

The Impact of Severe Acute Respiratory Syndrome Coronavirus Type 2 on children with liver diseases: A Joint European Society for Pediatric Gastroenterology, Hepatology and Nutrition and Society of Pediatric Liver Transplantation Position Paper

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ABSTRACT

Children are seldom affected by severe forms of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2) infection. However, the impact of comorbidities in the clinical presentation and outcome of SARS-CoV2 in children is poorly characterized including that of chronic liver disease (CLD) and those taking immunosuppressive medications for autoimmune liver disease or following liver transplantation (LT). Although not the main target organ, a spectrum of liver involvement has been described in children infected with SARS-CoV2 and those presenting with Multisystem Inflammatory Syndrome in Children (MIS-C). The Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the Society of Pediatric Liver Transplantation (SPLIT) present an evidence-based position paper on liver involvement in children with SARS-CoV2 infection and its impact on those with CLD as well as LT recipients. All children may exhibit acute liver injury from SARS-CoV2 infection, and those with CLD and may experience hepatic decompensation. Preventative and therapeutic measures are discussed.

Keywords: SARS-CoV2; COVID-19; liver transplantation; autoimmune hepatitis; autoimmune liver disease; immunosuppression; MIS-C; PIMS-TS; Multisystem Inflammatory Syndrome in Children.

What is known

- Coronavirus disease 2019 (COVID-19) has challenged the healthcare systems and made difficult the access to care of children with chronic liver conditions.
- There is concern that children with chronic liver disease, or immunosuppressed for autoimmune liver disease or liver transplant, can be at higher risk from COVID-19.

What is new

- Children with chronic liver disease are at higher risk of developing severe COVID-19 and can experience decompensation of end stage liver disease during SARS-CoV2 infection.
- Routine discontinuation of immunosuppressive medications is not advised for liver transplanted children or those with autoimmune liver disease, owing to the absence of evidence of a greater risk from COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2)-associated liver injury is defined as the spectrum of liver damage that occurs during infection and disease, or correlated with coronavirus disease 2019 (COVID-19) treatment, with or without pre-existing liver disease^(1, 2). SARS-CoV2 may cause liver injury with multiple mechanisms. Viral entry into hepatocytes and cholangiocytes allows direct cytopathic effects from active replication⁽³⁾. Immune-mediated liver injury following the inflammatory response, hypoxic and vascular insults, and anti-SARS-CoV2 treatments are thought to be other means of damage^(4, 5). In adults, the role of a preexisting liver disease in magnifying SARS-CoV2-associated liver injury is well documented⁽⁶⁾. Uncertainties still exist regarding whether children with chronic liver disease (CLD) or those on immunomodulatory and immunosuppressive treatments for liver conditions have an additional clinical risk of severe SARS-CoV2 infection. This document focuses on the impact of SARS-CoV2 infection on children with CLD, including those with end-stage liver disease, liver transplant (LT) recipients and pre-transplant candidates.

Objectives

- To formulate evidence-based position statements using current knowledge of clinical and therapeutic management of acute liver injury during SARS-CoV2 infection, including COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C);
- To formulate evidence-based position statements using current knowledge for the clinical and therapeutic management of SARS-CoV2 infection in children with CLD (including children with autoimmune liver disease maintained on immunosuppressive, immunomodulator, or biologic therapies) and in children after LT.

Methods

The Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the Society of Pediatric Liver Transplantation (SPLIT) sponsored this manuscript. A working group consisting of selected ESPGHAN members (G.I., E.N., and P.C.) and SPLIT members (M.Ma., N.E., M.K., S.L., M.Mi., V.N.) drafted this position paper. Representatives of the respective societies reviewed and approved the manuscript.

Relevant clinical questions were formulated (Table 1) by the leads of the working group (G.I., M.Ma.) and agreed upon by the other members. Relative position statements intended to answer the questions were based on available evidence from selected key publications cited in PubMed (www.ncbi.nlm.nih.gov/pubmed) and Embase (www.embase.com/#search) from inception to May 1, 2021. The following search words were used “severe acute respiratory syndrome coronavirus type 2”, “SARS-CoV-2”, “SARS-CoV2”, “coronavirus disease 2019”, “COVID-19”, “multisystem inflammatory syndrome in children”, “MIS-C”, “PIMS”, “acute liver injury”, “immunosuppressive agents”, “liver transplantation”, “immunosuppression”, “chronic liver disease”, “infant”, “child” and “adolescent”, “vaccine”. Fundamental characteristics of the abstracts judged pertinent to the review were noted and full-length articles or reviews were selected from the abstracts. Citations were

chosen based on their relevance to the context. Due to the paucity of well-characterized pediatric data, relevant adult studies and guidelines were evaluated, and extrapolations from adult literature were included where cited in the manuscript.

Consensus and voting

A consensus was formally achieved utilizing a structured quantitative method. The working group members voted on each recommendation using a 4-point scale (1: completely disagree; 2: disagree; 3: agree; 4: completely agree), and votes are reported for each recommendation. It was decided in advance that consensus was reached if >75% of the working group members voted 3 or 4. Consensus agreement was achieved for all questions.

