarities to those used for adults; yet they necessitate more care and supervision owing to the unique requirements of youngsters. The following are many essential preventative actions for COVID-19 in pediatric populations [14]:

4.1. COVID-19 Vaccinations in Children

Approval for the administration of COVID-19 vaccinations to children and/or adolescents has been granted in at least one country. The vaccines that fall under this category include Comirnaty, developed by Pfizer, Spikevax, developed by Moderna, and CoronaVac, developed by Sinovac Biotech. The license for Comirnaty in Australia has recently been expanded to include individuals between the ages of 12 and 15 years. This decision was made based on the findings from an ongoing phase III trial that involved a total of 2,260 adolescents [67]. The study findings indicated that the vaccine had a 100% effectiveness in preventing symptomatic COVID-19, with a confidence interval of 95% (78.1–100), starting from 7 days following the administration of the second dose. It is worth noting that the levels of neutralizing antibodies in individuals aged 12-15 were higher than those observed in those aged 16-25. Frequently observed mild-to-moderate adverse reactions, both local and systemic in nature, including injection site discomfort (80%), weariness, headache (60%), and fever (20%). The efficacy and safety of Moderna's Spikevax in teenagers aged 12-17 years have been demonstrated by a study with a sample size of 3,700 individuals. It is expected that permission for the usage of this vaccine in the 12-17 age range will be granted in Australia. There are ongoing or proposed trials that involve the administration of vaccinations to children aged six months and older. Preliminary findings indicate encouraging safety and effectiveness outcomes for the inactivated SARS-CoV-2 vaccination, CoronaVac, among children as young as 3 years old [68].

The primary source of information about the safety of adolescents is typically obtained from clinical studies, however these trials may not have the statistical power to detect few negative outcomes. Both the Comirnaty and Spikevax vaccines are associated with a low incidence of myocarditis, with a rate of 2.7 cases per 100,000 persons. This adverse event appears to be more prevalent among teenagers and young adults in comparison to individuals aged 30 years and older. Notwithstanding this issue, vaccine-induced cardiac events, which predominantly impact young males following the administration of the second vaccination dosage, are of brief duration and transpire with a frequency that is 3.7 times lower compared to the occurrence of such events resulting from an acute SARS-CoV-2 infection. The clinical study involving children for AstraZeneca's COVID-19 vaccine was temporarily halted because of the identification of thrombosis with thrombocytopenia syndrome, an infrequent however severe adverse occurrence that has a higher incidence among younger adults (3.4 cases per 100,000 persons under the age of 50) [69].

The incidence of severe disease resulting from acute COVID-19 is infrequent in children who are in good health. Consequently, the potential advantages of immunization for individual children may be somewhat diminished when compared to other age cohorts. Preliminary simulations indicate that the incorporation of 12–15-year-olds into wider vaccination distribution initiatives is unlikely to have a substantial impact on the general health outcomes of SARS-CoV-2 throughout the community. Moreover, it is important to acknowledge the existence of wider ethical implications in this context. The World Health Organization (WHO) has specifically called upon wealthier nations to carefully explore the option of allocating vaccination doses originally meant for children to the COVAX initiative. By doing so, these doses may be effectively given to adults residing in low and middle-income countries [14]. In conjunction with the proliferation of vaccination initiatives targeting adolescents and children, there exists a pressing necessity to enhance immunization rates among people employed in childcare, school, and hospital environments. The implementation of this kind of indirect protection will effectively serve to secure children, mitigate the occurrence of transmission events, and guarantee the ongoing provision of critical services for children [14].

4.2. The Importance of Hand Hygiene

It is important to instruct youngsters on the need of consistently practicing hand hygiene by frequently washing their hands with soap and water for a minimum duration of 20 seconds. When soap and water are not accessible, it is recommended to utilize hand sanitizer with at least 60% alcohol content [70].

4.3. The Practice of Wearing Masks

It is important to ensure that the mask is well fitted and provides a comfortable experience for the youngster. Assistance may be necessary for younger children in the process of donning and doffing masks.

4.4. Implementation of Physical Distancing Measures

Encourage the practice of physical separation wherever possible, especially in scenarios where children may encounter adults who are not part of their immediate home. It is advisable to refrain from participating in large gatherings. Large meetings or events should be limited or avoided, since they may possibly increase the chance of transmission.

4.6. Monitoring of Symptoms

It is imperative for parents and caregivers to maintain a state of constant vigilance in the surveillance of children for symptoms associated with COVID-19, namely fever, cough, and dyspnea. If any symptoms are observed, it is important to promptly seek counsel from a healthcare professional.

