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Abstract

The coronavirus disease 2019 (COVID-19) outbreak has evolved with different waves corresponding to subsequent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations. While the most severe cases have been observed in the elderly and in individuals with underlying comorbidities, severe pediatric and young adult cases have been observed, as well as post-infectious inflammatory syndromes and persistent symptoms leading to long-COVID. This manuscript describes the experience of a pediatric respiratory unit during the first year of the pandemic and reviews the corresponding literature with a special emphasis on children and young people with underlying conditions, such as immunosuppression, sickle cell disease, and cystic fibrosis.

1/ Introduction

Since its inception in December 2019, the coronavirus disease 2019 (COVID-19) outbreak has evolved with different waves, corresponding to subsequent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations. As of August 25, 2022, at least 600 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and 6.4 million individuals have died of this disease worldwide (1). The most severe cases have been observed in the elderly and in

individuals with underlying comorbidities, such as obesity, diabetes, hypertension, and immunosuppression. Initially thought of as being involved in the carriage and dissemination of the virus, it was quickly established during the first wave that young children were neither very contagious nor symptomatic with respect to COVID-19 (2). However, severe pediatric cases and post-infectious inflammatory syndromes have been reported worldwide (3). This manuscript describes the experience of a pediatric respiratory unit during the first year of the pandemic and reviews the corresponding literature with a special emphasis on children and young people with underlying conditions, such as immunosuppression, sickle cell disease, and cystic fibrosis.

2/ Pediatric epidemiology of SARS-CoV-2

At the beginning of the pandemic, Wu et al. described the first 72,314 cases of COVID-19 in China (4). Children and adolescents accounted for only 2% of these cases, and no deaths were reported among children under nine years of age. Since then, data from different countries have confirmed a lower initial incidence of infection in children (2–5%) and its reduced severity in children, although severe cases and deaths have been reported in all countries, including 28 deaths in France between 2020 and 2021 (1).

In late 2021–early 2022, a resurgence of cases in young adults and children was observed with the delta and omicron variants in France (5-7). This has caused the recrudescence of severe COVID-19 forms and hospitalizations in children, particularly in the age group of 0–9 years because of the limited vaccination coverage in this population (7-10).

3/ Clinical symptoms of COVID-19 and risk factors for severity in children

The first pediatric COVID-19 cases were described by authors from Shanghai,

China (11). They reported 2,135 children infected with SARS-CoV-2, with 56% boys and a median age of 7 years. The symptoms were mostly mild (51% of the cases) or moderate (38% with pneumonia and wheezing), and severe in only 6% of the cases with hypoxia and/or respiratory failure. Subsequently, it has been established that during the first wave, the infection is usually mild in children, with non-specific clinical signs, such as cough, fever, rhinitis, headache, and digestive signs (vomiting and diarrhea) (12-16). Very few studies have been conducted on paucisymptomatic ambulatory patients. Nevertheless, a French study in March 2021 (before vaccination of adolescents) showed that in 2,079 children presenting signs compatible with COVID-19, the PCR positivity rates for SARS-CoV-2 reached 7.3%, with rates increasing with age (17). In this study, apart from a loss of taste, no symptoms were predictive of COVID-19 compared with other viral infections. After the first wave, a systematic review of COVID-19 in pediatric patients evaluated 7,780 pediatric cases described in 131 studies from 26 countries from December 2019 to May 2020 (13). They concluded that children diagnosed with COVID-19 had an overall excellent prognosis, with only 3.3% of children requiring intensive care unit (ICU) care and seven deaths. More than 35% had underlying medical conditions, with immunosuppression being the most common (30.5%), followed by respiratory (21%) and cardiovascular (13.7%) disorders.

In hospitalized children, poorly tolerated fever and fatigue are common (8, 12). At hospital admission, respiratory symptoms are present in approximately 50% of cases, with more than half being associated with respiratory distress (8). Notably, the severity seems to be greater in infants under one year of age and adolescents (3). During the first wave, a retrospective cohort study was conducted in Colorado, USA, in 454 children with confirmed SARS-CoV-2 infection, with the aim of evaluating the risk factors for

severe COVID-19 (18). They showed that extremes of age (e.g. 0–3 months or >20 years), preterm birth history, comorbidities (immunosuppression, gastrointestinal condition, diabetes, and asthma), and an elevated CRP were predictors of severe disease in children. At the beginning of the pandemic, we described hemodynamic disorders and transient neurological manifestations in young infants (19). A systematic review of COVID-19 in 63 infants under three months of age reported moderate severity and non-specific clinical signs; however, one fifth of children required ICU care (20). Among hospitalized adolescents, children with underlying conditions, such as asthma, obesity, or sickle cell disease are overrepresented (3, 12, 21-24). Rare cases of pulmonary embolism associated with COVID-19 have also been reported in pediatric patients (25, 26).