I. Epidemiology and clinical features of SARS-CoV2 infection: relevance to pediatric hepatology

A. Clinical burden of SARS-CoV2 in children

As of July 2021, the World Health Organization (WHO) has confirmed 182,000,000 cases of COVID-19 worldwide, including 3,950,000 deaths, now tempered by the administration of 2,900,000,000 vaccine doses ⁽⁷⁾. The exact burden in children is poorly known. Once infected, up to 50% of children remain asymptomatic. Cough and/or fever are the most common presenting symptoms in children ⁽⁹⁾. Fatigue, headache, myalgia, nasal congestion, rhinorrhea, loss of taste or smell, sore throat, dyspnea, abdominal pain, diarrhea, nausea/vomiting, and poor appetite are also observed. In children with chronic disease of the native liver, 50% presented with respiratory symptoms, 47% with fever and 18% were asymptomatic. In children with LT, 36% presented with respiratory symptoms, followed by 34% with fever and 27% were asymptomatic ⁽⁸⁾. The clinical presentation of MIS-C can be severe, including hypotension and shock, while other symptoms include fever, abdominal pain, vomiting, diarrhea, skin rash and mucocutaneous lesions ⁽⁹⁾. Compared to adults, children are at lower risk of hospitalization and death from SARS-CoV2 infection, and are less likely to develop severe disease requiring intensive care unit (ICU) management, mechanical ventilation, and vasopressor support. ⁽¹⁰⁾ Compared to LT recipients, children with CLD (including children with end-stage liver disease) are more likely to be hospitalized and require intensive care ⁽⁸⁾.

B. Pathophysiology of the SARS-CoV2-related systemic and hepatic injury

SARS-CoV2 infects cells via the angiotensin-converting enzyme 2 (ACE2) and CD147 receptors, and exploits the cleavage of the viral S glycoprotein by the host transmembrane protease serum 2 (TMPRSS2). The virus primarily targets lung cells, undergoing intracellular replication. An innate immune response is triggered, releasing cytokines that promote a SARS-CoV2 specific T and B cell response. In some cases, the overproduction of cytokines can lead to severe lung inflammation, multi-organ failure, and death ^(11, 12). A reduced expression of the SARS-CoV2 receptors in respiratory epithelia, a lower threshold of interferon (IFN) antiviral response, a better monocyte/macrophage functioning, and other specific means of viral tolerance could explain the good outcomes generally displayed in childhood infection compared to adults ⁽¹³⁻¹⁵⁾.

ACE2, TMPRSS2 and CD147 are also present on hepatocytes and cholangiocytes, and ACE2 expression is increased in fibrotic and cirrhotic livers^(16, 17). Along with the over-expression of pro-inflammatory cytokines, infected hepatocytes downregulate key metabolic processes, accounting, at least in part, for the histological and biochemical features of the SARS-CoV2 liver involvement⁽¹⁸⁾. Cytopathic effects are also mediated by SARS-CoV2-induced hepatocyte mitochondrial dysfunction and impaired autophagy^(19, 20). Indirect means of SARS-CoV2-related liver injury are thought to be the systemic inflammatory IL-6 and IL-10 cytokine milieu⁽²¹⁾, hypoxic-ischemic damage, vascular endothelial changes⁽²²⁾, and drug-induced liver injury from SARS-CoV2 directed therapies^(23, 24). Figure 1 summarizes the influence of CLD on the pathophysiology of COVID-19, and the mechanisms of acute liver injury (ALI).

C. Psychosocial burden of SARS-CoV2 and health equity

COVID-19 has further revealed global health inequities with differential access to testing, medical care, therapeutics, and vaccination further driven by structural and systemic racism. In the United Kingdom, Black and South Asian individuals and in the United States, Black, Hispanic, and Native American individuals have disproportionately higher rates of diagnosis, hospitalization, and mortality than white individuals⁽²⁵⁾. To prevent the ongoing disproportionate risk of mortality, equitable distribution of COVID-19 vaccination is critical and a global ethical imperative. Children, especially those with the least access to resources, remain deeply impacted from the pandemic with reduced access to healthcare, vaccinations and school, with rising food insecurity⁽²⁶⁾. Social isolation has led to increasing rates of depression, anxiety and suicidal ideation in children and adolescents^(27, 28).

II. **Diagnosis, management strategies and monitoring in children with SARS-CoV2 infection with chronic liver diseases or following liver transplantation**

A. General management of children with CLD or LT recipients with acute SARS-CoV2 infection

The general management of SARS-CoV2 infection in children with CLD or LT recipients does not differ from that of healthy children. Initial efforts should be focused on infection prevention through infection control measures. Infected children should be isolated to contain virus transmission in the hospital, community facility, or home. The decision on whether to admit a child with SARS-CoV2 infection depends on the clinical presentation, stratification of other potential risk factors (including time from LT, degree of immunosuppression and/or other co-morbid conditions) and on the feasibility of caring for the child at home. Four illness severity categories (mild, moderate, severe, and critical) have been described⁽²⁹⁻³¹⁾. Mild or moderate SARS-CoV2 infection (without or with clinical signs of non-severe pneumonia, respectively) should be managed with supportive care only. Severe pneumonia (tachypnea, and hypoxia) and critical (acute respiratory distress syndrome, sepsis, and septic shock) SARS-CoV2 infection requires treatment with antivirals and glucocorticoid steroids together with respiratory and hemodynamic support. Antimicrobials should not be administered unless there is clinical suspicion of superimposed opportunistic infection. In hospitalized children, the clinical condition will guide the intensity of monitoring by routine blood sampling,

including liver function tests, blood gas analysis, serum inflammatory markers, blood/urine/sputum cultures, urinalysis, and serial chest radiologic imaging.

