Pediatr Pol 2022; 97 (2): 71-80
DOI: https://doi.org/10.5114/polp.2022.116503
Submitted: 30.03.2022, Accepted: 26.04.2022, Published: 10.06.2022

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

SPECIAL PAPER

Updated principles of prevention, diagnosis and treatment of COVID-19 in children in Poland – recommendations for paediatricians and family medicine doctors

Magdalena Marczyńska[1,2], Maria Pokorska-Śpiewak[1,2], Ewa Talarek[1,2], Magdalena Figlerowicz[3], Bolesław Kalicki[4], Ernest Kuchar[5], Ewa Majda-Stanisławska[6], Małgorzata Pawłowska[7], Artur Sulik[8], Adam Sybilski[9,10], Leszek Szenborn[11], Jacek Wysocki[12,13], Jarosław Peregud-Pogorzelski[14], Teresa Jackowska[15,16]

[1]Department of Children's Infectious Diseases, Medical University of Warsaw, Poland
[2]Regional Hospital for Infectious Diseases, Warsaw, Poland
[3]Department of Infectious Diseases and Paediatric Neurology, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine, Central Clinical Hospital of the Ministry of Defence (MON), Warsaw, Poland
[5]Department of Paediatrics with Medical Assessment Unit, Medical University of Warsaw, Warsaw, Poland
[6]Department of Paediatric Infectious Diseases, Medical University of Lodz, Lodz, Poland
[7]Department of Infectious Diseases and Hepatology, *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University, Torun, Poland
[8]Department of Paediatric Infectious Diseases, Medical University of Bialystok, Bialystok, Poland
[9]2nd Department of Paediatrics, Centre of Postgraduate Medical Education, Warsaw, Poland
[10]Department of Paediatric and Neonatal Diseases of the Central Clinical Hospital of the Ministry of the Interior and Administration, Warsaw, Poland
[11]Department of Paediatrics and Infectious Diseases, Wroclaw Medical University, Wroclaw, Poland
[12]Department of Preventive Medicine, Poznan University of Medical Sciences, Poznan, Poland
[13]Department of Infectious Diseases, Specialized Health Care Center for Women and Children, Poznan, Poland
[14]Department of Pediatrics, Pediatric Oncology and Immunology, Pomeranian Medical University, Szczecin, Poland
[15]Department of Paediatrics, Centre of Postgraduate Medical Education, Warsaw, Poland
[16]National Consultant in the Field of Paediatrics, Warsaw, Poland

ABSTRACT

Since late 2021, we have observed a significant increase in the proportion of children infected with SARS-CoV-2. The course of the disease in children is usually sparsely symptomatic or asymptomatic. However, the predominance of new virus variants makes children more likely to become symptomatically ill and require hospitalisation. This paper aims to update recommendations for managing a child with COVID-19 in out- and inpatient settings. Current options for prevention and antiviral treatment are discussed, noting the limited availability of therapy for children. In most children with COVID-19, the basis for treatment remains symptomatic and supportive therapy and measures to reduce SARS-CoV-2 infection spread.

KEY WORDS:

COVID-19, children, SARS-CoV-2.

ADDRESS FOR CORRESPONDENCE:

Prof. Magdalena Maria Marczyńska, Department of Children's Infectious Diseases, Medical University of Warsaw, Poland, e-mail: magdalena.marczynska@wum.edu.pl

INTRODUCTION

A pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared by the World Health Organization on 11 March 2020. In less than 2 years, our knowledge and experience regarding the course and management of COVID-19 have increased [1]. In these updated recommendations, we present principles for diagnosing and treating COVID-19 in children in Poland. By January 2022, the Delta variant of SARS-CoV-2 was the dominant strain in Poland, accounting for 89% of cases (data as of 7 January 2022). At the time of writing (29 March 2022), it had been replaced in Poland by the Omicron variant (92%). However, the latter is more contagious and associated with a predicted 3-fold lower risk for a severe course of the disease (13.6% vs. 4.9%). Since the beginning of 2022, the rates of new cases of COVID-19 reported in European Union and European Economic Area countries are highest among people aged 15 to 24 years, followed by people aged 25 to 49 years and children under 15 years. In January 2022, the number of new infections increased in all age groups.

We have observed a gradual increase in cases of infected children in Poland. However, children in most cases present mild or moderate COVID-19 that generally does not progress to a severe form of the disease. Although almost 2 years have passed since the pandemic declaration, appropriate data are lacking on the treatment of children with COVID-19. Therefore, recommendations are based on results and data concerning efficacy and safety among adults and the risk estimation for disease progression in children [2, 3].

The paper presents the updated principles for the prevention, diagnostics and care of children infected with SARS-CoV-2. The paediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection, the subject of separate publications, is not discussed.

