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Review Article

COVID-19 in Children and Adolescents: Characteristics and Specificities in Immunocompetent and Oncohematological Patients

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Abstract. SARS-CoV-2 pandemic affected fewer children and adolescents with lower morbidity and mortality rates than those reported for adults. This review focused on the clinical course, risk factors for severe COVID 19, mortality, treatment options, and prevention measures in the pediatric and adolescent setting with special attention to pediatric oncohematological patients. SARS-CoV-2 infection was often asymptomatic in these subgroups of patients, but 47 to 68% of them required hospitalization, and 9-10% of those hospitalized needed intensive care with a COVID 19 attributable mortality of about 4%. The multisystem inflammatory syndrome associated with COVID 19 was less frequent than that reported in the non-oncohematological pediatric population. Noteworthy, the course of COVID 19 was more severe in low-middle income countries. The key measures to prevent SARS-CoV-2 infection are reducing patient exposure to the SARS-CoV-2 and vaccination, now available for parents and caregivers and patients and siblings above 12 years of age. The treatment of COVID 19 in pediatric patients is mainly based on supportive care with dexamethasone and heparin prophylaxis for severely ill patients. Other measures, such as convalescent plasma, remdesivir, and monoclonal antibodies, have been used in limited cases or within experimental protocols. Further studies are needed regarding the risks factors and outcomes of SARS-CoV-2 infection in pediatric immunocompromised patients.

Keywords: COVID 19; SARS-CoV-2 infection; Coronavirus; Pediatric; Pediatric malignancy.

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Introduction. Coronaviruses (CoVs) are a family of enveloped positive-sense single-stranded RNA viruses, which can infect humans, other mammals, or avian species.[1] Severe acute respiratory syndrome coronavirus (SARS- CoV) and the Middle East respiratory syndrome coronavirus (MERS- CoV) have been described in the human species respectively in 2002 and 2012, causing a respiratory illness with high mortality rates.[2] At the end of 2019, a novel highly infective and pathogenic Coronavirus designated as severe acute respiratory coronavirus 2 (SARS-CoV-2) was reported in the city of Wuhan, China, causing an outbreak of unusual viral pneumonia and rapidly spreading around the world.[3]

This new coronavirus targets both upper and lower respiratory tract tissues, and an efficient human-to-human transmission even before the onset of symptoms has been observed.[4] It is mainly transmitted by droplets and aerosol from symptomless and symptomatic infected subjects, with a median incubation period of 5.7 days (range 2-14).[5]

Covid-19 in Adults and Adults with Cancer. The spectrum of infection severity in symptomatic patients ranges from mild disease (81%), severe disease (14%), critical disease (5%), to death (2.3%).[6] On September 28, 2021, more than 200 million cases have been reported worldwide, with more than 4 million 300 thousand deaths,[7] but the numbers are increasing day by day. Since the pandemic onset, age was documented as the major risk factor for mortality.[8] In a recent systematic review and meta-analysis,[9] age was confirmed as the most important risk factor for both severe clinical course (Odds Ratio> 75 years of 1.93 (1.32-2.52)) and mortality (Odds Ratio> 75 years 5.82 (1.86-9.79)). Other risk factors were obesity and the presence of comorbidities, in particular cardiovascular diseases, chronic pulmonary and chronic kidney diseases. In the same study, adult patients with active cancer showed an increased risk, with Odds ratios for the severe course and mortality 1.48 (1.26-1.69) and 2.15 (2.15-2.16), respectively.

Other reports in the literature confirm increased risk of severe COVID-19 course in adult cancer patients: a 3.61-fold higher risk of severe COVID-19 was reported in cancer patients compared to patients without cancer;[10] and among cancer patients, a 2.45-fold increased risk of death was reported in COVID-19 adult patients compared to non-infected adults.[11] In addition, 2-fold higher mortality due to COVID-19 has been reported for patients with hematological malignancies compared to the non-cancer population.[12,13] Moreover, the highest frequency of severe COVID-19 events has been reported in patients with hematologic cancer, lung cancer, or metastatic cancer (stage IV).[6]

Table 1 shows the most important risk factors for a severe course and mortality of SARS-CoV-2 infection.