B. Diagnostic testing

Recommendations for SARS-CoV2 testing have been developed by major national and international health agencies and apply to both children with and without underlying liver disease⁽³²⁻³⁴⁾. The diagnosis of acute SARS-CoV2 infection relies on viral testing by molecular analysis of nucleic acid amplification, polymerase chain reaction (PCR), or antigen detection from nasal, nasopharyngeal, or oropharyngeal samples^(34, 35). Molecular assays (nucleic acid amplification and PCR) have emerged as the “gold standard” for testing a child for acute SARS-CoV2 infection⁽³⁶⁾. Sensitivity of antigen tests is generally lower than that of nucleic acid amplification assays, and more time-dependent. However, antigen tests have low cost and some are approved for point-of-care use delivering rapid results. The advantages of antigen tests need to be balanced against lower sensitivity, especially among asymptomatic individuals and in children. In children with mild respiratory symptoms, the sensitivity of the nasopharyngeal antigen test was 45-62% compared with 83% in adults⁽³⁷⁻³⁹⁾. Confirmatory testing with a nucleic acid amplification test should be considered after negative antigen test results in symptomatic individuals and after positive antigen test results in asymptomatic individuals⁽⁴⁰⁾.

Serologic assays for SARS-CoV2 infection demonstrating antibodies against SARS-CoV2 in serum are not recommended for the diagnosis of acute infection. Serologic assays may be used together with viral detection tests in the clinical assessment of individuals presenting late in their course and specifically, for children suspected to have MIS-C. Antibody testing is essential for surveillance, epidemiological studies, and determining whether the tested individual was previously infected⁽⁴¹⁾.

Statement:

1. *The diagnostic approach and the general management strategies of children with SARS-CoV2 infection do not differ between those with and without CLD or those who have undergone LT.*

(Agreement: 4/4/4/4/4/4/4/4)

III. Acute liver injury and implications for chronic liver conditions

A. SARS-CoV2 infection

SARS-CoV2 infection has been associated with ALI with varying degrees of severity. In children, as in adults, most patients have mild-to-moderate ALI (transaminases < 2 to 2-5 times the upper limit of normal), and the severity of liver involvement parallels the seriousness of SARS-CoV2 infection in general⁽⁴²⁻⁴⁴⁾. More severe liver injury, characterized as transaminases > 5 times the upper limit of normal, is seen in the setting of shock, hypoxia/respiratory compromise, longer overall hospital length of stay, and higher serum inflammatory markers. Liver injury may be due to direct viral cytotoxic effects or indirect injury secondary to cytokine-mediated global inflammatory responses and ischemia^(45, 46). The presence of ACE2 receptors in biliary and liver epithelial cells predispose the liver to potential targeting by SARS-CoV2 infection. Cholestatic jaundice has been described in

adolescents as a possible presentation of SARS-CoV2 infection⁽⁴⁷⁾. Additional liver injury may result from drug-induced liver injury from SARS-CoV2 directed therapies⁽⁴⁸⁾. Severe SARS-CoV2 infection with ALI may be challenging to differentiate from MIS-C, a multisystem inflammatory condition that may include significant liver injury described in detail below⁽⁴⁹⁾.

Statement:

2. *SARS-CoV2 infection causes ALI of varying degrees to patients with and without underlying liver disease by multiple potential mechanisms.*

(Agreement: 4/4/4/4/4/4/4/3)

B. MIS-C

MIS-C (or PIMS-TS, Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV2) is a rare but severe late complication described in children associated with previous or ongoing SARS-CoV2 infection⁽⁵⁰⁻⁵³⁾. Unlike severe pediatric COVID-19, the syndrome mainly affects children without comorbidities⁽⁵⁴⁾. It is defined by the presence of prolonged fever and elevated inflammatory markers, coagulopathy, acute gastrointestinal involvement, evidence of previous or ongoing SARS-CoV2 infection, associated with two of the following: *i*) mucocutaneous inflammatory involvement; *ii*) hypotension or shock; *iii*) clinical, laboratory or echocardiographic features of myocardial dysfunction⁽⁵⁵⁾. Liver involvement in COVID-19 and MIS-C are distinct entities⁽⁵⁶⁾. In MIS-C, the injury is usually limited to modest increases in serum transaminases; however, ALF has been described in critically ill children with MIS-C with multi-organ failure⁽⁴³⁾. Elevated transaminases occur in 24-83% of patients with MIS-C^(43, 49, 57-63), usually in the early phase of the syndrome. Notably, half of patients with MIS-C reported persistently elevated liver enzymes one month after discharge⁽⁴³⁾. Cantor et al. retrospectively assessed liver involvement in children with MIS-C and found that 43% had elevated transaminases⁽⁴³⁾. Patients with elevated transaminases had lower albumin levels but similar prothrombin time compared to patients without liver injury, and exhibited more severe cardiovascular involvement, higher rates of shock at presentation, greater respiratory support requirement and longer hospitalization times. A trend towards higher body mass index (BMI) was observed in children with MIS-C and elevated transaminases⁽⁴³⁾.

Statement:

3. *Children diagnosed with MIS-C can have acute liver injury with elevated liver enzymes that is most commonly self-limited, though ALF has also been reported.*

(Agreement: 4/4/4/4/4/4/4/3)

C. Children with underlying CLD

Patients with CLD represent a vulnerable population with a theoretically increased risk of infection and/or severe COVID-19⁽⁶⁴⁾. Initial reports suggested that CLD was associated with increased disease severity⁽⁶⁵⁻⁶⁷⁾, although subsequent analyses have challenged this conclusion⁽⁶⁷⁻⁷⁰⁾. Severe COVID-19, however, is uncommon in children^(71, 72). In a multicenter cohort (2,780 patients from the United States, including children > 10 years),

patients with a preexisting liver disease had a higher risk of mortality (RR: 3.0; 95% CI: 1.5 – 6.0; $p = 0.001$), even after propensity matching for metabolic comorbid indicators (BMI, diabetes, hypertension); the risk was even higher for patients with cirrhosis (RR: 4.6; 95% CI: 2.6 – 8.3; $p < 0.001$)⁽⁷³⁾. However, there are insufficient data to draw definite conclusions in children. Metanalyses of the published literature in adults and children with SARS-CoV2 infection have identified several medical conditions correlated with higher disease severity and need for intensive care⁽⁷⁴⁾. Some of the factors identified include diabetes, hypertension, coronary artery and cardiovascular disease, chronic pulmonary disease, malignancy, chronic kidney disease, older age, and male gender; though the heterogeneity between studies varied substantially.

