

Steckbrief COVID-19 – Clinical characteristics in children and adolescents

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<http://www.kinderkliniken.insel.ch/de/coronavirus/>

Causative agent	SARS-CoV-2 ¹ (betacoronavirus, most closely related to SARS-CoV among the 7 human coronaviruses)
Receptor	<ul style="list-style-type: none"> • Angiotensin-Converting Enzyme 2 (ACE2 receptor)² • ACE2 mainly expressed in lung, intestinal, renal and vascular tissues³, but also in oral mucosa [Xu] • nasal ACE2 expression correlates positively with age, being lowest at <10 years of age⁴
Immunology/ Pathogenesis	<ul style="list-style-type: none"> • Current hypotheses explaining apparent disease mitigation in children and “trained innate immunity” are summarized⁵⁻⁷ • Pathogenesis of putative “Pediatric Inflammatory Syndrome temporally-associated with SARS-CoV-2 (PIMS-TS)” currently unknown, likely to involve immune dysregulation during subacute phase of mild COVID-19 disease⁸ • severe disease associated with cytokine storm similar to MAS/secondary HLH⁹ • convalescent sera contain neutralizing antibodies against the S1/S2 spike protein; titers correlate positively with age (adults) [Wu] • protective role of reduced cellular expression⁴ or higher circulating ACE2 levels in children¹⁰ and of “trained innate immunity”?¹¹
Transmission	<ul style="list-style-type: none"> • droplet; contact $\frac{1}{2}$ life in aerosol ~1 hour, $\frac{1}{2}$ life on plastic/steel 6-8 hours^{12,13}; detected also in patient rooms [Chia], clinical significance unknown • viral transmission can start 1-2 days before the onset of symptoms («serial interval» < incubation period^{14,15}; recovery of virus from NPA before onset of symptoms^{16,17} • viral RNA in NPA from children until <u>6 to >22</u> days after disease onset¹⁸⁻²¹ • viral RNA in feces from day <u>~5 to > 4 weeks</u> after disease onset^{19,21-25} • viral load and duration of shedding do not correlate with severity of COVID-19^{20,21,26} • Infectious virus (culture positive) in NPA correlates positively with RNA copy number²⁷[L’Huillier] • <u>vertical transmission: no RT-PCR positive cases reported</u>; 2 reports on the presence of IgM in neonates to be interpreted with caution^{28,29} • SARS-CoV-2 RNA detected in milk of an infected mother and her newborn infant³⁰
Incubation period	<ul style="list-style-type: none"> • 4-6 days (range, 1 to >14 days) • presymptomatic transmissibility 1-2 days • relapse or reinfection? Recurrent symptoms and shedding of RNA 1 month after primary infection reported in a pediatric case³¹

<p>Epidemiology</p>	<ul style="list-style-type: none"> • basic reproduction rate R_0 2.2 (90% CI, 1.4-3.8)^{32,33} • high risk for «superspreader events» (dispersion parameter k_d)³³ • Switzerland: age <10 years, 0.4%; age 10-19 years, 2.6% of all cases • Sweden: age <10 years, 0.5%; age 10-19 years 1.3% of all cases • Germany: survey on hospitalized children infected with SARS-CoV-2 • Spain: 0.8% of COVID-19 positive persons were <18 years of age³⁴ • transmission to children mainly within families^{19,20,23,34-36} • studies suggest that subclinical infection rather than resistance to infection is the major factor explaining low case numbers in children [Bi, Davies] • children unlikely to be index cases in household transmission (Zhu) • population screening data from Iceland³⁷ and Italy with no infections among <10-year-old vs. 0.8-2.6%³⁸ in older individuals
<p>Clinical manifestations</p>	<ul style="list-style-type: none"> • common: asymptomatic^{24,39,40} • common: fever <u>~40%</u>^{19,20,35,36,39,41-44}; 54% in Italian series⁴⁵ • common: cough <u>~50%</u>^{19,20,36,39,43-45} • common: pharyngitis <u>~40%</u>³⁶ • common: mild diarrhea^{19,23,40,41} • <u>infrequent</u>: rhinorrhea^{36,44,45}, <u>wheezing</u>^{19,20,35,40,41,43} • infrequent: malaise, headache, myalgias • olfactory dysfunction very common in adults^{46,47} • conjunctivitis (RT-PCR positive) reported in adults⁴⁸ • “COVID toe”: painful, vasculitic, frost-bite like finger/toe lesions in often otherwise asymptomatic children reported (Spain⁴⁹, Italy⁵⁰, US) • varicella-like papulovesicular rash reported in adults and children in Italy^{51,52} • Erythema multiforme⁵³ • Pediatric Inflammatory Multisystem Syndrome (PIMS-TS)⁵⁴ resembling toxic shock syndrome/Kawasaki disease (KD). Clusters reported in several countries (UK^{55,56}, Italy⁵⁷, France [Toubiana], Spain, Switzerland⁵⁸, Italy, US⁵⁹⁻⁶¹); SARS-CoV-2 PCR in NPA positive or negative; serology positive; case definition reported in UK and Germany • classic KD in SARS-CoV-2 positive patients reported⁶² • pre-COVID classic KD without cross-reactive SARS-CoV-2 antibodies [Chang] • co-infections in up to 50% of pediatric cases in China (most commonly <i>M. pneumoniae</i>)^{34,39,44,63}
<p>Laboratory findings</p>	<p><u>CBC differential, CRP, chemistry uncharacteristic in mild cases</u>^{24,36,44,45,64}</p> <ul style="list-style-type: none"> • leucopenia, lymphopenia and thrombocytopenia uncommon^{19,20,45,64} • CRP/PCT normal to moderately elevated^{19,36,39,43-45,65} • PIMS-TS: WBC↑, lympho↓, CRP↑↑, PCT↑↑, IL-6↑↑, Ferritin↑↑, NT-proBNP↑↑^{55,57} [Toubiana]