Late sequelae related to COVID-19 infection, better known as post-acute COVID-19 syndrome, are commonly reported in adults. The post-acute COVID-19, defined as the persistence of symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms, is characterized by pulmonary (dyspnea, decreased exercise capacity and hypoxia, reduced diffusion capacity, restrictive pulmonary physiology, and ground-glass opacities and fibrotic changes on imaging), cardiovascular (palpitations, chest pain, myocardial fibrosis or scarring, arrhythmias, tachycardia), hematological (thromboembolism), renal (reduced eGFR), endocrine (new or worsening control of existing diabetes mellitus, subacute thyroiditis and bone demineralization) and neuropsychiatric (fatigue, myalgia, cephalea, dysautonomia, and cognitive impairment, anxiety, depression, sleep disturbances) involvement.[14]

In the largest series[15,16] at least one of these symptoms was reported in 30-87% of patients.

The most frequently reported symptoms were: fatigue (35-64%), dyspnoea (11-44%), sleep disturbances (24-26%), anxiety / depression (20-25%) and chest pain (5-21%).

Table 1. Main Risk factors for severe clinical course and mortality in adults and children/adolescents.

Adults[9]	Children and Adolescents[37,38]
Age > 75 y	Obesity
Obesity	Chronic Lung Disease
Male sex	Neurologic Disorders
Cardiovascular disease	Immunosuppression
Chronic arterial disease	Chronic Metabolic Disease
Hearth Failure	Blood Disorders
Chronic Lung Disease	Cardiovascular Disease
Active Cancer	Chromosomal abnormality
Immunosuppression	Chronic Kidney Disease
Chronic Kidney Disease	Malignancy

SARS-CoV-2 Infection and Covid-19 in Children and Adolescents. Due to their developing immune system, children, compared to adults, are more susceptible to infectious diseases. However, the susceptibility to SARS-CoV-2 infection in children seems to be lower, with a low incidence of severe COVID-19[17] and only rare fatality cases, estimated between 2 and 5 cases per million for subjects below 18 years of age.[18]

About 80-90% of infected children and adolescents (80%)[19,20] present with symptoms, usually mild or moderate. Since the first months after the start of the pandemic, children presented clinically milder cases and a better prognosis than adults.[18] This resulted in a lower hospitalization rate,[19] ranging from 2.5 to 4.1%. Among hospitalized patients, 15% were admitted to the ICU.[21]

COVID-19 symptoms in children are similar to those in adults. The most frequent are fever (46%), cough (37%), headache (15%), diarrhea (14%), sore throat (13%), nausea/vomiting (10%), myalgia (10%), abdominal pain (7%), rhinorrhea (7%) and shortness of breath (7%).[22,23]

Several organ-specific involvements have been reported: heart failure, myocarditis, pericarditis, arrhythmias, pulmonary embolism in the cardiovascular system;[24–26] encephalopathy, stroke, Guillain-Barrè syndrome, cerebral edema, status epilepticus, transient ischemic attack in the nervous system;[27,28] urticarial, maculopapular, vesicular skin rash, livedo reticularis, chilblain-like lesions as skin manifestations.[29] The most fearful complication of COVID-19 infection in pediatric age is the multisystem inflammatory syndrome in children (MIS-C), described as early as April 2020. MIS-C is characterized by fever, multisystem organ involvement, laboratory evidence of inflammation, and severe course (**Table 2**). Other features may include acute myocardial dysfunction, respiratory failure, Kawasaki-like disease, and toxic shock syndrome.[30,31]

MIS-C appears to be relatively rare, occurring in <1%

Table 2. WHO Multisystem inflammatory syndrome in children and adolescent definition.