In a retrospective study, adult patients with NAFLD had a higher risk of COVID-19 disease progression (6.6% vs 44.7%; $p < 0.001$) and persistently abnormal liver function (70% vs 11.1%; $p < 0.001$) compared to patients without NAFLD⁽⁷⁵⁾. In another multicenter observational study on 363 adults, patients with NAFLD had significant higher rates of ICU admission (50.9% vs 35.2%; $p = 0.0095$) and need for mechanical ventilation (49.1% vs 30.4%; $p = 0.006$)⁽⁷⁶⁾.

Focusing on pediatrics, in a metaanalysis on 285,004 children with confirmed SARS-CoV2 infection, 9,353 (3.3%) had at least one underlying comorbidity, of which 5.4% were obese. Among 507 obese children, 64 had severe COVID-19 or required ICU admission, with a calculated risk of severity of 2.87 (95% CI 1.16 – 7.07)⁽⁷⁷⁾. Obesity and NAFLD are associated with increased production of pro-inflammatory cytokines like IL-6 or TNF- α by adipose cells and Kupffer cells⁽⁷⁸⁾. A dysregulated hepatic innate immunity may contribute to worse outcomes with SARS-CoV2 infection. Obesity is the most common comorbidity reported in children with severe SARS-CoV2 infection^(8, 79–81). Over half of children who require hospitalization for severe illness have an underlying medical condition, most commonly obesity^(8, 65, 81–83). Most children have mild clinical symptoms, though hepatic manifestations can be significant^(82, 84–88).

Since the proportion of NAFLD patients in published obese cohorts remains unknown, the question as to whether NAFLD is an independent risk factor of COVID-19 severity warrants further studies in children. Nevertheless, regarded adult data, children with NAFLD especially those with obesity, should be considered a risk group for severe COVID-19.

For children with end stage liver disease listed for LT, two patients developed new onset ascites in the setting of SARS-CoV2 infection and were reported to the International NASPGHAN/SPLIT registry. One child has subsequently been transplanted and the other child remains listed for transplantation at the time of writing⁽¹⁰⁾.

Statements:

4. *Children with end stage liver disease may experience hepatic decompensation during SARS-CoV2 infection.*

(Agreement: 4/4/4/4/4/4/4/3)

5. *Children with CLD, including obese patients with suspected or documented NAFLD, may be at higher risk of developing severe COVID-19.*

(Agreement: 4/4/4/4/4/4/3/3)

D. Acute liver failure

While ALI with preserved synthetic function is common in patients with SARS-CoV2 infection, ALF is rare with few cases reported in the literature^(89–94). Children surviving ALF without the requirement for LT have been reported⁽¹⁰⁾. Transcriptome analysis of liver tissue collected during autopsy of subjects who succumbed to severe COVID-19 revealed transcriptional shifts resulting in tissue remodeling, mitochondrial dysfunction and lower hepatic detoxification resulting in the clinically observed liver injury and dysfunction⁽⁹⁵⁾. The death of an 11-year-old patient from complications of ALF secondary to COVID-19 has been reported. Additionally, successful LT has been performed in a child with ALF secondary to COVID-19.^(96,97) ALF is seen more often in patients with severe illness and multiorgan dysfunction. The etiology of ALF in this setting may be the result of direct viral cytotoxicity, immune mediated liver injury (cytokine storm) and/or drug-induced liver injury⁽⁹⁰⁾. A comprehensive analysis to better understand which patients are at risk of developing ALF in the setting of SARS-CoV2 infection is needed.

Statement:

6. *ALF in SARS-CoV2 infection is rare. The role of SARS-CoV2 infection in causing pediatric ALF, leading to death or LT, is uncertain.*

(Agreement: 4/4/4/4/4/4/3/3/3)

IV. Liver transplant recipients and immunocompromised children

A. Impact of immunosuppressive drugs in SARS-CoV2 infection

As previously observed in SARS-CoV1 and MERS-CoV epidemics, morbidity related to SARS-CoV2 infection is mediated by exaggerated immune responses rather than the direct cytopathic effect of the virus⁽⁹⁸⁾. While there was initial concern that immunocompromised patients could be at increased risk to develop severe SARS-CoV2 infection, studies involving pediatric and adult solid organ transplant recipients have not demonstrated worse outcomes or increased mortality. Immunosuppression maintenance in solid organ transplant adult recipients has not been associated with a more severe COVID-19 course^(8,99–101). Moreover, corticosteroids have been reported to reduce 28-day mortality in an open-label randomized controlled trial in adults, with the greatest benefit in those requiring invasive mechanical ventilation⁽¹⁰²⁾. In other studies, corticosteroid use was associated with a shorter stay in the intensive care unit and decreased need for invasive ventilation^(103,104). Calcineurin inhibitors have a potential role in inhibiting Coronavirus replication⁽¹⁰⁵⁾, and data from the European Liver Transplant Registry demonstrated an association of tacrolimus treatment with less severe SARS-CoV2 adult infections⁽¹⁰⁶⁾. In addition, antimetabolites such as mycophenolic acid exhibit antiviral properties in vitro⁽¹⁰⁷⁾. Similar to adults, children with chronic autoimmune liver disease on immunosuppressive maintenance medications do not appear to be at greater risk from COVID-19^(8,108–111). Similarly, children on chronic immunosuppression for other conditions such as inflammatory bowel diseases^(112,113), rheumatologic^(114,115) and renal disorders^(116,117) do not exhibit increased mortality or risk of severe COVID-19 when compared with age-matched children without chronic conditions. An

