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## Management of hepatitis C in children and adolescents during COVID-19 pandemic

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### Abstract

In recent years, significant progress in the antiviral treatment of chronic hepatitis C (CHC) has been made due to the development of interferon-free therapies. Three different highly effective, oral direct-acting antiviral (DAA) regimens have been approved for use in adolescents with CHC between the ages of 12-years-old and 17-years-old in Europe. According to the current recommendations, all treatment-naïve and treatment-experienced children with CHC virus infection should be considered for DAA therapy to prevent the possible progression of hepatitis C virus-related liver disease and its complications. However, the novel coronavirus disease 2019 outbreak, which was classified as a pandemic in March 2020, is currently spreading throughout the world, resulting in a disruption of the healthcare system. This disruption is having a negative impact on the care of patients with chronic diseases, including children with CHC. Thus, several efforts have to be made by pediatric hepatologists to prioritize patient care in children with CHC. These efforts include promoting telemedicine in the outpatient setting, using local laboratory testing for follow-up visits, and engaging in the home delivery of DAAs for patients under antiviral therapy whenever possible.

**Key words:** Children; Chronic hepatitis C; COVID-19; Direct-acting antiviral; Hepatitis C virus

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**Core tip:** The novel coronavirus disease 2019 outbreak, classified as a pandemic, is currently spreading throughout the world, resulting in a disruption of the healthcare system. This disruption is having a negative impact on the care of patients with chronic diseases, including children with chronic hepatitis C. In this review, we describe several



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efforts that have to be made by pediatric hepatologists to prioritize patient care in children with chronic hepatitis C. They include promoting telemedicine in the outpatient setting, using local laboratory testing for follow-up visits, and engaging in the home delivery of drugs for patients under antiviral therapy whenever possible.

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## INTRODUCTION

Hepatitis C virus (HCV) infection is considered a major cause of liver-related mortality and morbidity worldwide, rendering it an important public health problem<sup>[1,2]</sup>. It is estimated by the World Health Organization (WHO) that 71 million people [95% confidence interval (CI): 64-103 million] are infected with HCV globally, which represents approximately 1% of the population<sup>[1,3]</sup>. The prevalence of HCV infection in children aged 1-year-old to 19-years-old is 0.15%, corresponding to 3.5 million people (95% CI: 3.1-3.9 million)<sup>[1,4]</sup>. However, since major gaps in our current knowledge on the epidemiology of chronic hepatitis C (CHC) exist in both adults and children, most HCV-infected people are unaware of their infection<sup>[1]</sup>. Thus, the true prevalence of HCV infection in children and adolescents might be underestimated<sup>[5]</sup>. In 2016, the WHO released a global health sector strategy for eliminating viral hepatitis by 2030 that includes global and country-wide targets for the testing, treatment, and prevention of CHC<sup>[6]</sup>.

Chronic HCV infection leads to a progressive disease, with 10%-20% of infected patients developing cirrhosis and approximately 7% of adult patients with cirrhosis progressing to hepatocellular carcinoma<sup>[7,8]</sup>. Data reporting liver disease progression in the pediatric population infected with HCV are limited<sup>[9]</sup>. This progression is usually described as a mild disease in children and adolescents; however, severe cases have also been described occasionally<sup>[9-12]</sup>. Liver fibrosis and inflammation in children suffering from CHC is a time-dependent process, with approximately 2% of infected children developing advanced liver disease during childhood<sup>[13-16]</sup>. In the case of vertical HCV transmission, the progression of liver disease may occur at a younger age than in children infected horizontally in the later years of life, resulting in severe liver disease in their teens or in young adulthood<sup>[9,17]</sup>. Thus, effective antiviral treatment in children with CHC could prevent the development of end-stage liver disease, cirrhosis, and hepatocellular carcinoma in young adults.