4.7. Effective Respiratory Hygiene Practices

It is important to instruct youngsters on the proper technique of utilizing a tissue or their elbow to shield their mouth and nose during episodes of coughing or sneezing. Furthermore, it is crucial to promote the appropriate disposal of utilized tissues and underscore the importance of frequent hand hygiene.

4.8. Sanitization and Sterilization

It is advisable to consistently engage in the practice of cleaning and disinfecting surfaces and items that are regularly handled, especially in locations where youngsters spend a considerable duration of time.

4.9. Ventilation to enhance interior ventilation

It is recommended to open windows and doors in order to facilitate the flow of fresh air within enclosed areas.

4.10. Education

It is important to provide children with age-appropriate education on the significance of these preventative measures, assuring their comprehension of the underlying rationale for these activities.

4.11. The Concept of Quarantine and Isolation

It is crucial for youngsters to understand the importance of quarantine, which is implemented for those who have been exposed to COVID-19, and isolation, which is enforced for individuals who have tested positive for the virus. It is imperative for parents and caregivers to comply with the prevailing local health rules pertaining to the recommended length of isolation and quarantine.

4.12. Minimize Proximity to Individuals at Elevated Risk

It is advisable to promote the practice of reducing close physical interactions among children with persons who are at a heightened risk of experiencing severe sickness in the event of contracting COVID-19, such as elderly family members or individuals with pre-existing health disorders.

4.13. Promote Mental Health Support

The ongoing global epidemic has the potential to induce stress among youngsters. In order to enhance individuals' mental and physical well-being, it is important to offer emotional support, uphold regular routines, and promote engagement in physical exercise and healthy dietary habits [71].

5. Prognosis and outcomes

5.1. Morbidity

A considerable number of pediatric patients have their COVID-19 infection resolved without any complications. There have been recorded cases of neonates born to COVID-19 pregnant mothers demonstrating small increases in poor outcomes, such as respiratory difficulties. The National Institutes of Health (NIH) is now doing research to assess the prevalence and therapeutic possibilities for children with SARS-CoV-2 infection. While the long-term implications of this illness in adults have been detailed, there is a dearth of precise evidence regarding its prevalence and treatment in young populations. This continuing project tries to address the knowledge gap [72]. The disease known as "Long COVID," which is defined by the presence of symptoms lasting more than three months, mostly affects those aged 12 and up. This medical ailment, which is marked by a variety of symptoms such as exhaustion, shortness of breath, cognitive impairment, and depressed symptoms, affects the patient's ability to resume normal activities, resulting in significant long-term morbidity. The available data is highly heterogeneous, resulting in a wide range of prevalence estimates (from 0% to 27%) for children with COVID-19. A recent thorough study found that the persistence of symptoms associated with 'long COVID' in children is uncommon and frequently does not last more than 8 weeks beyond the first diagnosis. The formulation of a specific definition for 'long COVID' in children, as well as the discovery of objective means of surveillance, are critical objectives in this area. Furthermore, further research is needed to evaluate linked risk factors, prevalence, and natural history [73]. The MIS-C results show good short- to medium-term outcomes, with a low incidence of coronary artery aneurysms and an even lower death rate." The 6-month follow-up examination of D

5.2. Mortality

The mortality rate associated with COVID-19 in the pediatric population is extremely low, with estimates ranging from 0.005% to 0.01%. Although children with obesity or pre-existing disorders have a much higher risk of death than those who do not have co-morbidities, the incremental increase in absolute risk is negligible. The available information on COVID-19 outcomes in neonates is presently being compiled. The fatality rates for all causes vary from 1.7% to 2.0%, although it is crucial to take caution when interpreting these data because most fatalities were judged to be unrelated to COVID-19 [76]. Mortality rates vary significantly among countries, which can be ascribed to a variety of factors such as starvation, restricted access to healthcare, delayed diagnosis, and underreporting of people with minor symptoms. These determinants have an important role in influencing the outcome of COVID-19 infection in low-income countries [77].

6. Conclusions

The impact of COVID-19 on children has been significant, with a wide range of symptoms observed, varying from moderate upper respiratory tract infection to severe cases including acute respiratory failure and Multisystem Inflammatory Syndrome in Children (MIS-C). The primary approach to managing acute infection continues to be supportive care, complemented with antiviral and immunomodulatory medication in instances of severe illness, which are rather uncommon. The field of vaccine development is seeing tremendous advancements, with several vaccine candidates currently undergoing evaluation for their efficacy and safety in juvenile populations.

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