exception is represented by the autoimmune polyendocrine syndrome type 1 due to mutations in the *AIRE* gene, and possible rare cause of autoimmune hepatitis, in which preexisting anti-endogenous IFN-I antibodies can lead to severe pneumonia⁽¹¹⁸⁾. Overall, maintenance immunosuppressive medications do not appear to predispose to more severe SARS-CoV2 infection in children with autoimmune liver disease or in LT recipients^(110, 119, 120).

Statement

- 7. Based on the limited available pediatric data and in line with guidelines for adults, routine reduction or withdrawal of established immunosuppressive therapy in children with autoimmune liver disease is not recommended. Reductions could be considered based on general principles for managing infections in immunosuppressed patients and to decrease the risk of superinfection.*

(Agreement: 4/4/4/4/4/4/4/4)

B. The course of COVID-19 in liver transplant (LT) recipients

A recent meta-analysis⁽¹²¹⁾ of 2,772 pooled adult solid organ transplant recipients, including 505 LT recipients, showed an incidence of lower respiratory tract infection of 79.7%, ICU admission rate of 29% and mortality of 18%, all of which are comparable to the general population⁽¹²²⁾. LT status did not significantly increase the risk of death in adults with SARS-CoV2 infection, although older age and presence of comorbidities did^(99, 100).

A study from the joint North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and Society of Pediatric Liver Transplantation (SPLIT) SARS-CoV2 pediatric registry described 47 LT recipients under the age of 21 years and found that no patients required mechanical ventilation or died. From this cohort, almost 30% were asymptomatic and most commonly presented with respiratory symptoms (36%), fever (34%) and GI symptoms (25%). Immunosuppression changes included reduction (28%), discontinuation of a second agent (15%) and no adjustments in 68%⁽⁸⁾. While interpreting these data the reader should consider the inherent bias of a registry design. The registry continues to grow, and since the initial publication there are now 180 LT children reported. Of these, 30 patients required non-ICU hospital admission (median = 5 days), and 3 patients required ICU level care with no requirement for vasoactive support or mechanical ventilation; 3 patients required supplemental oxygen, and 1 renal replacement therapy; no deaths were reported [unpublished data]. These data are in accordance with other case reports and case series, which report that children on post-transplant immunosuppressive regimens, similar to the general population of children, tend to experience mild disease^(119, 120, 123–127). However, one case reported a three-year-old boy transplanted at the age of 18-months for biliary atresia who developed multiorgan failure after SARS-CoV2 infection and died on day 6 after hospital admission⁽¹²⁸⁾.

In summary, current evidence suggests that children after LT may not be at higher risk of severe complications of COVID-19 infection and that they present with similar symptoms and similar mild disease course as the general pediatric population. However, due to limited data and evolution of viral mutations, caution and further studies are needed.

Statement

- 8. Based on current evidence that the degree of immunosuppression may not predict worse outcomes from SARS-CoV2 infection, standard immunosuppression should not be routinely reduced or withdrawn in children following LT with mild or moderate SARS-CoV2 infection.*

(Agreement: 4/4/4/4/4/4/4/4)

C. Impact on organ donation and clinical practices

The COVID-19 pandemic initially resulted in a significant decrease in transplant activity. Data from the United States (US) showed an approximate 10% reduction in all solid organ pediatric transplantations in 2020 compared to 2019. A significant decrease in living donor LT (LDLT) compared to deceased donor donation has been reported in some centers, which likely reflects a reduction in elective procedures during the early phase of the pandemic⁽⁹⁸⁾. In Europe, only 10 out of 18 (55%) pediatric transplant centers remained active in March of 2020, seven centers limited their activity to urgent cases and one center completely suspended their transplant program⁽¹²³⁾. Data from India showed a reduction in the number of referrals in mid 2020 and higher average PELD scores in LT candidates compared to 2019. Timely LDLT could not be performed in two children due to COVID-lockdown related delays and both died on the waiting list⁽¹²⁴⁾. Nevertheless, successful LT is feasible in the setting of a pandemic⁽¹²⁹⁾ and has been safely performed shortly after recovery from SARS-CoV2 infection⁽¹³⁰⁾.

There is not enough evidence to guide the acceptance of deceased donor grafts from donors actively infected with SARS-CoV2 or transplantation of recipients with ongoing SARS-CoV2 infection. Cases should be gauged on an individual basis balancing the urgency of the LT with the potential risk of disease transmission to the recipient and other care providers, as well as post-transplant complications.

The COVID-19 pandemic has necessitated the advancement and increased use of telemedicine technologies to deliver pre- and post-transplant care. According to a US adult survey, telemedicine is now being used by programs for transplant evaluations (65%), waitlist management (58%) and post-transplant care (98%)⁽⁹⁸⁾. In Europe, outpatient visits of pediatric transplant patients were initially impacted in 17 out of 18 centers (96%) and seven centers (40%) started or increased the use of telemedicine during the pandemic. Ongoing adjustments in telemedicine utilization and in-person visits are evolving with a likely continuation of telemedicine beyond the confines of the pandemic.