## MANAGEMENT OF HCV INFECTION IN CHILDREN AND ADOLESCENTS

Since 2015, the development and approval of novel, oral, interferon-free, antiviral treatment with direct-acting antivirals (DAAs) has substantially improved the treatment of HCV infection<sup>[18,19]</sup>. With an efficacy approaching 100% and a short duration of therapy, DAAs are a highly effective, safe, and well-tolerated alternative for previously used therapies based on interferons<sup>[18,19]</sup>. Currently, approximately 10 different DAA combinations have been approved for use in adults, increasing the prospect of HCV elimination on a population level<sup>[1,18]</sup>. However, treatment options based on DAA for children are currently limited<sup>[1,18]</sup>. Only three DAA regimens have been approved for use in adolescents by the European Medicines Agency (EMA) in Europe<sup>[1,20-24]</sup> (Table 1). The first DAA regimens, a fixed-dose combination of sofosbuvir/ledipasvir and sofosbuvir with ribavirin, were approved by the EMA in 2017 for use in adolescents between 12-years-old and 17-years-old with CHC<sup>[20,25]</sup>. The first regimen with pangenotypic activity, *i.e.* glecaprevir/pibrentasvir, was approved by the EMA in 2019 for adolescents aged 12-years-old to 17-years-old<sup>[24]</sup>. In addition, in 2019, the United States Food and Drug Administration (FDA) approved sofosbuvir/ledipasvir and sofosbuvir with ribavirin for use in children between 3-years-old and 11-years-old, and in March 2020, the FDA approved another pangenotypic combination, *i.e.* sofosbuvir/velpatasvir, for the treatment of chronic HCV patients as young as 6 years of age or weighing at least 17 kg<sup>[26-28]</sup>. However, the

**Table 1 Direct-acting antivirals approved for adolescents aged 12 to 17 years in Europe (May 2020)<sup>[20,22-24]</sup>**

Direct-acting antivirals regimen (doses per d)	Hepatitis C virus genotype	Patients	Duration of treatment in wk
Sofosbuvir/ledipasvir (400/90 mg)	1	Treatment-naïve with or without cirrhosis or treatment-experienced without cirrhosis	12
		Treatment-experienced with cirrhosis	24
	4, 5, 6	Treatment-naïve or treatment-experienced, with or without cirrhosis	12
Sofosbuvir + ribavirin (400 mg + 15 mg/kg)	2	Treatment-naïve or treatment-experienced, with or without cirrhosis	12
	3		24
Glecaprevir/pibrentasvir (300/120 mg)	All genotypes	Without cirrhosis	8
	All genotypes	With cirrhosis	12
	3	Treatment experienced	16

FDA approvals are not applicable in Europe. According to the current recommendations, all treatment-naïve and treatment-experienced children with CHC virus infection should be considered for DAA therapy to prevent the possible progression of HCV-related liver disease and its complications<sup>[20,21]</sup>. In children younger than 12-years-old with CHC, antiviral treatment should be deferred until interferon-free regimens are available<sup>[21]</sup>. Since liver disease in HCV-infected children is usually mild, and they rarely have comorbidities or take medicines posing potential risk for drug interactions, pediatric patients seem to be ideal candidates for DAA treatment. However, treatment options for children in many regions are currently limited<sup>[1]</sup>. Due to the high costs of DAAs, very few countries have implemented recommendations for CHC treatment in adolescents in their national policies<sup>[1]</sup>. In addition, there are no approved treatment options for children younger than 12-years-old in Europe. Thus, only a small number of children and adolescents with CHC have been treated globally, especially in low- and middle-income countries<sup>[1]</sup>. Considering the positive results from the clinical trials on DAA efficacy and safety, the first real-life therapeutic programs for pediatric patients infected with HCV based on DAAs were launched in Europe in 2019.

## CORONAVIRUS DISEASE 2019 AND THE LIVER

Since the end of 2019, a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has caused an outbreak of coronavirus disease 2019 (COVID-19), resulting in an emerging global threat rapidly spreading throughout the world<sup>[29,30]</sup>. On March 11, 2020, the WHO declared the COVID-19 a pandemic<sup>[31]</sup>. In March 2020, the epicenter of the pandemic moved from China to the United States and Europe. Children seem to be less likely to be affected by the disease. According to the available data, the proportion of children among all infected patients ranged between 0.6% and 5.2% in different regions<sup>[32-34]</sup>. The clinical course of COVID-19 in children seems to be less severe than that in adults, with fewer clinical symptoms and case-fatality rates close to 0%<sup>[29,30]</sup>.