COVID-19 PROPHYLAXIS IN CHILDREN

Immunisation is the most effective method of reducing the number of infections and preventing a severe course of the disease. So far, no vaccine is available for children under the age of 5. From 7 June 2021, children from the age of 12 have been vaccinated. In addition, from 16 December 2021, the immunisation programme has included children older than 5 years. Registration for vaccination is available via the patient.gov.pl website or a 24-hour hotline or directly at the selected vaccination centre. In Poland, the percentage of persons fully vaccinated against COVID-19 is 57.7% (as of 3 February 2022). The percentage of vaccinated children aged below 18 years is unsatisfactory, amounting to approximately 47% in the population aged 12–18 years, including 56% of adolescents ≥ 16 years and 12.5% of children aged from 5 to 11 years (data of the Ministry of National Education and Ministry of Health).

At present, two COVID-19 vaccines are available for the **immunisation** of children in Poland.

1. mRNA vaccine (Comirnaty):

- 30 micrograms/dose – for active immunisation of people aged over 12 years,
- 10 micrograms/dose – for active immunisation of children aged 5 to 11 years.

The primary vaccination schedule consists of two doses given at least 3 weeks (21 days) apart.

Children with the immunity disorders listed below are recommended to follow a three-dose primary vaccination schedule:

- ongoing cancer treatment,
- ongoing immunosuppressive treatment for various reasons,
- after solid organ transplantation during treatment with immunosuppressants or biological agents,
- after stem-cell transplant within the previous 2 years,
- moderate or severe primary immunodeficiency disorders,
- HIV infection,
- treatment with high doses of corticosteroids or biological agents that may suppress the immune response,
- renal replacement treatment (RRT) due to renal failure.

The third (booster) dose of the vaccine should be given at least 28 days after completion of the two-dose vaccination schedule [4].

For children aged 12 years and above, a booster dose is allowed in Poland at least 5 months after completing the primary vaccination schedule (for persons vaccinated with two doses) [5].

2. mRNA vaccine (Spikevax)

It is for active immunisation of persons from the age of 6 years.

Spikevax is given as two injections, usually into the muscle of the upper arm, 28 days apart. Adults and adolescents from the age of 12 are given 100 micrograms per dose; children aged 6 to 11 years are given 50 micrograms per dose. An additional dose may be given to people aged 6 years and older with a severely weakened immune system, at least 28 days after their second dose. A booster dose of 50 micrograms may be given at least 3 months after the second dose to people aged 18 years and older [6].

The administration of the COVID-19 vaccine is contraindicated in people with a history of severe anaphylactic reaction to previous doses of the vaccine or any of its components. After vaccination, a child should stay at the vaccination centre for at least 15 minutes, and at least 30 minutes in case of a known history of hypersensitivity to other substances. A physician qualifies children under the age of 15 for vaccination.

When the next dose is delayed, it should be given at the first possible opportunity. No restart of the vacci-

nation schedule is expected. Children after COVID-19 can be vaccinated 30 days after obtaining a positive result of the genetic or antigen test for SARS-CoV-2 [7].

There are no formally approved methods of **pharmacological COVID-19 prophylaxis** in children younger then 12 years. In the EU, including Poland, Ronapreve (casirivimab + imdevimab) is approved for use in pre- and post-exposure prophylaxis for the Alpha and Delta variants of SARS-CoV-2 in adults and adolescents aged ≥ 12 years weighing ≥ 40 kg [8]. Monoclonal antibodies are indicated in persons at high risk of severe COVID-19 (see the risk groups listed below). In **post-exposure prophylaxis**, medication should be administered as soon as possible after contact with the COVID-19 patient. The post-exposure dose is 600 mg of casirivimab and 600 mg of imdevimab in a single intravenous (IV) infusion or subcutaneous (SC) injection.

In **pre-exposure prophylaxis** (SARS-CoV-2 PrEP), the initial dose is 600 mg of casirivimab and 600 mg of imdevimab in a single IV infusion or SC injection. Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab in a single IV infusion or SC injection can be given every 4 weeks until prophylaxis is no longer required. No data exist concerning the use of the medication longer than 24 weeks (6 doses) [8].

For SARS-CoV-2 PrEP, including prevention of the Omicron variant infection, the National Institutes of Health (NIH) in the United States of America recommends the use of a combination of two monoclonal antibodies (tixagevimab and cilgavimab; evusheld formulation) every 6 months [9, 10] in adults and adolescents (aged ≥ 12 years and weighing ≥ 40 kg) who:

- have moderate or significant immunodeficiency and may have an inadequate immune response to COVID-19 vaccination (BIIa),
- cannot receive complete vaccination with any available vaccine against COVID-19 due to a documented history of serious adverse reactions to a COVID-19 vaccine or any of its components (AIIa),
- are receiving active treatment of solid tumours or haematological malignancies,
- have undergone solid organ transplantation or received immunosuppressive therapy,
- have received chimeric antigen receptor T-cell therapy or haematopoietic stem-cell transplant (within 2 years from the transplant or immunosuppressive treatment),
- have a moderate or severe primary immunodeficiency disorder (e.g. DiGeorge syndrome, Wiskott-Aldrich syndrome),
- have advanced (AIDS) or untreated HIV infection (with a CD4+ T-cell count of < 200/mm^3),
- are receiving treatment with high-dose corticosteroids (i.e. ≥ 20 mg of prednisone or equivalent daily for ≥ 2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive agents, anti-cancer chemotherapy classified as strongly immunosuppressive, tumour necrosis factor inhibitors, or other biological therapies exhibiting immunosuppressive or immunomodulatory properties (e.g. B-cell depleting agents).