Statement

- 9. The decision of whether to perform a deceased donor LT in a child from a SARS-CoV2 infected donor or into a SARS-CoV2 infected child should be made on a case-by-case basis, balancing the risk related to the underlying indication with the risk related to SARS-CoV2.*

(Agreement: 4/4/4/4/4/4/3/3)

V. Treatment and prognosis of acute SARS-CoV2 infection

Two phases have been recognized in the clinical course related to the pathogenesis of SARS-CoV2 infection. In the early course of the infection, the disease is driven by replication of the virus and antivirals have the greatest effect. Later, the disease is caused by the immune/inflammatory response to the virus and immunosuppressive/anti-inflammatory therapies are indicated. Table 2 summarizes the treatments available for children with COVID-19.

A. Supportive care

Supportive care to liver patients with SARS-CoV2 infection includes ensuring an adequate intake of daily calories and water, administration of antipyretic drugs for a body temperature above 38.5°C and supplemental oxygen/ventilatory support when indicated.

B. Antivirals

Remdesivir is the only antiviral approved for use in adult and children >12 years of age and >40 kg for the treatment of SARS-CoV2 infection (200 mg IV on day 1 and 100 mg/day for up to 5 consecutive days)^(131–133). It is recommended for use in hospitalized patients who require supplemental oxygen. No clear benefit has been demonstrated for those who require mechanical ventilation. For selected hospitalized children <12 years of age and <40 kg, the emergency use authorization remains in effect. Elevated liver biochemistries have been observed in patients treated with remdesivir⁽¹³³⁾. Aminotransferases and bilirubin should be checked prior to starting the drug and during treatment for both children with and without a pre-existing liver conditions.

C. Anti-inflammatories

Steroids (dexamethasone) improve survival in hospitalized adults who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation.

D. Monoclonal antibodies

The anti-SARS-CoV2 monoclonal antibodies bamlanivimab plus etesevimab⁽¹³⁴⁾ and casirivimab plus imdevimab⁽¹³⁵⁾ are available through emergency use authorizations for patients > 12 years of age and > 40kg who are at high risk for disease progression. Anti-SARS-CoV2 antibody-based therapies may have the greatest effect in the earliest stages of infection, before the host has mounted an effective immune response. There is no experience on the use of these drugs in children. The efficacy of these agents is challenged further by the emergence of viral mutations expressing different viral associated proteins.

E. Vaccines

The SARS-CoV2 viral spike glycoprotein has been used in COVID-19 vaccines through various delivery systems and vectors. As of September 2021, four COVID-19 vaccines were available for use (Pfizer-BioNTech⁽¹³⁶⁾, Moderna⁽¹³⁷⁾, AstraZeneca⁽¹³⁸⁾, Janssen - Johnson & Johnson⁽¹³⁹⁾). The Pfizer-BioNTech mRNA vaccine has been authorized for ages <18 years (specifically ≥12 years) by FDA and EMA. EMA recently (July 2021) approved for the same age cohort the use of the Moderna mRNA vaccine. The landscape of the SARS-CoV2

vaccine clinical trials is constantly changing and several vaccines candidates are currently being evaluated in children. The Pfizer-BioNTech has been approved for children 12 years old and older, and it is now recruiting children between the age of 6 months to 11 years. The clinical trial of the Moderna vaccination included 3,000 adolescents (aged 12–17 years), and the phase 2/3 clinical trial in children ages 6 months and 11 years was started. The phase 2 clinical trial for AstraZeneca in 300 children ages 6–17 years old was started in February 2021 but halted in April. The clinical trial of Johnson & Johnson vaccine in children is being strategized. In absence of specific evidence about safety and efficacy of SARS-CoV2 vaccines in young patients with chronic liver conditions, related recommendations are based on the high expected benefit, acceptability, and feasibility. Children and adolescents with compensated and decompensated cirrhosis, CLD (including NAFLD, non-alcoholic fatty liver disease), end stage liver disease awaiting transplantation, as well as LT recipients on immunosuppressive medications should be prioritized for early vaccine access because at risk for poorer outcomes from SARS-CoV2 infection, and to warrant routine access to healthcare. It is reasonable to vaccinate prior to transplantation or before starting immunosuppressive treatment for immune-mediated liver disease. In patients who are listed for LT, vaccination is indicated even if a vaccine with a two-dose schedule is used and LT is likely to occur before the second dose can be administered. Specifically, vaccination can provide protection after the first dose and should not delay deceased donor transplantation⁽¹³⁶⁾. It is difficult to predict the best time to administer the vaccine (either the first or the second dose) after LT. It has been suggested that adults receiving a LT can be vaccinated as early as six weeks posttransplant⁽¹⁴⁰⁾. Reducing immunosuppression to elicit the immune response is not recommended. Pre- or post-vaccination serological testing is not recommended outside specific immunogenicity studies⁽¹⁴⁰⁾. Recent data regarding antibody response rates show that a little over half of solid organ recipients develop anti-spike antibodies after vaccine schedule completion^(141–143) but further studies are needed to determine clinical relevance and are ongoing.

Statements:

10. There are insufficient data to recommend for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in children with liver disease.

(Agreement: 4/4/4/4/4/3/3/3)

11. SARS-CoV2 vaccination should be recommended for all children 12-17 years of age with chronic liver disease, including autoimmune liver disease on immunosuppressive therapies, patients with cirrhosis, transplant recipients, those on the waiting list for LT and their caregivers. The same recommendation applies to younger children in which safety is currently being evaluated.

