

## ORIGINAL ARTICLE

## Hepatology

# Considerable differences in management of cytomegalovirus infection in patients with biliary atresia

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**Abstract**

**Objectives:** Patients with biliary atresia (BA) and ongoing cytomegalovirus (CMV) infection may have poorer outcomes after Kasai portoenterostomy than uninfected patients. Still, there is no consensus on the usefulness of viral testing and antiviral treatment (AVT). This study aims to explore the need for future research on AVT for CMV infection by assessing how CMV infection in BA patients is managed in different centers.

**Methods:** An online questionnaire with 10 questions was offered to participants at an international congress on BA, organized in collaboration with the European Reference Network for rare liver diseases in 2022. Answers to questions were either dichotomic or multiple choices of different numeric intervals. Ongoing CMV infection was defined by detecting cytomegalovirus-immunoglobulin M (CMV-IgM) in serum or cytomegalovirus-deoxyribonucleic acid (CMV-DNA) by polymerase chain reaction in blood or urine.

**Results:** There were 43 respondents from 36 centers in 26 countries. The total number of BA patients per year was between 208 and 380 from centers with 0–5 to >20 BA patients yearly (median 6–10). CMV infection was tested in 27 centers (75%), of which 18 (67%) use AVT. The rate of CMV infection varied between 0%–5% and 40%–50% (median 5%–10%). Willingness to treat the infection did not differ between centers with low and high rates of CMV infection.

**Conclusions:** Most centers test for CMV infection, and a considerable proportion use AVT despite the lack of evidence of its benefits. A future randomized study on treating CMV infection in BA patients is necessary and feasible.

**KEYWORDS**

antiviral treatment, ganciclovir, survey

## 1 | INTRODUCTION

Biliary atresia (BA) is a severe disease that causes cholestatic jaundice and liver failure in infants. BA is treated with surgery to restore bile drainage. Even though the surgery, called Kasai portoenterostomy, is often successful, BA is the most common reason for liver transplantation in children.<sup>1,2</sup> The reported rate of BA varies between 1:5000–1:20,000 worldwide.<sup>3–7</sup>

The etiology of BA is unknown, but it has been suggested that BA can be divided into four different clinical variants, that is, isolated BA, syndromic BA, cystic BA, and cytomegalovirus (CMV) associated BA.<sup>8</sup> This suggests that the disease might have more than one cause. A few studies show that patients with BA and CMV infection might have lower jaundice clearance after surgery than uninfected patients.<sup>9,10</sup> On the other hand, a recent

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North American multicenter study reported no difference in jaundice clearance or native liver survival between infected and uninfected patients but showed a higher pretransplant mortality rate for CMV-infected patients.<sup>11</sup> If the overall outcome is influenced by CMV infection this might open up for the use of antiviral treatment (AVT) in some of the patients with BA.<sup>12</sup>

CMV infection is common in all populations, and most infected persons have mild or no symptoms. The first CMV infection in life will give life-long immunity, and a population's seropositivity (for cytomegalovirus-immunoglobulin G [CMV-IgG]) will increase with age. However, some individuals will develop severe symptoms from CMV infection and be very ill from CMV hepatitis. CMV hepatitis includes symptoms and laboratory abnormalities similar to BA; therefore, it can be hard to distinguish between these diseases in infants. If a patient has both diseases simultaneously, the clinician must decide if the CMV infection needs to be treated or if it is just "an innocent bystander."

The reported rate of CMV infection in patients with BA is 10%–78%<sup>13–20</sup>; thus, it is more common in these patients than in otherwise healthy 2-month-old infants, where the incidence of CMV infection has been reported to be 6%.<sup>21</sup>

Studies on AVT in infants with CMV hepatitis but without BA found treatment with ganciclovir to be effective in the acute phase of the disease, but treatment did not prevent long-term complications.<sup>22</sup> In a retrospective report from the UK, the use of AVT significantly improved outcomes for CMV-positive BA patients.<sup>12</sup> Moreover, a recent study from Sweden showed that AVT effectively reduces the viral load in patients with BA with no major side effects.<sup>10</sup> A European survey study from 2019 showed that surgeons from 7 out of 15 pediatric centers (47%) would use AVT if the patients with BA were CMV positive.<sup>23</sup>

The role of CMV infection in BA is unclear, the reported rate of CMV infection varies, and consensus about AVT is lacking. Therefore, this survey study aimed to further explore the need for a future study on AVT by assessing how CMV infection in patients with BA is managed in different centers around the world. The long-term goal is for the outcome after surgery of CMV-infected patients to equal the outcome of uninfected patients.