Children and adolescents 0–19 years of age with fever > 3 days
AND two of the following: - Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet). Hypotension or shock. - Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP). - Evidence of coagulopathy (by PT, PTT, elevated d-Dimers). - Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).
AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.
AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

of confirmed COVID-19 cases in children, corresponding to about 5-7 cases per million people per month.[32,33] Among the hospitalized patients, the MIS-C rate varies between 10 to 25%.[34] Currently, no long-term follow-up studies that define with certainty the prognosis of patients with MIS-C are reported. In a systematic review including 16 studies and a total of 655 MIS-C patients, 10% of patients (68) required critical care, and the mortality rate was 1.7% (11 deaths).[35]

Treatment of MIS-C is mainly based on organ support, immunoglobulins, and steroids.[36–38]

Regarding COVID-19 sequelae, these appear to be much less frequent than in adults: in a cohort of 25 children, Denina et al.[39] no COVID-19-related sequelae up to 4 months after the infection were reported.

In a larger collection of cases,[40] out of 151 children with COVID-19, whom 36% with asymptomatic course and 64% with mild, moderate, or severe disease, 12 patients (8%) had post-acute COVID-19 symptoms. The most frequent documented symptoms were mild post-viral cough (6 patients), fatigue (3 patients), or both post-viral cough and fatigue (1 patient). Resolution of symptoms was seen in all cases in up to 8 weeks.

Risk Factors for Severe Disease and Mortality. Most pediatric patients affected by COVID-19 have a symptomless or paucisymptomatic course that allows home management. In a review including more than 7400 COVID-19 positive children, only 2% of cases presented severe symptoms with dyspnea and hypoxemia, and critical conditions in 0.7%. The reported fatality rate was 0.08% (6 patients).[24] Similarly low (0.28%) is the mortality rate reported by Wang et al. [41] in a meta-analysis that collects data from more than 11,000 COVID-19 positive children. However, some pediatric patients may require hospitalization, particularly those with one or more comorbidities. Kim et al.[42] reported the different clinical characteristics on a total of 576 hospitalized patients, with a median age of 8 years and equal male/female distribution: 222 patients (38.5%) had one or more comorbidities, such as obesity (38%), chronic lung disease (18%), prematurity defined as gestational age <37 weeks (15.4%), neurologic disorder (14%), immunocompromised condition (5.4%). In a similar European study,[43] out of 582 patients with a median age of 5 years, 25% of hospitalized patients had one or more comorbidities. The latter group of patients had a 3.7 greater relative risk of admission to ICU. About one-third of hospitalized patients required intensive care and about 5% mechanical ventilation.[42,44]

Regarding mortality, children and young people have a lower risk than adults.[45] However, several authors reported case series of deceased pediatric patients. McCormick et al.[46] reported 112 deaths, with a median age of 17 years (range 0-21 years): 63% were male, and 86% of patients presented with at least one of the following conditions: obesity (42%), asthma (29%), and developmental disorders (22%). Similarly, Bixler et al.[47] reported 121 deaths in patients under 21 years old: only 30 (25%) were patients otherwise healthy, whereas 91 (75%) patients had at least one comorbidity, and 54 (45%) had two or more comorbidities: asthma (28%), obesity (27%), neurologic and developmental conditions (22%), cardiovascular diseases (18%), cancer or immune system disorder (14%) and diabetes mellitus (9.1%). In a systematic review that analyzed 9335 children with COVID-19, 27% of patients had underlying comorbidity, and among them, the most frequent was immunosuppression.[48] Conversely, other authors reported a similarly favorable course, compared to healthy children, in patients undergoing immunosuppressive treatment for inflammatory bowel diseases, rheumatic diseases, and kidney diseases.[49–51] **Table 1** summarizes the major risk factors for severe COVID-19 in pediatric patients.