In children, a specific hyperinflammatory syndrome with multiorgan involvement associated with COVID-19 has been described and named as multisystemic inflammatory syndrome in children (C-MIS) or pediatric multisystemic inflammatory syndrome (PIMS) (27-29). PIMS occurs 2–8 weeks after a SARS-CoV-2 infection that may have been asymptomatic. It shares several similarities with Kawasaki syndrome, which has also been described as possibly secondary to viral infection. PIMS is rare, but potentially serious. At the end of August 2022, 1,070 cases of PIMS related to COVID-19 were reported to the French health authorities (61% boys, median age: 8 years with 32% of cases in children under 5 years of age and 72% under 11 years of age) (30). The main clinical symptoms of PIMS are persistent fever, systemic inflammation, gastrointestinal manifestations (abdominal pain, vomiting, and diarrhea), mucocutaneous abnormalities (skin rashes and conjunctivitis), headache, and cardiac dysfunction (27-29, 31). A large American study of 1080 children hospitalized for PIMS

with a median age of 8 years reported 60% hospitalizations in the ICU for heart failure, coronary dysfunction, hemodynamic shock, or myocarditis; and 18 (2%) deaths (27). In France, among the 1070 cases of PIMS, 725 (68%) patients were hospitalized in the ICU and one 9-year-old child died (30).

Another long-term consequence of SARS-CoV-2 infection in adults and children is long-COVID (32, 33). The definition proposed by the WHO for this condition is that it generally occurs three months after the onset of SARS-CoV-2 infection, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis (34). A systematic review, which evaluated 80,071 children and adolescents from 21 studies, reported a long-COVID prevalence of 25.24% (33). The most prevalent clinical manifestations were mood symptoms (16.5%), fatigue (9.7%), and sleep disorders (8.4%). Moreover, this review showed that children with a history of SARS-CoV-2 infection had a higher risk of persistent dyspnea, anosmia/ageusia, and fever. A large prospective pediatric cohort of children admitted to hospital with confirmed COVID-19 also showed that a quarter of children had persistent symptoms (>5 months) at the time of follow-up with fatigue, sleep disturbance and sensory problems being the most common (35). In this study, almost one in 10 children reported multisystem impacts with at least two categories of persistent symptoms. Children in mid-childhood and adolescents (aged 6–18 years) as well as those with history of allergic diseases (defined here as asthma, allergic rhinitis, eczema or food allergy) were at higher risk of persistent symptoms. Although long-COVID represents a significant public health concern that may increase in the future, there are still no guidelines for its diagnosis and management in children (32, 33).

4/ Focus on atypical respiratory manifestations of COVID-19 in children and young

people observed in a French expert center during the first year of the pandemic

Approximately 50% of children hospitalized with COVID-19 have respiratory involvement, more than half of which is associated with respiratory distress (8, 12). An international study conducted between February and October 2020 in 671 children hospitalized with confirmed and symptomatic COVID-19 reported a 13.3% incidence of viral pneumonitis (9). Similar to adults, some underlying conditions have been shown to be associated with a higher risk of developing severe respiratory diseases, particularly chronic respiratory diseases (asthma, cystic fibrosis (CF), and bronchopulmonary dysplasia), immunosuppression, cancer, sickle cell disease, and neurological disorders (3, 12, 13, 21, 22, 26, 36-39). Below, we describe some of these particular cases, with a focus on patients hospitalized in our pediatric pulmonology unit during the first year of the pandemic. The description of the cases hospitalized in our unit has been approved by the local ethics committee of our institution, which waived the need for patients' consent (PED_COVID N°20200717191204).