## 2 | METHODS

### 2.1 | Participants

Participants in an international multidisciplinary congress on BA (BARD-Bruges-2022), organized in collaboration with the European Reference Network

#### What is Known

- Patients with biliary atresia (BA) and infection with cytomegalovirus (CMV) may have poorer native liver survival than uninfected patients.
- Antiviral treatment for CMV infection effectively reduces the viral load.

#### What is New

- Fifty percent of centers use antiviral treatment for CMV infection in patients with BA.
- A prospective study on antiviral treatment for CMV infection in patients with BA is both needed and feasible.

(ERN) for rare liver diseases in June 2022, were invited to fill out an online questionnaire. The participants in the congress were initially invited to answer the questionnaire during an oral presentation followed by two E-mail reminders (reaching 151 congress participants). The respondents were identified by name and workplace to ensure that only one answer from each center was analyzed.

### 2.2 | Questionnaire

The questionnaire contained questions concerning the management of CMV infection in patients with BA. The complete questionnaire and introductory text can be found in Supporting Information: Digital Content 1.

The survey consisted of 10 multiple-choice questions and was composed using SurveyMonkey. It was open from June 18 to October 4, 2022. Answers to questions were either dichotomic or multiple choices of different numeric intervals. Ongoing CMV infection was defined by detecting CMV-IgM in serum or CMV-DNA by polymerase chain reaction (PCR) in blood or urine.

### 2.3 | Inclusion criteria

Any clinician answering the questionnaire. All respondents are listed in Contributors, Supporting Information: Digital Content 2.

### 2.4 | Exclusion criteria

When one center had more than one respondent, only the first respondent's answers were analyzed. When the respondent was unidentifiable, none of the answers were analyzed.

**TABLE 1** Country of residence for the respondents of the survey.

Country	Number of responding centers per country
Asia	
Bangladesh	1
Hong Kong	1
India	1
Singapore	1
Taiwan	1
Thailand	1
Uzbekistan	1
Europe	
Denmark	1
Finland	1
France	2
Germany	2
Hungary	1
Italy	3
Netherlands	1
Poland	1
Portugal	1
Romania	1
Spain	1
Sweden	2
Switzerland	1
United Kingdom	2
North America	
United States of America	5
South America	
Argentina	1
Colombia	1
Mexico	1
Oceania	
New Zealand	1

## 2.5 | Statistical analyses

Data were analyzed using descriptive statistics. Continuous data was compared using the Mann–Whitney  $U$  test, and categorical data was compared using cross-tabulation and the  $\chi^2$  test. In case of missing data, the respondents' data was not used in the respective analyses.

**TABLE 2** Yearly number of patients with BA.

Number of BA patients per year in each center	Number of centers	Calculated number of BA patients per year in all centers combined
0–5	14	0–70
6–10	13	78–130
10–20	5	50–100
>20	4	80–>80
Sum	36	208–>380

*Note:* Table of how many patients with BA each 36 centers in the study manage yearly. The third column is their calculated combined number of patients per year. Abbreviation: BA, biliary atresia.

## 2.6 | Ethical approval

As this was a survey using estimations on center levels and no individual patient data, no ethical approval was requested.

## 3 | RESULTS

### 3.1 | Respondents' background

There were 43 respondents (24 pediatric gastroenterologists/hepatologists, 17 pediatric surgeons, and 2 transplant surgeons) from 36 centers in 26 countries globally. The countries in which the respondents reside are listed in Table 1.

### 3.2 | Yearly number of patients for each center

Both small and large centers were represented in the survey. The respondents reported their yearly number of patients using intervals shown in Table 2. The yearly number of patients with BA for all centers combined was between 208 and 380.