Covid-19 in Children and Adolescents with Cancer. While cancer is an established risk factor for severe COVID-19 in adults, it has thus far not been considered so in children. In fact, the main risk factors for severe COVID-19 course in children are medical complexity, genetic, neurologic or metabolic conditions, congenital heart disease, obesity, diabetes, asthma or other chronic lung diseases, sickle cell disease, and immunosuppression.[52,53] Unlike the adult oncohematological population, data regarding COVID-

19 infection in pediatric oncohematological patients are relatively scarce. The incidence of COVID-19 is higher in patients with cancer than in the general population, both in adults[54] and children/adolescents.[55] This incidence could be explained by the increased susceptibility of immunosuppressed patients towards viral respiratory community infections and by the need for frequent hospital visits with higher exposure to contagion. From the beginning of the pandemic, recommendations for the prevention of infection have been released by the scientific community of pediatric oncology[56] that are still valid today: physical and social distancing of children on active treatment for cancer, patient screening before chemotherapy, limitation of hospital access for parents/caregivers, creation of dedicated COVID-19 free wards, implementation of telemedicine and the use of adequate personal protective equipment for health personnel, patients and parents or caregivers. However, the adherence to these measures has been variable during the pandemic, depending on country or region socio-economic level and readiness to implement the plans to prevent the diffusion of SARS-CoV-2 infection.

Cases of COVID-19 in children and adolescents with cancer have been reported worldwide. In the systematic review by Meena et al.,[57] collecting data from 33 studies (18 case reports and 15 case series),[55,58–89] clinical and outcome of 226 children with cancer and COVID-19 were described: 53% of the patients were affected by hematological malignancies and 47% by solid tumors. The median age was seven years with a male to female ratio of 1.7:1; 34 patients were in intensive chemotherapy and 17 post-HSCT. Sixty-three patients were symptomless, 47 had mild-moderate and 20 severe infections. Interestingly, out of 169 patients with data regarding chemotherapy, 123 (72.8%) had a treatment delay, and 10 had a regimen modification. In this review, morbidity and mortality related to SARS-CoV2 infection and the risk of severe COVID-19 was higher compared with the general pediatric population. Indeed, 96 of 226 patients (47%) required hospitalization, and 21 needed ICU admission. Fifteen patients (11.5% of hospitalized patients) died due to COVID-19. A meta-analysis of 15 studies, including pediatric patients with hematological malignancies and solid tumors, showed that the overall survival rate was 99.4%, with no statistically significant differences in the risk of hospitalization, ICU admission, and need for ventilation between patients with hematological conditions malignancies and solid tumors.[90]

Nicastro et al.,[91] in a review on COVID-19 in immunosuppressed children, observed that pediatric cancer patients have overall good COVID-19 outcomes, though still slightly worse than the general population.

In a European cohort of 582 hospitalized pediatric patients,[43] 27% were affected by malignancy and presented a relative risk of ICU admission 2.7 times higher than the entire group; on the contrary, 29 patients on immunosuppressive treatment and 3 affected by immunodeficiency did not show an increased risk of ICU admission.

The largest collection of COVID-19 infection in the pediatric oncology field has been recently published:[92] this study included data of 1319 patients under the age of 19 from 131 institutions of 45 countries who completed the 30-day follow-up. Deaths attributable to COVID 19 infection were 3.8% (50 out of 1319), more than ten times higher than the general pediatric population.

An important risk factor associated with severe or critical illness was low-income or lower-middle-income country status, with a relative risk 5.8 times greater than high-income country status. Other risk factors were an age between 15 and 18 years, lymphocytes <300/mmc, neutrophils <500/mmc, comorbidities, and being on intensive chemotherapy. Oncological treatment was modified globally in 55.8% of patients, and, among them, chemotherapy was suspended in 80% and reduced in 13.1%. In addition, radiation therapy was delayed in 6.6%, whereas surgery was postponed in 6.7% of patients.