In general, patients with pre-existing morbidities are at higher risk of a severe course of COVID-19, however, liver disease was not specifically listed in the published studies so far<sup>[35]</sup>. It is possible that patients with advanced liver disease are at increased risk of SARS-CoV-2 infection due to cirrhosis-induced immunodeficiency<sup>[36]</sup>. On the other hand, immunosuppression might provide some protection against cytokine storms, which contribute to multiorgan failure associated with COVID-19<sup>[37,38]</sup>. Patients with chronic liver disease including cirrhosis may be at higher risk of death resulting from COVID-19, but risk factors in specific liver diseases have not been defined<sup>[39]</sup>. It was revealed that SARS-CoV-2, similarly to SARS-CoV, uses angiotensin-converting enzyme 2 as its entry receptor<sup>[40]</sup>. Both liver and bile duct cells express angiotensin-converting enzyme 2. Thus, the liver is a potential target for SARS-CoV-2 infection<sup>[39,40]</sup>. It results in liver injury, which is observed in 15% to 58% of patients, more commonly in severe COVID-19 cases<sup>[39,40]</sup>. The incidence of liver disease in death cases of COVID-19 was as high as 58% to 78%<sup>[40]</sup>. Liver disease manifests mainly with elevated aminotransferase levels and/or slightly elevated bilirubin level<sup>[39,40]</sup>. Liver

injury is usually transient and does not require specific treatment<sup>[39]</sup>.

Severe liver injury as a result of SARS-CoV-2 infection is uncommon in pediatric patients. In the rare cases of severe COVID-19 in children, increase in aminotransferase level was only mild (not exceeding  $2 \times$  upper limit of normal)<sup>[39]</sup>. There are only limited data on SARS-CoV-2 infection in patients with chronic viral hepatitis<sup>[35]</sup>. Thus, it remains unknown whether patients with chronic viral hepatitis B and/or C are more susceptible to liver injury from SARS-CoV-2<sup>[39]</sup>. Observations from China suggest that chronic hepatitis B does not affect the outcome of COVID-19<sup>[41]</sup>. No case of SARS-CoV-2 infection has been described among pediatric patients with CHC; however, the impact of the COVID-19 pandemic on the management of patients with chronic HCV infection is significant, with several aspects requiring attention<sup>[35]</sup>.

## MANAGEMENT OF PEDIATRIC PATIENTS WITH CHRONIC HEPATITIS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has led to the disruption of the healthcare system. This disruption has had a negative impact on the care of patients with chronic diseases, including children with CHC, which may not only pose a risk for individual patients but also have a negative influence on viral hepatitis elimination programs<sup>[42]</sup>. The treatment and management of patients with HCV infection is influenced by closing clinics and avoiding nonemergent visits<sup>[42]</sup>. In many cases, DAA therapies in children are conducted in infectious disease departments, which are now on the front line of fighting the pandemic. This change of focus may result in a reduction in both the diagnosis and treatment rates of hepatitis patients<sup>[42]</sup>. It is essential to maintain the care of children with CHC and to find potential methods to prioritize the care of these patients despite the limited healthcare resources<sup>[35]</sup>. This may be achieved by adapting to the unique logistical and pharmacological issues caused by the pandemic<sup>[39]</sup>. Recent recommendations from the European Association for the Study of the Liver-European Society of Clinical Microbiology and Infectious Diseases and the American Association for the Study of Liver Diseases Expert Panel consensus statement on the care of patients with liver disease during the COVID-19 pandemic may also be useful for pediatricians caring for children with CHC<sup>[35,39]</sup>.