Since 24 March 2022 the European Medicines Agency has approved tixagevimab plus cilgavimab (Evusheld) for SARS-CoV-2 PrEP in adults and adolescents 12 years of age and older, weighing at least 40 kg, with moderate to severe immunodeficiency. The recommended dose is 150 mg tixagevimab and 150 mg cilgavimab given as two separate intramuscular injections.

COVID-19 DIAGNOSTICS IN CHILDREN

COVID-19 diagnostic methods in children are the same as in adults.

The basis of COVID-19 diagnosis is detecting SARS-CoV-2 genetic material in the nasopharyngeal swab (collected from 1–2 days before symptoms up to day 10 after symptom onset) using a real-time polymerase chain reaction (RT-PCR) assay or a positive result of the second-generation antigen test (collected up to day 7 from the onset of symptoms). When clinical symptoms suggest SARS-CoV-2 infection and the antigen test is negative, RT-PCR testing (as a confirmatory test) is indicated.

Testing for SARS-CoV-2 infection should be performed:

1. **In children with symptoms** of upper respiratory tract infection or gastroenteritis (with suspicion of SARS-CoV-2 infection).
2. **After exposure to COVID-19 in:**
   2A. Children with few or no symptoms at risk for severe COVID-19;
   2B. Children with few or no symptoms whose caregivers or household members have risk factors for severe COVID-19.
3. On hospital admission, to prevent the spread of the infection between patients [11].

Management of a child with a positive result of the test for SARS-CoV-2 depends on the clinical symptoms and comorbidities [12–16] (Table 1).

Definitions of severe COVID-19:

- severe COVID-19 – the emergence or increase in demand for oxygen compared to a baseline without the need for the use of mechanical ventilation (non-invasive or invasive),
- severe, critical COVID-19 – demand for non-invasive or invasive mechanical ventilation, with multiple organ dysfunction.

In December 2021, the United States Food and Drug Administration (FDA) issued emergency use authorizations for two antiviral agents for use in patients with mild or moderate SARS-CoV-2 infection at risk of severe COVID-19: ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir; both agents can be used up to day 5 from disease onset. Unfortunately, in Poland, molnupiravir is only available for the treatment of adults;

TABLE 1. Groups of children at risk of severe COVID-19 [12–17]

Newborns and infants
Obese children with a BMI of ≥ 120% of the value corresponding with the 95th percentile for BMI or ≥ 30 kg/m^2
Adolescents with a BMI ≥ 85th percentile for age and sex according to CDC (https://www.cdc.gov/growthcharts/clinical_charts.htm)
NIH
Adolescents aged ≥ 16 years (NIH)
Children with the following comorbidities:
• congenital **heart defects** (cyanotic), myocardiopathies, chronic cardiovascular diseases
• **metabolic** diseases
• **neurological** diseases
• **genetic** disorders, e.g. Down syndrome, muscular dystrophies impairing respiration
• **neoplastic diseases**
• **chronic renal diseases**
• **cystic fibrosis, broncho-pulmonary dysplasia,** chronic diseases of the respiratory tract (with obstruction)
• **immunodeficiency** after organ transplantation
• non-controlled **diabetes mellitus**
• **dependency on medical equipment** (tracheostomy, gastrostomy, positive pressure ventilation not related to COVID-19)
• bronchial asthma, bronchial hyperreactivity or other **chronic diseases of the respiratory tract requiring daily treatment administration**
• sickle-cell disease

BMI – body mass index, CDC – clinical growth charts, NIH – National Institutes of Health

Paxlovid will be available soon. Paxlovid can be used in people aged ≥ 12 years weighing ≥ 40 kg (NIH, FDA) [18].

Recommendations for out- and inpatient management of children with confirmed SARS-CoV-2 infection without or with COVID-19 symptoms depending on comorbidities:

1. Children without COVID-19 symptoms (e.g. performing the test after exposure, travelling):

   1a. Without symptoms or risk factors for a severe course of the disease:

The child needs to be isolated at home. A remote medical consultation is recommended, during which the caregiver should receive information about the following:

- date of the follow-up remote consultation after 2–4 days to determine the child's health condition and assess adherence to medical recommendations,
- need for an immediate medical visit at the outpatient clinic or hospital in case of the onset of specific symptoms (cough, diarrhoea, fever) or any symptoms that worry the caregiver.

A phone number for emergencies should be provided during a remote medical consultation.

1b. Without symptoms, from a risk group for severe COVID-19:

The course of disease **in newborns and infants up to 6 months of life** with a positive SARS-CoV-2 test may be oligosymptomatic, challenging to predict and often accompanied by additional infections (pneumonia, otitis media, urinary tract infections). In these cases hospitalisation of the children up to 6 months should be considered.

In adolescents aged ≥ 12 years and weighing ≥ 40 kg, the use of monoclonal antibodies needs to be considered [3, 9, 10].

In Poland, after a benefit and risk assessment, the administration of monoclonal antibodies is only possible in inpatient settings. Treatment is recommended for adolescents with severe immunodeficiency, during cancer treatment, with obesity or chronic respiratory system diseases, or dependant on medical equipment.