Currently, given the small number of fatal cases in pediatric oncology, the risk factors for mortality are not known. On the contrary, in the adult hematological oncology field, worse overall survival was associated with advanced age, an uncontrolled or progressive disease status, the diagnosis of acute myeloid leukemia, aggressive non-Hodgkin's lymphoma, indolent non-Hodgkin lymphoma or plasma cell neoplasm, and the presence of COVID-19 in severe or critical form.[13]

According to the European Society for Blood and Marrow Transplantation (EBMT) data, the mortality in 382 patients with COVID-19 after stem cell transplant was 25% with a 6-week overall survival rate of 77.9% 72.1% for allogeneic and autologous recipients, respectively.[88] In this series, only 3 of 32 pediatric patients (29 allogeneic transplants and 3 autologous transplants) died, all after allogeneic stem cell transplant, the 6-week overall survival being 93.4%. In multivariate analysis, the risk factors for lower survival were older age, ICU admission, and the moderate/high immunodeficiency index, whereas a better performance status was protective.

The comparison between the clinical course in the general pediatric/adolescent population and the pediatric/adolescent cancer patients is shown in **Table 3**.

Treatment. The treatment of pediatric cancer patients with COVID-19 is similar to that of immunocompetent populations affected by COVID-19. Several pediatric guidelines[48,90-92] stated that the cornerstone of treatment is the supportive measures, such as the administration of fluids and electrolytes, nutritional support, support of the

Table 3. Differences in clinical course of COVID 19 infection between the general pediatric/adolescent population and pediatric/adolescent patients with cancer.

	Pediatric/Adolescent Population	Pediatric/Adolescent Cancer Patients
% Symptomatic SARS-CoV2 positive	80%[17]–90%[16]	30%[52]-35%[87]
Hospitalization rate (% of symptomatic)	2.5-4.1[17]	47%[52]-67%[87]
ICU admission rate (% of hospitalized patients)	15%[20]	17.5%[87]-22%[52]
Mortality rate	0.08%[21]-0.28[36]	4.8%[52]-3.8[87]

respiratory function with the administration of oxygen, or the use of non-invasive or invasive ventilation systems, support of cardiac function with inotropes, support of renal function, and antibiotic treatment in case of bacterial superinfection.[96,97]

The underlying immunosuppression of pediatric cancer patients can prolong the viral phase of COVID-19 and reduce, delay or even nullify the inflammatory phase of the disease.

Since the onset of the pandemic, several drugs have been used in the treatment of pediatric cancer patients with COVID-19:[55,61,63,66–68,73,74,76,81–83,85,87,88] the most used drug was hydroxychloroquine, followed by steroids and oseltamivir. In addition, the use of lopinavir/ritonavir, azithromycin, remdesivir, tocilizumab, convalescent plasma, chloroquine, and IVIG has also been reported in the literature.

The use of these drugs was based on the protocols adopted for adults, but no treatment specific for the pediatric age has been developed. Currently, some drugs initially used, such as hydroxychloroquine/chloroquine (both in outpatients[98] and in hospitalized patients),[99,100] lopinavir/ritonavir,[101–103] and azithromycin)[104–107] are no longer recommended due to their demonstrated ineffectiveness.

Instead, the following are the currently used drugs for the treatment of COVID-19, concerning the adult and pediatric literature.

Steroids. Steroid therapy has shown conflicting results in adults hospitalized due to SARS-CoV-2 infection.[108] In a systematic review and meta-analysis, the use of systemic glucocorticoids was evaluated on a total of 15.754 patients:[109] neither a reduction in mortality nor in the duration of hospitalization and period of viral shedding was demonstrated. Steroid therapy has not shown efficacy even in adult oncology: Rivera et al.[110] reported a numerical (but not statistically significant) increase in 30-day all-cause mortality in 109 patients treated with high-dose steroids compared to negative controls.

However, the efficacy of dexamethasone has been demonstrated in hospitalized patients receiving oxygen, noninvasive or invasive mechanical ventilation, determining lower 28-day mortality.[111] Unfortunately, the same benefit was not found in patients not receiving respiratory support.