Immunocompromised children

As of yet, there are limited published data describing the outcomes of immunocompromised children infected with SARS-CoV-2 (40-43). In adults, the risk of the worst COVID-19 evolution has frequently led to the postponement of anti-cancer therapies (43, 44). However, in childhood, most cancers require intensive treatment, which, if postponed, may be life-threatening. We observed an atypical respiratory course of severe SARS-CoV-2 infection in a 16-year-old adolescent, who was immunocompromised when infected with SARS-CoV-2 (45). This teenager was diagnosed with bone Ewing sarcoma, which was initially treated with chemotherapy and surgical resection. Given the partial response to this treatment, high-dose chemotherapy

followed by autologous hematopoietic stem cell transplantation (HSCT) was considered. HSCT was delayed by two weeks because of SARS-CoV-2 infection (isolated dysgeusia initially). Nevertheless, the patient developed an acute respiratory distress syndrome (ARDS) after the HSCT, which required ICU care with 15 days of invasive ventilation, systemic corticosteroids, convalescent plasma, and tocilizumab. Thoracic computed tomography (CT) revealed alveolar condensations in the lower lobes with diffuse confluent ground-glass opacities. At ICU discharge, the patient remained dyspneic and hypoxic. The CT scan revealed a worsening condition with lesions suggestive of post-COVID-19 organized pneumonia (**Figure 1A**). The treatment consisted of high doses of corticosteroids for two months and respiratory rehabilitation with favorable outcomes.

Children with sickle cell disease

Several studies have reported that sickle cell disease is a risk factor for severe COVID-19, particularly in children (46, 47). At the beginning of the pandemic, we described the favorable outcome of a 16-year-old girl with sickle cell disease who developed acute chest syndrome (ACS) with pulmonary embolism secondary to SARS-CoV-2 infection (26). This adolescent had a severe form of sickle cell disease with a history of repeated vaso-occlusive crises and bilateral ischemic retinopathy, with no history of ACS. Seven days after the onset of SARS-CoV-2 infection, which initially manifested as an isolated fever, she developed ACS with acute chest pain and ARDS. CT pulmonary angiography confirmed ACS and showed bilateral pulmonary embolism (**Figure 1 B1&B2**). She was admitted to the ICU and required four days of noninvasive ventilation, six weeks of anticoagulation, and one pulse of intravenous tocilizumab. The patient subsequently returned to her pre-COVID clinical status.

Young people with cystic fibrosis (pwCF)

Since the first wave of COVID-19 in France in March 2020, all 47 CF centers (which follow approximately 7,500 pwCF (48)) have been collaborating to conduct a prospective observational study to describe the clinical manifestations of SARS-CoV-2 infection in French pwCF. During the first wave (March to June 2020), 31 French pwCFs were reported to be infected with SARS-CoV-2, 12 of whom were post-lung transplantation (49). The majority of patients had CF-related diabetes (61%) and moderate respiratory disease in the year prior to infection (65% had a pre-infection FEV1 >70%). More recently, this study was updated with a description of 223 French pwCFs diagnosed with COVID-19 during the first year of the pandemic (50). It showed a higher risk of infection in adults and post-transplant individuals. Using objective clinical markers (e.g., respiratory failure and/or death), this study highlighted that the risk factors for severity included low lung function and diabetes in non-transplanted individuals and post-transplant status. An international registry was also set up at the beginning of the pandemic, which described 181 pwCFs (32 post-transplant) with COVID-19 during the first wave (51). The impact of SARS-CoV-2 infection appeared to be similar in pwCF and the general population, with 11 patients admitted to the ICU (7 post-transplant) and seven deaths (3 post-transplant).

This international consortium also detailed more precisely the 105 pediatric international COVID-19 cases: 54% were males, with a median age of 10 years, and a median FEV_1 of 94% (52). Only 24 children were hospitalized, six children required additional oxygen therapy, and two children required noninvasive ventilation. The hospitalized children had significantly worse lung function before infection. One child died six weeks after testing positive for SARS-CoV-2 because of respiratory worsening that was not attributed to COVID-19. We observed similar features in the pediatric CF

center host of our pediatric pulmonology unit. Most children with CF who were diagnosed as infected by SARS-CoV-2 during the first COVID wave remained asymptomatic; the diagnosis was confirmed by a systematic assessment of SARS-CoV-2 serology or by SARS-CoV-2 RT-PCR performed in case of contact (10).

It is still difficult to estimate the true susceptibility of pwCF to SARS-CoV-2 infection. Indeed, they are used in barrier gestures, such as wearing masks, frequent hand washing, and social distancing, in order to limit exposure and avoid infection. Epidemiological studies performed during the first wave of the pandemic have shown that the incidence remained low, with a short-term evolution that appeared relatively favorable in non-transplanted pwCF, but more severe in post-transplant patients.