Asymptomatic children aged less than 12 years at high risk of severe COVID-19 should be carefully monitored. Hospitalisation is encouraged in case of disease symptoms (fever, cough, diarrhoea).

Children with severe comorbidities who are cared for in specialist centres should, after diagnosis of SARS-CoV-2 infection, inform the doctor or department where they are being treated about the infection due to possible particular circumstances in the management of the child or contact persons. When hospitalisation is necessary, children should receive treatment in departments or clinics where they were previously treated. In such departments, so-called red isolation zones equipped with sanitary units with an airlock (single rooms) should be separated, providing complete protection for the personnel, including personal protective equipment.

SARS-CoV-2-infected patients requiring hospitalisation to diagnose and treat a co-morbidity should be referred to multi-speciality hospitals (under isolation conditions).

2. Children with mild symptoms of SARS-CoV-2 infection require medical assessment

   2a. Without comorbidities – symptomatic treatment is recommended (AIII)

Newborns, infants and children aged below 6 years require direct medical assessment [2, 19]. Older children also require medical assessment if they have symptoms that worry their caregivers. Then, depending on their clinical status, the child is referred for further home care or to the hospital. Notably, newborns and infants, according to the criteria outlined in the frame, are always a risk group. Therefore, even initially mild symptoms may

worsen in the following hours or days, becoming a risk to health and life.

For children treated at home, we recommend a follow-up remote medical visit or a visit to the outpatient clinic after 2–3 days (depending on the child's health condition) to determine the current state of health and assess adherence to the recommendations. In addition, the child's parent or caregiver should receive information about the need for immediate contact and a medical visit when worrying symptoms occur (please provide a phone number for contact in case of emergencies).

Symptomatic and supportive treatment includes:

- easily digestible diet,
- appropriate fluid intake,
- antipyretics (when body temperature is above 38°C): paracetamol or ibuprofen at doses calculated per kilogram of body weight (BW).

Treatment with antibiotics is required in case of an acute otitis media, pneumonia or urinary tract infection diagnosis. When selecting antibiotics, valid recommendations should be followed, considering the child's health condition and age. Oral antibiotics are administered in outpatient settings. Parenteral antibiotics need to be used in inpatient settings. When the child's health condition improves, a sequential treatment (switching to oral medication) with continuation at home under the supervision of a doctor from the outpatient clinic is indicated.

In contrast to adults, no clear recommendations on inhaled corticosteroids have been developed for children. Inhaled corticosteroids should only be indicated individually, e.g. in acute laryngotracheobronchitis or obstructive bronchitis. Due to frequent measurement errors in younger children, we do not recommend routine oxygen saturation measurement by caregivers. Generally, available pulse oximeters are not indicated for children. Thus, a measurement performed by an untrained person will be unreliable, unnecessarily causing significant concern. **Medical personnel should always measure the oxygen saturation during every medical visit.**

2b. In a risk group for severe SARS-CoV-2 infection

- **Symptomatic and supportive treatment** (see 2a)

Two **monoclonal antibody** formulations are registered in Poland for the treatment of COVID-19 in patients aged ≥ 12 years and weighing ≥ 40 kg who do not require oxygen therapy and have an increased risk of progression to severe COVID-19: **casirivimab** with **imdevimab** (Ronapreve) and **sotrovimab** (Xevudy).

- **Considering the use of monoclonal antibodies: Xevudy or Ronapreve**

Casirivimab with imdevimab (**Ronapreve**) is indicated for the treatment of patients infected with Alpha and Delta (not Omicron) variants at a dosage of 600 mg of casirivimab and 600 mg of imdevimab administered in a single IV infusion or SC injection. Casirivimab with imdevimab should be used up to 7 days from the onset of COVID-19 symptoms. The product should only be used in facilities providing patient surveillance in the event of infusion-related adverse reactions or anaphylaxis. Ronapreve is not effective against the Omicron variant.

Sotrovimab (**Xevudy**) is indicated for the treatment of patients with confirmed mild to moderate SARS-CoV-2 infection (including cases of the Omicron variant) at high risk of a severe course of the disease. It should be given in a single dose of 500 mg IV no later than day 5 of the illness [20].

- **If sotrovimab cannot be used, one of the following antiviral agents below should be considered:** remdesivir or, for patients 18 years of age or older, molnupiravir or Paxlovid [9, 18, 21].

Remdesivir (Veklury) is used in adolescents aged ≥ 12 years and weighing ≥ 40 kg **(BIIa)**. Medication should be used during the SARS-CoV-2 replication period, i.e. not later than up to day 7 after symptom onset. In patients not requiring oxygen therapy, the treatment duration is 3 days: 200 mg on the first day, followed by 100 mg on days 2 and 3, in at least a 60-minute IV infusion. The safety, efficacy and dosage in children are based on studies in adults.

In Poland, remdesivir may be administered only in inpatient settings with the possibility to react when a severe anaphylactic reaction occurs and monitor the patient during and for at least 1 hour after IV infusion.