(Agreement: 4/4/4/4/4/4/4/3)

12. Future studies are needed to determine COVID-19 vaccine immunogenicity in children with chronic liver disease and LT recipients.

(Agreement: 4/4/4/4/4/4/4/4)

F. Therapeutic approach to MIS-C

Treatments for MIS-C consist primarily of supportive care, antiplatelet and anticoagulation therapy and care directed against the underlying inflammatory process. Supportive measures are lifesaving and include fluid resuscitation, inotropic and respiratory support up to extracorporeal membranous oxygenation. Of note, therapies for MIS-C, including aspirin, enoxaparin and immunomodulatory therapies (intravenous immunoglobulins and steroids) can cause drug-induced liver injury. Anakinra and tocilizumab (recombinant human interleukin-1 and 6 receptors antagonists, respectively) may rarely cause clinically apparent liver injury and are more frequently associated with elevated serum aminotransferases⁽¹⁴⁴⁾.

VI. Social distancing and infection prevention

Preventive strategies are of paramount importance, particularly for children with chronic liver disease or LT recipients⁽¹⁴⁵⁾. However, the social behaviors recommended for personal safety and infection control do not differ from the general populations. The different gradations of social distancing, use of masks and face coverings, school openings, sport events and gatherings, and travelling are regulated by the local authorities based on epidemiological considerations.

Statement:

13. Children with CLD or LT recipients should follow similar social behavior to the general population regarding social distancing, mask-wearing and hand washing.

(Agreement: 4/4/4/4/4/4/4/3)

VII. Conclusions

The present document aims at providing evidence-based guidance to health care providers about liver involvement in children with SARS-CoV2 infection and recommendations for the management of children with underlying liver disease and LT recipients. These populations are generally not at substantial risk of severe SARS-CoV2 infection, though critical attention is warranted for children who: present in ALF, have end-stage liver disease and are listed for transplantation as acute decompensation has been reported, or who are in the immediate post-transplant period with the highest degree of immunosuppressive burden. As COVID-19 vaccine distribution is underway, further studies are required to understand immunogenicity in LT recipients and children with CLD on immunosuppressive therapies. The resulting position statements in this document are primarily derived from expert review and summarize evidence from adults with cirrhosis or solid organ transplantation and the general pediatric population in addition to data from pediatric solid organ transplant recipients and children with CLD. Further studies are needed to better guide SARS-CoV2 therapeutics and management, inform timing of LT following SARS-CoV2 infection, understand COVID-19 vaccine immunogenicity and explore other special considerations in children with CLD or who have undergone pediatric LT.

DISCLAIMER:

ESPGHAN and SPLIT are not responsible for the practices of physicians and provide guidelines and position papers as indicators of best practice only. Diagnosis and treatment are at the discretion of physicians.

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Figure legend

Figure 1. Pathophysiology of the liver injury in SARS-CoV2 infection. A) Immune pathophysiology of mild and severe COVID-19. In severe cases, viral and host factors may result in an inhibited IFN type I response, resulting in a proinflammatory cytokines and chemokines production. This milieu causes lung recruitment of macrophages and T cells, responsible for a cytokine storm, causing further neutrophil recruitment and NETosis, ultimately leading to tissue injury, diverted adaptive immune response, systemic inflammation, and organ dysfunction, including liver. In children, the detrimental role of a preexisting chronic liver disease (due to increased hepatocyte ACE2 expression, innate and adaptive immune dysfunction, macrophage hyperactivation) is counterbalanced by the immunotolerant phenotype associated with the young age. B) Acute liver injury during SARS-CoV2 infection can occur via direct and indirect mechanisms. The systemic inflammatory cytokine milieu causes sinusoidal endothelial activation, with subsequent thrombosis and hypoxic-ischemic injury. Direct cytopathic effects, and drug-induced injury are also possible especially in cholangiocytes. ACE2: angiotensin-converting enzyme 2; CCL2: C-C Motif Chemokine Ligand 2; CXCL8: C-X-C Motif Chemokine Ligand 8; CD4+: CD4+ lymphocyte; CD71+ EC: CD71+ erythroid precursors; CLD: chronic liver disease; CTL: cytotoxic T cell; EC: epithelial (respiratory) cell; Hep: hepatocyte; IFN: interferon; IL-2, -6, -8, -10: interleukin-2, -6, -8, -10; KC: Kupffer cell; MDSC: myeloid-derived suppressor cells; Mφ: macrophage; SEC: sinusoidal endothelial cell; Th: helper T cell; TLRs: Toll-like receptors; TMPRSS2: transmembrane protease, serine 2; TNF- α : Tumor necrosis factor- α .