The most important issue is that both patients and medical staff should avoid SARS-CoV-2 exposure and infection. The precise management of the patients depends mostly on the local COVID-19 burden<sup>[35]</sup>. It is essential to educate the patients on risk and precaution on COVID-19, especially in cases complicated by cirrhosis or end-stage liver disease, when the risk of severe course of COVID-19 exists<sup>[39]</sup>. In most regions, physical distancing and avoiding direct face-to-face contact have been officially implemented. Thus, all patients suffering from chronic liver diseases should adhere to these common rules<sup>[35]</sup>. Visits to outpatient or inpatient clinics should be avoided unless necessary. Since in most cases children with CHC present with mild disease and are in stable, good condition, visits to hepatological clinics are not essential and may be postponed. In case of patients already on DAA treatment, therapy should be continued<sup>[39]</sup>. It is reasonable to use telemedicine for follow-up visits in patients under antiviral treatment and to send them prescriptions by e-mail or organize a home delivery of DAAs, as appropriate. Routine laboratory testing may be performed in a local laboratory through primary care physicians only in cases when it is truly necessary. Collaboration between hepatologists and local health care providers and primary care physicians is essential for further management of patients during pandemics. Whenever possible, liver-related diagnostic procedures (*e.g.*, ultrasound, elastography, or liver biopsy if required) should be avoided unless they are likely to change management. In addition, an inclusion of the patients in the clinical trials should be deferred. While planning DAA treatment, its priority should be determined. In patients with stable CHC, therapy may be safely postponed to after COVID-19 pandemic. However, in selected cases with known advanced liver disease (*e.g.*, with significant fibrosis: Liver stiffness measurement  $> 7$  kPa) or in patients with human immunodeficiency virus coinfection, decision on starting therapy despite COVID-19 pandemic should be considered. If a visit to an outpatient clinic is needed, standard operating procedures should be adopted, *e.g.*, separation from patients suspected for COVID-19, remodeling of waiting areas, keeping distance between patients, reduction of waiting times, and minimizing exposure to the medical staff<sup>[35]</sup>. The number of family members who accompany patients to their visits should be limited to one healthy parent or guardian<sup>[39]</sup>. All patients should be screened for symptoms of COVID-19 (*e.g.*, fever, cough, shortness of breath, sore throat, rhinitis), and their

temperature should be checked as they enter the clinical space<sup>[39]</sup>. There are currently no specific recommendations on screening for SARS-CoV-2 infection in patients with CHC. As in individuals without HCV infection, children with CHC should be tested for COVID-19 in case of the presence of clinical symptoms suggesting the SARS-CoV-2 infection or having household contact with an infected family member. Our unpublished observations of over 100 pediatric patients with COVID-19 suggest that children usually acquire infection from infected close relatives. Thus, family history should be assessed in order to stratify the risk of the SARS-CoV-2 infection. In addition, testing should be considered in patients requiring hospitalization in order to reduce a risk of spreading the infection by an asymptomatic person in the hospital setting. Recommendations for the management of pediatric patients with CHC are summarized in [Table 2](#).

Despite the fact that CHC does not seem to increase the risk of a severe course of COVID-19, in case of coinfection, an early admission and inclusion to the experimental antiviral therapy of COVID-19 should be considered, following local recommendations<sup>[35]</sup>. Interestingly, one of the DAAs, sofosbuvir alone or in combination with ribavirin, has been suggested for the experimental treatment of COVID-19<sup>[35,43]</sup>. In all hospitalized COVID-19 patients, regular monitoring of aminotransferase levels is recommended, particularly in cases treated with tocilizumab or remdesivir, due to their hepatotoxicity<sup>[39]</sup>. As COVID-19 is only rarely associated with elevated liver enzymes in children, all pediatric patients with high aminotransferase levels during the SARS-CoV-2 infection should be evaluated for other etiologies and underlying liver diseases, including hepatitis A, B, or C and drug-induced liver injury<sup>[39]</sup>.

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## CONCLUSION

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The open issue is how this COVID-19 pandemic will influence diagnostic and treatment strategies regarding CHC and its elimination program. Despite the special attention required by the COVID-19 pandemic, we should not forget about other diseases and chronically ill patients, including viral hepatitis. Several efforts have to be made by pediatric hepatologists to prioritize patient care in children with CHC and to avoid regression regarding programs leading to HCV elimination.



**Table 2 Recommendations for the management of pediatric patients with chronic hepatitis C virus infection during the coronavirus disease 2019 pandemic<sup>[35,39]</sup>**

Management	Recommendation
Physical distancing	Recommended
Patient education on risk and precaution on COVID-19	Recommended
Testing for severe acute respiratory syndrome coronavirus infection	Recommended in patients with clinical symptoms suggesting COVID-19, or with household contact with an infected family member, or requiring hospitalization
Visits to specialized centers	Should be postponed
Routine laboratory testing	Should be performed (only if truly necessary) locally/offsite
Direct-acting antiviral therapy already initiated	Should be continued
Starting direct-acting antiviral treatment	May be postponed in patients with stable chronic hepatitis C. If possible, it should be considered in patients with significant fibrosis or human immunodeficiency virus/hepatitis C virus coinfection
Telemedicine/visits by phone	Recommended instead of face-to-face visits whenever possible
Drug supply	Home delivery or sending prescriptions by e-mail
Liver-related diagnostic procedures	Should be deferred unless they are likely to change management

COVID-19: Coronavirus disease 2019.

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