Molnupiravir (Lagevrio) is recommended in young adults or adolescents (aged ≥ 18 years) from a risk group when the administration of remdesivir is not possible. Molnupiravir is administered orally as soon as possible after diagnosis, up to day 5 from symptom onset, at 800 mg twice a day for 5 days (**CIIa**). No data exist on the use of molnupiravir in patients vaccinated against COVID-19. In vaccinated patients, due to the lower efficacy of molnupiravir, decisions should be made on an individual basis because the risk-benefit ratio is likely to be less favourable.

Nirmatrelvir 300 mg **with ritonavir** 100 mg (Paxlovid) is approved in the EU only for emergency use in adults. The US Food and Drug Administration and NIH recommend the product for use in adolescents from risk groups aged ≥ 12 years and weighing ≥ 40 kg. Paxlovid should be administered orally as soon as possible after diagnosis, up to day 5 from symptom onset, twice daily for 5 days (AIIa). The medication is contraindicated in patients with serious renal or hepatic impairment and pregnant women. Paxlovid is still not available in Poland [18].

3. Children with moderate COVID-19, requiring hospitalisation, with normal oxygen saturation (SpO_2 ≥ 94%)

In children, mild and moderate COVID-19 is not an indication for thromboprophylaxis. **Children hospitalised for COVID-19 should undergo assessment for embolism risk,** including coagulation tests. If a child has risk factors for embolism, a consultation with a haematologist is indicated before prophylaxis initiation [3].

Factors for the risk of embolism in children hospitalised due to COVID-19:

- age ≥ 12 years or after puberty,
- hospitalisation in the intensive care unit (ICU), mechanical ventilation, need for the use of vasopressor amines,
- obesity,
- central line,
- immobilisation,
- sickle-cell disease,
- autoimmune diseases,
- nephrotic syndrome,
- cystic fibrosis exacerbation,
- need for hospitalisation for > 3 days,
- history of embolism, thrombophilia (patient, the immediate family – first-degree consanguinity),
- oestrogen therapy,
- cardiac arrhythmias,
- heart diseases with venous stenosis or impaired venous return.

3a. Children without risk factors for severe COVID-19

- **Symptomatic treatment:** antipyretics, correction of water-electrolyte balance, inhaled corticosteroids when additional indications exist (see 2a).
- **Empirical antibiotic therapy, if** additional **indications** exist, following the current recommendations for treatment of bacterial infections (see 2a).
- **Administration of antivirals and monoclonal antibodies in children with mild or moderate disease (without factors for a severe course of the disease) is not justified unless** used in clinical trial settings.

3b. Children from risk groups for severe COVID-19, especially with profound immunodeficiency, during chemotherapy for malignancy, during biological treatment with chronic lung disease or with significant obesity.

We recommend using:

- **symptomatic treatment** (antipyretic, correction of water-electrolyte balance, eventually inhaled budesonide),
- **empirical antibiotic therapy if** additional **indications** exist.

In adolescents from the age of 12 years (particularly aged ≥ 16 years), we recommend the use of **monoclonal antibodies:**

- **Sotrovimab** (Xevudy; see 2b);
- **Casirivimab + imdevimab** (Ronapreve), used in infections caused by the Delta variant, is ineffective against the Omicron variant (see 2b);

If the administration of antibodies is not possible (including children aged < 12 years and weighing < 40 kg), then one of the antiviral agents should be used (see 2b);

- **Remdesivir** (Veklury) in adolescents aged ≥ 12 years and weighing ≥ 40 kg **(BIIa)** not requiring oxygen therapy – as soon as possible after diagnosis and not later than up to day 7 from symptom onset for 3 days (see 2b).

The use of remdesivir in children aged < 12 years with moderate COVID-19 and SpO_2 of ≥ 94% weighing from 3.5 to < 40 kg should be considered individually. The off-label* use within life-saving therapy (no approval in this age group) is only recommended in patients from a group at high risk of severe COVID-19. Remdesivir is administered IV up to day 7 from the onset of symptoms for 3 consecutive days at a dose of 5 mg/kg of BW (first day) and 2.5 mg/kg BW (second and third day), only in the form of a lyophilised powder for solution for IV injection (not in a ready-to-use form for injection 100 mg/20 ml; the solution has to be prepared according to the package leaflet) **or** for patients 18 years of age or older:

Nirmatrelvir + ritonavir (see 2b) **or**

Molnupiravir (see 2b).

4. Children in a severe general health condition requiring oxygen therapy (SpO_2 < 94%) – hospitalisation in a facility equipped with a paediatric intensive care unit (PICU)

We recommend using:

- **symptomatic treatment** (antipyretic, correction of water-electrolyte balance, eventually inhaled budesonide),
- **empirical antibiotic therapy if** additional **indications** exist,
- **thromboprophylaxis or anticoagulation therapy as indicated,**
- **antiviral treatment** – regardless of additional comorbidities.

Remdesivir (Veklury) – in patients with pneumonia necessitating oxygen therapy (SpO_2 < 94%), the treatment duration is **5 days** [21, 22].