Diagnosis	<ul style="list-style-type: none"> • RT-PCR from NPA; some laboratories offer quantitative copy number • RT-PCR in NPA less sensitive than BAL/sputum in adults⁶⁶ • IgM/IgA appear on day ~5 of illness, IgG on day ~14^{17,67} • First NPA rapid antigen test approved by FDA, performance to be established • Serologic tests available, role in clinical practice to be determined
Radiology	<ul style="list-style-type: none"> • conventional CXR: normal or non-specific findings • chest CT: unilateral or bilateral, uni- or multifocal, peripheral, commonly subpleural lesions; focal lesions typically with central consolidation and halo sign or ground glass opacities (GGOs)^{20,36,39,43,44,68} • <u>no</u> pleural effusion^{39,68} • <u>no</u> hilar lymphadenopathy^{39,68}
Clinical course	<ul style="list-style-type: none"> • common: asymptomatic (reported all ages)^{18-20,35} • common: upper respiratory tract infection (children and healthy adults)^{19,36,45} • common: pneumonia (absent, mild or moderate clinical disease)^{36,39,43,69,70} • very rare: severe lung disease requiring mechanical ventilation (3/171 [1.8%] reported by Lu³⁶, 2 infants reported in detail⁴⁴)^{23,36,43,45} • several fatal cases in SARS-CoV-2 positive infants and children reported^{36,71}; several deaths associated with pediatric multisystem inflammatory syndrome recently reported⁵⁵ • infants < 1 year of age are overrepresented among hospitalized children with COVID-19 in China⁴⁰, Spain³⁴, US⁷², Italy⁷³, Germany
Clinical course – co-morbidities	<ul style="list-style-type: none"> • no specific pediatric risk factors identified to date • PICU admissions more common in children with co-morbidity⁷⁴ • Role of ethnicity and obesity as risk factor for PIMS-TS currently debated^{55,74-76} [Toubiana]
Clinical course - immunodeficiency	<ul style="list-style-type: none"> • <u>Primary immunodeficiency (PID)</u>: severe disease appears to be rare, no deaths among patients with PID reported to IPOP • mild disease reported in XLA (Bruton)⁷⁷ • <u>Cancer</u>: Accumulating evidence indicating <u>low risk</u> of severe disease in pediatric cancer patients in Italy, Spain⁷⁸, France², Switzerland, US⁷⁹ • <u>Transplant patients</u>: No evidence for severe disease among solid organ transplant recipients^{80,81} • <u>Autoimmune disease</u>: Benign course in 8 children with IBD on immunomodulators/biologicals reported⁷⁰
Clinical course - pregnancy	<ul style="list-style-type: none"> • infections reported mainly in 3rd trimester; characteristic complications have not been reported to date^{82,83} • no virologically confirmed evidence for vertical transmission and fetal infection⁸³⁻⁸⁶; 2 reports on IgM positive neonates to be interpreted with caution^{28,29}
Clinical course - neonates	<ul style="list-style-type: none"> • asymptomatic infection in neonates (including normal chest CT) has been reported^{23,39,84} • 3 infected neonates reported with early and short viral RNA shedding (DOL #2+4 only)⁸⁷ • complicated perinatal/postnatal courses among non-infected neonates of COVID-19 infected mothers have been reported⁸⁸

Treatment	<ul style="list-style-type: none"> • supportive • drugs with antiviral activity against SARS-CoV-2 in vitro: remdesivir (nucleoside analog)^{89,90}, lopinavir/ritonavir⁹⁰, hydroxychloroquine⁹¹ • Remdesivir reported effective in adults (randomized, placebo-controlled US trial) • Remdesivir recommended first line agent in children with severe disease⁹² • Lopinavir/ritonavir reported ineffective in one controlled trial⁹³ • immunomodulation with mAbs, e.g. tocilizumab⁹⁴, siltuximab (anti-IL6) may be effective in treating cytokine storm • ACE2/viral entry blocker (e.g., Nafamostat) effective in vitro^{95,96} • recommendations against use of NSAID are NOT supported by the EMA, WHO, expert opinion⁹⁷
Prevention	<ul style="list-style-type: none"> • Inpatients: precautions according to Swissnoso/PIGS • Outpatients: precautions according to BAG, KAZA • Neonates: no separation of well mother/child pairs needed (Swissnoso/PIGS, SGGG, WHO, DGPI, AAP); management IMC/NICU according to local infection control policy • BCG vaccine: protective effect currently debated⁶ • Dramatic decrease in pediatric ER visits⁹⁸ an increase in deaths unrelated to COVID-19^{99,100} • Decrease in incidence of fractures associated with lockdown¹⁰¹ • Phase 1 study using 1 dose of an Ad5-vectored vaccine induces neutralizing antibodies and T-cell response in adults¹⁰² • Quick graphical summary of vaccines under development [Galloway]

Team Kinderinfektiologie (Pediatric Infectious Disease)

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