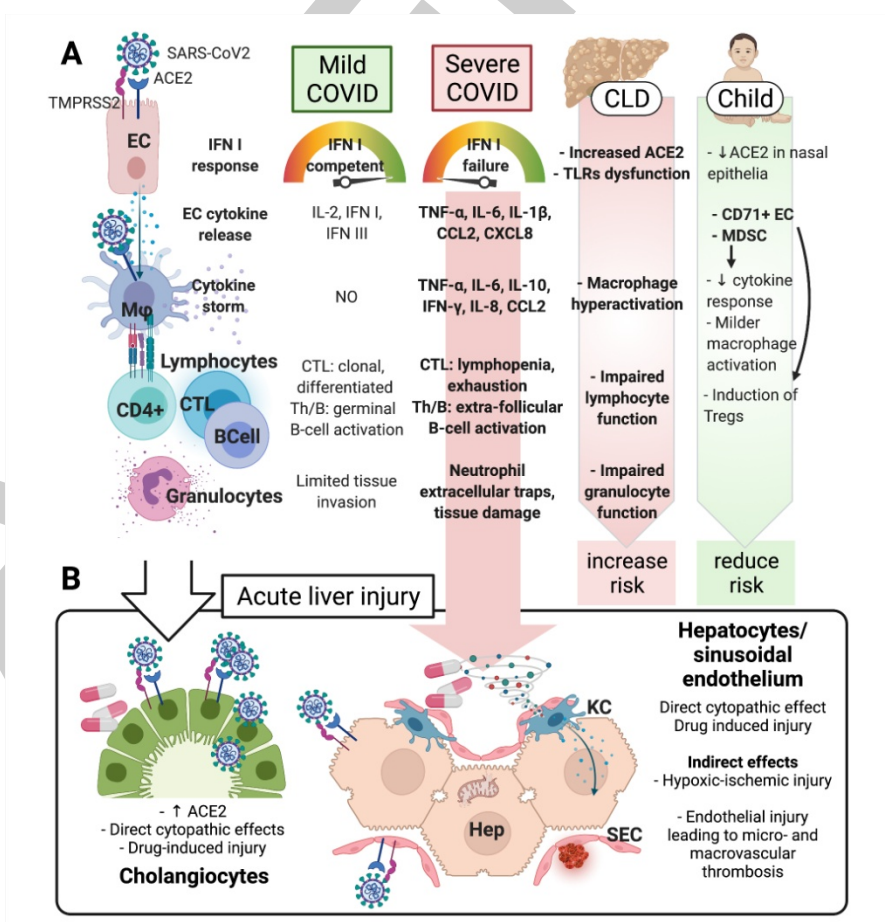


Table 1. Research questions addressed by the Working Group.

Does the diagnostic accuracy of molecular analysis by nucleic acid amplification and serologic tests for SARS-CoV2 differ between children with CLD or immunosuppressed for LT and the pediatric general population?
Does SARS-CoV2 infection cause acute liver injury in children with or without CLD?
Does MIS-C cause acute liver injury in children?
Is CLD a risk factor for acquiring SARS-CoV-2 or for a more severe infection in children?
Does SARS-CoV2 infection cause acute liver failure in children?
Balancing the risk of a hepatic disease flare and the estimated risk of SARS-CoV2 infection, should UNINFECTED children with CLD on treatment with immunomodulators and biologic therapies continue their medical treatment?
Balancing the risk of a hepatic disease flare and the estimated risk of SARS-CoV2 infection, should INFECTED children with liver diseases on treatment with immunomodulators and biologic therapies continue their medical treatment?
Balancing the risk of graft rejection and the estimated risk of SARS-CoV2 infection, should UNINFECTED LT children continue their immunosuppressive regime?
Balancing the risk of graft rejection and the estimated risk of SARS-CoV2 infection, should INFECTED LT children continue their immunosuppressive regime?
Balancing the risk of the condition underlying indication to liver transplantation and the estimated risk of SARS-CoV-2 infection, should deceased donor liver transplant be avoided in case of ongoing SARS-CoV-2 donor/recipient infection?
Are the same behavioral measures used by the general population during the pandemic (e.g., hand hygiene, and social distancing) recommended for decreasing the risk of contracting SARS-CoV-2 in children with CLD, immunosuppressed for autoimmune liver diseases, and recipients of LT?

Table 2. Treatment options for acute SARS-CoV2 infection and vaccines schedules

Treatment	Summary of main indications
Supportive care (adequate intake of daily calories and of water, antipyretic drugs, oxygen/ventilatory support)	As for clinical practice
Remdesivir (children older 12 years of age; > 40 Kg)* Dose: 200 mg intravenous on day 1 and 100 mg/day for up to 5 consecutive days	Recommended for use in hospitalized patients who require supplemental oxygen not on mechanical ventilation
Steroids (dexamethasone)	Recommended in hospitalized children who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation
Monoclonal antibodies (bamlanivimab plus etesevimab and casirivimab plus imdevimab)	No experience on the use in young children; emergency use for patients > 12 years of age and > 40kg at high risk for disease progression‡
Vaccines[¶]	Schedule
Pfizer-BioNTech (children older 12 years of age; US Food and Drug Administration and European Medicines Agency)	2 intramuscular injections given 3 weeks (21 days) apart†
Moderna (children older 12 years of age; European Medicines Agency)	2 intramuscular injections given 4 weeks (28 days) apart†

*Limited data exist regarding Remdesivir use in children < 12 years of age (see Chiotos K, et al; J Pediatric Infect Dis Soc 2021;10:34-48).

‡The relevant risk categories are: obesity; chronic kidney disease; diabetes; sickle cell disease; immunosuppressive disease or immunosuppressive treatment; congenital or acquired heart disease; neurodevelopmental disorder; medical-related technology dependence; asthma, reactive airway disease, or other chronic respiratory disease. However, given the overall low rate of adverse infection outcomes, in children and adolescents the presence of this risk condition would not necessarily be sufficient to indicate use of such agents (see Wolf J, et al; J Pediatric Infect Dis Soc 2021;10:629-634).

¶As of September 2021.

†An additional dose at least 28 days after the second dose could be considered in immunocompromised individuals, including organ transplant recipients [see 1) Center for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States, August 31 2021. CDC: Atlanta; 2021; and 2) European Centre for Disease Prevention and Control. Interim public health considerations for the provision of additional COVID-19 vaccine doses, 1 September 2021. ECDC: Stockholm; 2021.].