Dosage:

- in children aged ≥ 12 years and weighing ≥ 40 kg – loading dose of 200 mg on the first day; from days 2 to 5, 100 mg daily in at least 60-minute IV infusion,
- in children aged < 12 years and weighing from 3.5 to < 40 kg – loading dose of 5 mg/kg of BW on the first day; from days 2 to 5, 2.5 mg/kg of BW once daily in an IV infusion.

If the child requires mechanical ventilation during treatment and is transferred to the PICU, treatment should be continued (up to 5 days). In children under 12 years, remdesivir may be used as a life-saving therapy*.

CORTICOSTEROID TREATMENT

Dexamethasone is indicated in hospitalised children and adolescents with COVID-19 receiving remdesivir and oxygen therapy. Exceptions are children with profound immunodeficiency, in which the use should be considered on an individual basis. In addition, alternative corticosteroids can be used for treatment, such as prednisone, methylprednisolone or hydrocortisone. The dosing regimen for dexamethasone in children is 0.1–0.15 mg/kg of BW/dose once daily (maximum dose of 6 mg) for up to 10 days.

In patients with respiratory failure treated in the ICU, higher doses of dexamethasone are recommended depending on their health condition.

Other corticosteroids (instead of dexamethasone) in children requiring oxygen therapy:

Methylprednisolone is preferred in children with asthma at a dose of 2 mg/kg of BW/24 hours in two divided doses, maximum 60 mg/24 hours [23].

Hydrocortisone in preterm infants – 0.5 mg/kg of BW every 12 hours for 7 days or 0.5 mg/kg of BW for 3 days.

Other agents that can be used in children in severe general health conditions requiring oxygen therapy:

- **Baricitinib (Olumiant**) – JAK-1 inhibitor. Use may be considered in children aged ≥ 2 years with high inflammatory marker levels or with contraindications to steroid use* [24, 25].

Dosage recommended in children:

≥ 2–9 years – 1 tablet of 2 mg once daily during hospitalisation, and no longer than 14 days.

≥ 9 years – 1 tablet of 4 mg once daily, no longer than 14 days.

Contraindications for treatment include renal failure, hepatic failure, lymphopenia of < 200 cells/µl and neutropenia of < 500 cells/µl:

- **Tocilizumab** (RoActemra) – IL-6 inhibitor. The agent is used in children with COVID-19-related cytokine storm* [2, 26, 27] (Table 2).

Insufficient evidence exists confirming the efficacy of tocilizumab in children hospitalised for COVID-19 or with MIS-C associated with SARS-CoV-2 infection. Therefore, the decision should be made individually, always considering the benefits and possible risk of complications.

Tocilizumab is used in children over the age of 3 years. The medicine is applied once in a 60-minute IV infusion. A second dose may be given if no improvement occurs (after 8–12 hours). The dosage depends on the child's BW:

- < 3 0 kg: 12 mg/kg,
- ≥ 30 kg: 8 mg/kg (maximum 800 mg) (Table 3).

The use of medicines against COVID-19 requires a detailed analysis of the indications for use, potential adverse effects and possible interactions [28, 29]. The management recommendations are updated according to the latest knowledge as new scientific reports become available, which is incredibly dynamic. Therefore, the presented recommendations are current as of the day of submitting the article to the editor. The reader is asked to follow the changes and always read the summary of product characteristics before using the medicine.

CONCLUSIONS

In children with suspected or diagnosed COVID-19 and mild symptoms, the management is focused on preventing disease spread to other persons (i.e. isolation), monitoring the clinical status and supportive care provided in home settings.

TABLE 2. Criteria for high risk of the occurrence of cytokine storm in children

IL-6 level ≥ 3 × upper normal limit
Ferritin level > 300 µg/l, two-fold increase within 24 hours
Ferritin > 600 µg/l at baseline or LDH > 250 U/l
D-dimers > upper normal limit

The symptomatic treatment of COVID-19 does not differ from that used in other upper respiratory tract or gastrointestinal infections.

Most children with mild or moderate COVID-19 will not develop severe disease and thus should only receive a symptomatic treatment (AIII). The risk and benefits resulting from the causative treatment should be assessed based on the disease severity, age and risk factors.

Appropriate data are lacking on the treatment of children with COVID-19. Therefore, recommendations are based on results and data concerning safety among adults and the estimated risk for progression of the disease in a child.

Antiviral therapy should be considered individually depending on the clinical course of the disease and risk factors increasing the risk for COVID-19 progression. Medications used in a medical experiment require the ethics committee's approval*.

Children with severe COVID-19 require hospitalisation in a facility equipped with an ICU and antiviral treatment, which should be initiated not later than up to day 5–7 from the onset of symptoms.

*The off-label administration requires the written consent of the legal representative (parents and caregivers) and consultation with an expert. We recommend obtaining the approval of the local ethics committee, which may cover the use of the medication in a defined group of patients. Centres wishing to conduct experimental treatment in clinical trial settings should always seek approval of the ethics committee based on point 37 (Unproven Interventions in Clinical Practice) of the Declaration of Helsinki published in 1964 by the World Medical Association as amended [30]. Grading of recommendations assessment, development and evaluation: A – strong, B – moderate, C – optional

Levels of evidence:

I – ≥ 1 randomised trials without significant limitations,
IIa – other trials with randomisation or subgroup analyses of randomised trials,
IIb – non-randomised or observational cohort studies,
III – expert opinion.