A Multidisciplinary Guidance on the Use of Immunomodulatory Therapies for COVID-19 in Pediatrics[112] published in December 2020 concluded that steroid therapy is not recommended for mild/moderate disease course, while it may be beneficial for severe or critical illnesses. Therefore the risk and benefits should be evaluated on a case-by-case basis.

Currently, there are no randomized trials that demonstrate the efficacy of steroid therapy in patients with cancer or immunodeficiency, neither in the adult nor in the pediatric population.

Remdesivir. Remdesivir showed mixed results in the adult population: while in the WHO solidarity trial[103] on 11,330 patients, of which 2750 treated with Remdesivir, no improvements of mortality, of the need for invasive ventilation and duration of hospitalization was found in patients treated with remdesivir, Beigel et al.[113] reported a significant reduction in mortality and days to recovery in a population of 1062 patients (of which 80 with cancer)treated versus placebo; in the analysis of subgroups based on respiratory support, efficacy was demonstrated in patients not receiving oxygen or receiving oxygen, but not in patients receiving high-flow oxygen, non-invasive ventilation, or invasive ventilation. In a study conducted on 2186 adults with cancer, including 470 with hematological malignancy,[110] 124 were treated with remdesivir alone: its use was associated with a reduction in 30-day all-cause mortality in comparison with positive controls (Odds Ratio 0.41), however without statistical significance.

In the multicenter Interim Guidance on Use of Antivirals for Children With Coronavirus,[114] experts suggested as a first choice the use of remdesivir for children with severe illness, defined as a supplemental oxygen requirement without the need for non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). The evidence of good tolerance[113,114] and the efficacy data deriving from the adult population suggest using remdesivir instead of other antivirals. and. However, no efficacy and safety data are currently available in pediatric cancer patients.

Monoclonal Antibodies. The use of anti-Spike

monoclonal antibodies to prevent severe COVID-19 has shown promising results in the adult population: several studies[115–117] demonstrated a reduction of hospitalizations and deaths among patients treated with banlanivimab + etesevimab and casirivimab + imdevivab.

The best results were obtained with an early administration of antibodies, and, therefore, their indication is mainly in the early stages of the disease.[118,119] In 38 adult patients with active cancer,[120] the use of neutralizing monoclonal antibodies led to a lower hospitalization and mortality rate than those previously described among active cancer patients.

Based on the evidence available in December 2020, a panel of experts[121] expressed an opinion against the routine use of monoclonal antibody therapy in pediatric patients, including those at high risk of severe evolution.

Convalescent Plasma. Several randomized trials demonstrated that convalescent plasma has no significant impact on the main outcome indicators of COVID-19 in adult patients.[122,123] However, the efficacy could be linked to the anti-SARS-CoV-2 antibody titer: Joyner et al. [124] demonstrated a reduction in the risk of death in hospitalized patients who were not receiving mechanical ventilation by administration of convalescent plasma with higher anti-SARS-CoV-2 IgG antibody levels, compared to those treated with plasma with lower antibody levels.

Other factors that could influence the effectiveness of this treatment are the timing of administration and the severity of the infection: Libster et al.[125] showed that early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced disease progression.

Convalescent plasma with high neutralizing antibody titers could find an indication in B-cell depleted patients,[126] although there are currently no randomized studies that can confirm benefits in this cohort.

In the adult cancer population, convalescent plasma has shown efficacy in treating COVID-19. In a retrospective study[127] conducted on 966 adult patients with hematologic malignancy, hospitalized for COVID-19 infection, the outcome of patients treated with plasma (n = 143) compared to those who did not receive it (n = 823) was evaluated. In patients treated with plasma, a favorable Hazard Ratio of 0.6 in 30-day all-cause mortality, 0.4 for ICU admission, and 0.32 for mechanical ventilation was found.

However, the efficacy of plasma in the adult cancer population remains unclear in the absence of randomized trials.[128]

Convalescent plasma was generally well tolerated in the adult population,[129] and no specific adverse reactions were reported.