5/ Radiological signs of COVID-19 in children

When a child is hospitalized for respiratory distress associated with COVID-19, chest radiography should be performed. If the chest radiograph is observed to be abnormal with the presence of serious respiratory clinical signs and/or underlining conditions known to lead to severe COVID-19 (sickle cell disease, obesity, etc.), CT pulmonary angiography should be performed to identify COVID-19 complications, such as ARDS and pulmonary embolism. A meta-analysis of the CT scans of 1747 children with COVID-19 found 63.2% of abnormalities on chest CT, including 39.5% of ground-glass opacities and 65.1% of bilateral lung lesions, but also rare abnormalities, such as pulmonary nodules (25.7%), patchy shadows (36.8%), halo signs (24.8%), consolidation (24.1%), air bronchogram signs (11.2%), cord-like shadows (9.7%), crazy-paving pattern (6.1%), and pleural effusion (9.1%) (53). Compared to adults, ground-glass opacities are less frequently reported, as is the bilaterality of lesions (54). It is also important to note that pulmonary embolism must be considered in adolescents,

especially in cases of thromboembolic risk factors or suggestive biological markers (25). In PIMS, respiratory involvement is relatively rare or mild (mainly bronchial thickening), whereas extra-respiratory radiological involvement is more common with cardiomegaly, mesenteric inflammation, hepatosplenomegaly, periportal edema, ascites, or thickening of the digestive walls (31, 55).

6/ Management of COVID-19 in children

The management of SARS-CoV-2 infections in children is mostly based on adult recommendations and has evolved through various waves of the pandemic. Recent recommendations have been developed by the National Institutes of Health (56). Most children require only symptomatic treatment, particularly fever control with acetaminophen. In cases of severe respiratory diseases, treatment with dexamethasone is discussed in a manner similar to that in adults. Therefore, systematic antibiotic therapy was not recommended. Other therapies, such as paxlovid, remdesivir, tocilizumab, convalescent plasma, and monoclonal antibodies, have been shown to be effective (56).

Prophylactic management is based on barrier gestures and the SARS-CoV-2 vaccine. Indeed, vaccination is recommended in children older than five years, for whom the BNT162b2 COVID-19 vaccine has been deemed safe, immunogenic, and effective (57). However, the vaccination rates in children remain limited in most countries, making it difficult to evaluate their effectiveness on a large scale (58).

7/ Conclusion

The knowledge of COVID-19 in children is evolving through consecutive waves of different SARS-CoV-2 variants. These variants have caused variable pathogenicity and transmissibility, with an increase in incidence in children in the coming months. Vaccination of children older than five years for whom the BNT162b2 COVID-19

vaccine has been shown to be safe and effective is also likely to modify the epidemiology and the immediate and post-infectious manifestations of COVID-19 in children.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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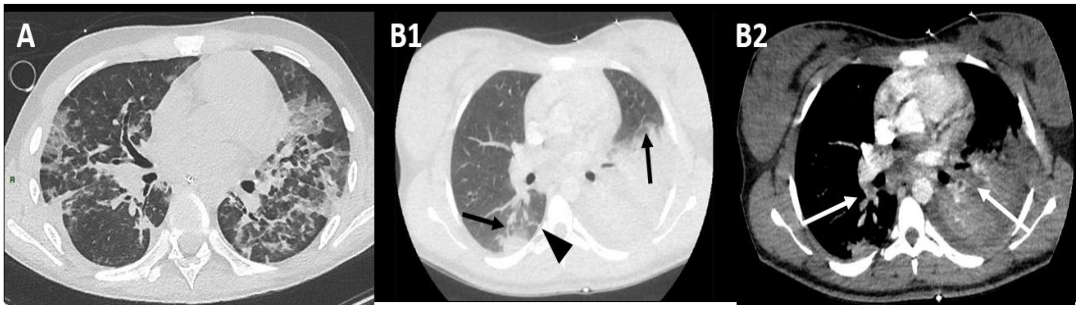

Figure 1.

A) **Post-COVID organizing pneumonia in an immunocompromised adolescent.** The lung computed tomography scan performed three weeks after the acute respiratory distress syndrome onset shows lesions of post-COVID organizing pneumonia with crazy-paving band-shaped condensations and peribroncho-vascular and scissural distortion.

B) **Post-COVID acute chest syndrome and pulmonary embolism in a child with sickle cell disease: 1)** The lung computed tomography scan performed at COVID-19 onset shows acute chest syndrome secondary to COVID-19 with

round subpleural consolidation with a ‘halo sign’ of ground-glass opacities (black arrows) and interlobular septal thickening (black arrowhead) on the right side, and lobar consolidation (lingula and lower lobe) with adjacent ground-glass opacities on the left side. **2)** The mediastinal window shows bilateral pulmonary embolism (white arrows) and left pleural effusion (white arrowhead).