DISCLOSURE

The authors declare no conflict of interest.

TABLE 3. Management of a child with COVID-19 according to the clinical condition and comorbidities

Clinical condition	Examinations/tests	Management
Outpatient care		
1a. Asymptomatic child not at risk of severe COVID-19	Online consultation with PC physician	Adequate hydration status – patient's daily fluid intake needs to be covered Body temperature measurement If symptoms occur, a medical visit is necessary
1b. Asymptomatic child at risk of severe COVID-19	Examination by a PC physician Always consider referral to the hospital	Observation in an outpatient setting In case of symptom onset, treatment is carried out in the hospital
2a. Child without risk factors, with scarce symptoms of upper respiratory tract infection, $SpO_2 \geq 94\%$, or scarce symptoms of gastroenteritis	Examination by a PC physician, including oxygen saturation measurement	Symptomatic treatment Consider inhaled corticosteroids Steroids should not be discontinued in a child previously treated with those medications for an underlying condition Empirical (oral) antibiotic therapy on an individual basis according to generally applicable recommendations
2b. Child with scarce symptoms at risk of severe COVID-19, $SpO_2 \geq 94\%$	Referral to hospital with places for children with COVID-19 A child with comorbidities, chronically treated, should be referred to a hospital or department providing ongoing care for the child	
3a. Stable form with respiratory and/or systemic symptoms, $SpO_2 \geq 94\%$, in a child without risk factors for severe COVID-19	Examination by a PC physician, including oxygen saturation measurement	Outpatient treatment as in 2a or referral to hospital – at physician's decision after examination of the child
Hospitalisation		
1b and 2b, especially immunosuppression,active cancer treatment, obesity (BMI ≥ 120% of the value corresponding with the 95th percentile), chronic respiratory diseases, dependent on medical equipment	2b. Examinations on an individual basis	Sotrovimab or Casirivimab with imdevimab (especially in adolescents aged >16 years, if infected with a variant other than Omicron) or For children in group 2b: symptomatic treatment, and in case of additional infections, management according to the principles of Good Medical Practice, and If monoclonal antibodies cannot be given Remdesivir for 3 days (in patients in group 2b) or Molnupiravir (from age 18 years) or Nirmatrelvir with ritonavir (from age 12 years)
3a. Stable form $SpO_2 \geq 94\%$ in a child without risk factors for severe COVID-19	Laboratory tests: CBC with smear, urea, creatinine, eGFR, glucose, Na, K, CRP, PCT, IL-6, D-dimers, fibrinogen General urinalysis Imaging examination • Chest X-ray, ultrasound • CT (when indicated) Diagnosis of other respiratory tract infections: influenza, RSV, multiplex (when possible)	Symptomatic treatment (correct hydration, antipyretics) Empirical antibiotic therapy on an individual basis Inhaled corticosteroids as indicated Thromboprophylaxis as indicated
3b. Stable form $SpO_2 \geq 94\%$ in a child with risk factors for severe COVID-19	Laboratory tests and imaging examinations as in 3a	Symptomatic treatment Empirical antibiotic therapy as indicated Inhaled corticosteroids as indicated Thromboprophylaxis as indicated Adolescents aged ≥ 12 years – monoclonal antibodies: sotrovimab or casirivimab with imdevimab Antiviral medications in children where monoclonal antibodies are not possible: • Remdesivir for 3 days (to be considered in children aged < 12 years) • Paxlovid (as in 2b)

TABLE 3. Cont.

Clinical condition	Examinations/tests	Management
4. Patient with SpO_2 < 94% requiring oxygen therapy, with normal oxygen saturation during oxygen supplementation	Laboratory tests and imaging examinations as in stable form + blood gas, LDH, ferritin Chest CT is recommended	Hospital with paediatric intensive care unit Standard oxygen therapy in the prone position Correct hydration Antibiotic therapy as indicated Thromboprophylaxis/therapy as indicated Dexamethasone (in patients treated with remdesivir) Remdesivir for 5 days IV, starting up to day 7 of symptom onset, dosage see text Eventually + baricitinib (when steroids are contraindicated) Tocilizumab – in cytokine storm*
5. Patient with respiratory failure, clinically unstable or critically ill	According to intensive care unit procedures	Intensive care unit Remdesivir* (up to 7 days after symptom onset) Tocilizumab* (in cytokine storm) Dexamethasone Management on an individual basis Antithrombotic therapy as indicated

BMI – body mass index, CBC – complete blood count, CT– computed tomography, PC – primary care