In a literature review,[130] in pediatrics, 8 case report studies with a total of 14 children treated with plasma (age range 9 weeks-18 years) were described: no adverse events related to plasma administration were documented. All patients had a positive outcome, and 7 of the 8 studies concluded that convalescent plasma could be a useful therapeutic option. However, given the small number and heterogeneity of the sample, more studies are needed.

Tocilizumab. Although tocilizumab (anti-IL-6R monoclonal antibody) has been emergently authorized in the USA in hospitalized patients over 2 years of age on steroid therapy and in need of oxygen, mechanical ventilation, or ECMO, there are currently no data on efficacy and safety in the pediatric population.

Tocilizumab showed variable efficacy in various retrospective and case-control studies in the adult population.[131,132] Furthermore, being associated with an increase in the rate of superinfection,[133] the risk/benefit ratio of its use is to assess carefully in oncology[134] patients.

Several case reports and case series[66,67,73,83] have shown that treatment with Tocilizumab is feasible and well-tolerated in pediatric cancer patients, but large studies are lacking.

Anticoagulation. The risk of thrombotic complications in children with COVID19 is not yet well defined, and thromboprophylaxis in these patients is limited to cases at higher risk of thrombosis.

There are two main pediatric consensus-based recommendations[135,136] suggesting the administration of low-dose low molecular heparin subcutaneously twice daily, targeting a 4-hour post-dose anti-Xa activity level of 0.2 to < 0.5 U/ml, as prophylaxis in children hospitalized for COVID 19. The indication to prophylaxis with heparin is the presence of an elevated D-dimer value (> 5 times above the upper limit) or of risk factors for hospital-related deep vein thrombosis (i.e., presence of a central venous catheter, mechanical ventilation, prolonged length of stay, complete immobility, obesity, active malignancy, cystic fibrosis exacerbation, sickle cell disease vaso-occlusive crisis, congenital or acquired cardiac disease with venous stasis or impaired venous return, previous history of venous thromboembolism (VTE), first-degree family history of VTE before 40 years of age, known thrombophilia, post-pubertal age, estrogen-containing oral contraceptive pill therapy, status-post splenectomy for underlying hemoglobinopathy).

Vaccination. COVID-19 infection in the pediatric setting has other consequences than health, such as social isolation and interruption of education. Furthermore, the pediatric patient could act as a vector of the disease within society and then pose risks for the adult population and certain subsets of pediatric patients at risk

of developing severe COVID 19.[137]

Therefore, vaccination against COVID 19 should be considered in the entire pediatric population.

To date, safety, immunogenicity, and efficacy studies have only been conducted in the population over 12 years of age. Frenck et al.[138] reported the experience of administering the BNT162b2 Covid-19 vaccine in the population aged 12 to 15 years in a multinational, placebo-controlled, observer-blinded trial: 2600 adolescents were enrolled, of whom half received the vaccine and half received placebo. The vaccine showed a favorable safety and side-effect profile, presenting mostly mild to moderate reactogenicity in the absence of serious vaccine-related adverse events. The vaccine efficacy was 100%.

Similarly, the mRNA-1273 vaccine showed a good safety profile and a serological response in the population between 12 and 17 years, comparable to that of young adults, with efficacy in preventing COVID 19.[139]

Walter et al. reported recently the results of phase 2-3 study where 2268 children of 5-11 years of age were randomized (ratio 2:1) to receive 2 doses of 10 mg of BNT162b2 vaccine, 21 days apart, versus placebo. After a median follow-up of 2.3 months from the second dose, the vaccine efficacy against documented COVID-19 was 90.7%; moreover, no vaccine-related serious adverse events were noted, and the serum antibody level of neutralizing antibodies against SARS-CoV-2 was comparable to that observed in a control group of subjects of 16-25 years vaccinated with the adult dose of 30 mg BNT162b2 vaccine.[140]

Although mRNA vaccines' safety and tolerability profile is favorable, myocarditis has been reported as a rare complication, especially in adolescent or young adult males. A recent Israeli study[141] showed that the incidence of myocarditis, albeit low, was increased in 16-19-year-old males who received the BNT162b2 mRNA vaccine (8.62 events / 100,000). The relative risk of developing myocarditis was 5.34 for the entire population and up to 13.6 in males between 16 and 19 years. It should be noted that after SARS-CoV-2 infection, the myocarditis complication is greater (11.54 events/100,000). The clinical presentation of myocarditis after vaccination was generally mild with response to conservative or symptomatic treatment.

Data on COVID 19 vaccines in patients with malignancy are limited since these patients were largely excluded from the phase III vaccine trials. However, the experience on 151 adult patients with cancer, of which 95 with solid tumors and 56 with hematological cancer, has recently been reported.[142] The vaccine was well-tolerated, and no vaccine-related deaths were reported. The serological response (IgG positivity) was found after the first dose in 38% of patients with solid tumors, 18% of hematological malignancies, 94% of healthy controls, while after the second dose in 95%, 60%, and 100%, respectively.

Several reports have been published in reference to specific cancers in the adult population: after the second vaccine dose the antibody response was 45-65% for chronic lymphocytic leukemias,[143,144] 40-70% in Non-Hodgkin lymphomas,[144,145] 94-100% in Hodgkin lymphomas,[144,146] 80-90% in acute lymphatic or myeloid leukemias,[144,146] 70-85% in post-transplant patients.[147,148] Several observations showed that, in the patients who have received anti-CD20 monoclonal antibody therapy, B-cell directed immunotherapy or patients with profound hypogammaglobulinemia or marked lymphopenia, the response to vaccination is very poor.[149,150]

Revon-Liviere et al. [151] reported the single-center vaccination experience of 10 patients between 16 and 21 years under treatment for solid tumors or within 6 months after treatment conclusion. Vaccination was well tolerated in all patients who presented exclusively mild local reactivity symptoms; 7 out of 10 patients showed positive serology after the first vaccine and 9 one month after the second. No patient developed COVID 19 disease.

Vaccination has been shown to be safe in adolescents and young adults (12-29 years) with a previous PEG-asparaginase allergy, showing no vaccine reaction.[152]

In Europe, the indication issued by National Authorities is to recommend the full vaccination with a vaccine approved by the European Medical Agency (EMA) in all people above 12 years of age, including frail patients due to the presence of comorbidities, immunosuppression, cancer treatment, chronic disease, and organ or stem cell transplant.[151]

Considering that vaccination is not yet available for patients under the age of 12, full vaccination of all eligible family members of cancer patients is of paramount importance because it reduces the viral transmission to these patients at high risk of severe COVID 19 course.[153]

Conclusions. Pediatric patients have a reduced incidence of severe COVID 19 compared to the adult population. However, a subset of pediatric patients is at greater risk for a severe course. This subset includes pediatric and adolescent patients with active cancer and immunosuppression.

In pediatric cancer patients, severity, morbidity, and mortality are higher than the general pediatric population, particularly in low-middle income countries.

The clinical course may be asymptomatic; however, 47-68% of patients require hospitalization and 9-10% admission to intensive care. Mortality attributable to COVID 19 infection is about 4%.

A key measure for these patients is the prevention of COVID 19 infection by reducing the risk of exposure and vaccinating contacts.

Data regarding the efficacy and safety of vaccination in adolescent cancer patients are still very limited; however, based on data collected on studies in adults, the safety profile and tolerability are reassuring.

In the case of COVID 19 infection, the cornerstone of treatment is supportive care. However, transferring the evidence gained from adults, some medical treatments, such as the use of dexamethasone for severely ill patients, the early adoption of convalescent plasma, the use of remdesivir to reduce the viral shedding, and the anticoagulant prophylaxis are reasonable in hospitalized patients. The use of monoclonal antibodies must be assessed on the basis of the patient clinical situation or within experimental protocols. Further studies are needed to elucidate better the risk factors, treatment, and outcomes of COVID 19 in pediatric cancer patients.

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