REFERENCES

1. Viner R, Mytton O, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pediatr 2021; 175: 143-156.
2. Parsons S, Sass L. Children's Hospital of the King's Daughters (CHKD) Treatment Guideline for COVID-19 in Children. Available from: https://www.chkd.org/uploadedFiles/Documents/COVID-19/CHKD%20COVID%2019%20treatment%20guideline.pdf (lastly accessed 20 March 2020).
3. Flisiak R, Parczewski M, Horban A, et al. Zalecenia diagnostyki i terapii zakażeń SARS-CoV-2 Polskiego Towarzystwa Epidemiologów i Lekarzy Chorób Zakaźnych 12 listopada 2021 roku. Aneks 1 do rekomendacji z 26 kwietnia 2021 roku. Available from: http://www.pteilchz.org.pl/wp-content/uploads/2020/10/Aneks-1-do-Rekomendacji-PTEiLChZ-26-04-2021-pl.pdf (lastly accessed 24 January 2022).
4. Charakterystyka Produktu Leczniczego COMIRNATY. Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_pl.pdf.
5. Available from: https://www.gov.pl/web/szczepimysie/trzecia-dawka.
6. Charakterystyka Produktu Leczniczego SPIKEVAX. Available from: https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_pl.pdf.
7. Kwestionariusz wstępnego wywiadu przesiewowego przed szczepieniem dziecka w wieku 5–11 lat przeciw COVID-19. Available from: https://pacjent.gov.pl/sites/default/files/2021-12/kwestionariusz%20logo%20grupa%205-11%20lat_9.12.21%20na%20stron%C4%99.pdf.
8. Charakterystyka Produktu Leczniczego Ronapreve. Available from: https://www.ema.europa.eu/en/documents/product-information/ronapreve-epar-product-information_pl.pdf.
9. Available from: https://www.covid19treatmentguidelines.nih.gov/ (lastly accessed 31 January 2022).
10. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-evusheld-for-prep/ (lastly accessed 31 January 2022).
11. Drain PK. Rapid diagnostic testing for SARS-CoV-2. N Engl J Med 2022; 386: 264-272.
12. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization rates and characteristics of children aged < 18 years hospitalized with laboratory-confirmed COVID-19 – COVID-NET, 14 States, March 1 – 25 July 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1081-1088.
13. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: a systematic review. EClinicalMedicine 2020; 24: 100433.
14. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc 2020; 9: 701-715.
15. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. J Pediatric Infect Dis Soc 2021; 10: 34-48.
16. Koletsi P, Antoniadi M, Mermiri D, et al. A toddler diagnosed with severe postinfectious bronchiolitis obliterans and COVID-19 infection. Pediatr Pulmonol 2021; 56: 2381-2384.
17. Andre N, Rouger-Gaudichon J, Brethon B, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: high risk of severe forms? Pediatr Blood Cancer 2020; 67: e28392.
18. Paxlovid – Summary of Product Characteristics. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid/summary-of-product-characteristics-for-paxlovid.
19. Paret M, Lighter J, Pellett Madan R, et al. SARS-CoV-2 infection (COVID-19) in febrile infants without respiratory distress. Clin Infect Dis 2020; 71: 2243-2245.
20. Available from: https://www.ema.europa.eu/en/documents/product-information/xevudy-epar-product-information_pl.pdf.
21. FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalised pediatric patients weighing 3.5 kg to < 40 kg or < 12 lat and ≥3.5 kg. Available from: https://www.fda.gov/media/137566/download.
22. US Food and Drug Administration. FDA News Release. COVID-19 Update: FDA broadens emergency use authorisation for Veklury (remdesivir) to include all hospitalised patients for treatment of COVID-19. Available from: https://www.fda.gov/news-events/press-announcements/covid-19-update-fda-broadens-emergency-

use-authorization-veklury-remdesivir-include-all-hospitalized (lastly accessed 1 September 2020).
23. Ranjbar K, Moghadami M, Mirahmadizadeh A, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalised COVID-19 patients: a triple-blinded randomised controlled trial. BMC Infect Dis 2021; 21: 337-344.
24. Food and Drug Administration. Letter of authorisation: EUA for baricitinib (Olumiant), in combination with remdesivir (Veklury), for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19). Available from: https://www.fda.gov/media/143822/download.
25. FDA broadens existing emergency use of Lilly and Incyte's baricitinib in patients hospitalised with COVID-19 requiring oxygen. Availably from: https://investor.lilly.com/news-releases/news-release-details/fda-broadens-existing-emergency-use-lilly-and-incytes.
26. Charakterystyka Produktu Leczniczego RoActemra. Available from: https://www.roche.pl/content/dam/rochexx/roche-pl/roche_poland_rwd/pl_PL/documents/SmPC/roactemra_koncentrat.pdf.
27. Tocilizumab (Actemra) [package insert]. Food and Drug Administration. 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf.
28. Liverpool Drug Interaction Group. Detailed recommendations for interactions with experimental COVID-19 therapies. Available from: http://www.covid19-druginteractions.org/ (lastly accessed 31 January 2022).
29. Liverpool Drug Interaction Group. Administration in cases of swallowing difficulties. Available from: http://www.covid19-druginteractions.org/ Updated 01/17/2022 (lastly accessed 31 January 2022).
30. Deklaracja Helsińska Światowego Stowarzyszenia Lekarzy (WMA1). Etyczne zasady prowadzenia badań medycznych z udziałem ludzi. Przyjęta przez 18. Zgromadzenie Ogólne Światowego Stowarzyszenia Lekarzy (WMA), Helsinki, Finlandia, czerwiec 1964 r., z późniejszymi zmianami.