### 3.3 | Workup and follow-up after Kasai portoenterostomy

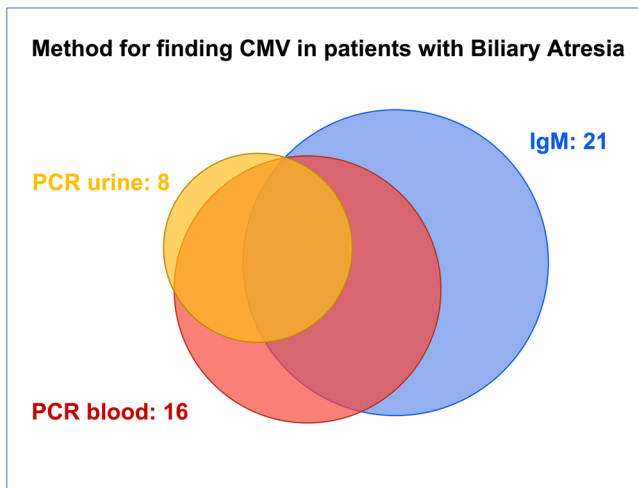
It was more common for pediatric gastroenterologists/hepatologists to be responsible for both workup before and follow-up after Kasai portoenterostomy, but in three centers workup and follow-up were carried out by pediatric surgeons. The workup was done by pediatric gastroenterologists/hepatologists in 26 centers, pediatric surgeons in 7 centers, general pediatricians in 2 centers, and "other" in 1 center. The follow-up was done by pediatric gastroenterologists/hepatologists in 27 centers, pediatric surgeons in 8 centers, and "other" in 1 center.

### 3.4 | CMV testing

Testing for CMV infection was performed in 27/36 centers (75%). The most used method was CMV-IgM, and the second most used was a combination of CMV-IgM and CMV-PCR in blood. The use of different methods is illustrated in the schematic Figure 1. The 10 centers that only used IgM to detect CMV infection reported a slightly lower rate of CMV infection (median 5%–10%) than the 16 centers that used IgM and/or PCR (median 10%–20%) ( $p = 0.36$ ).

### 3.5 | CMV infection

The rate of CMV-infected patients differed significantly between centers; the median rate of CMV was 5%–10%, and the highest was 40%–50%. Figure 2



**FIGURE 1** Illustration of methods used for finding cytomegalovirus infection in patients with biliary atresia in 27 pediatric centers. Details about how many centers use specific combinations of methods: IgM: 10, IgM and PCR in blood: 7, IgM, PCR in blood and PCR in urine: 4, PCR in blood and PCR in urine: 3, PCR in blood: 2, PCR in urine: 1. CMV, cytomegalovirus; IgM, immunoglobulin M; PCR, polymerase chain reaction.

visualizes the rates of CMV infection among patients with BA in the centers included. Information about the rate of CMV infection was available from 26 centers. One of the 27 centers that reported regular testing did not report the rate of CMV infection in their patients.

### 3.6 | CMV treatment

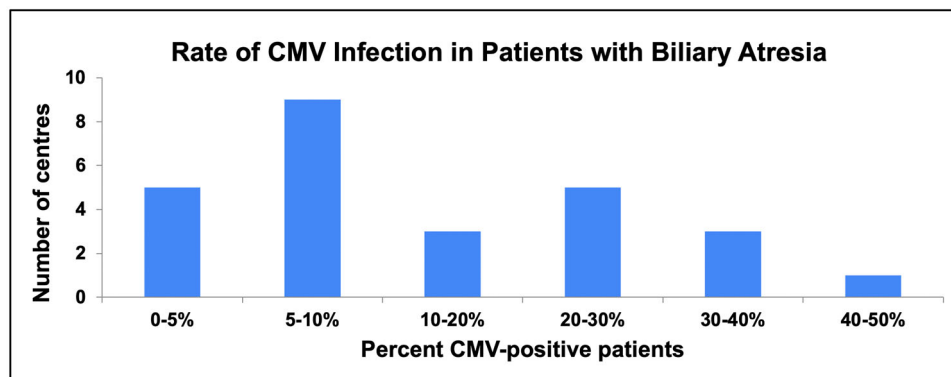
Of all 36 responding centers, 18 (50%) would use AVT if the patients with BA were CMV-positive. Of the 27 centers that routinely tested for CMV infection, 18 (67%) would use AVT if the patients with BA were CMV-positive. The use or nonuse of AVT was quite evenly distributed in centers across Europe, Asia, North America, and South America.

Willingness to treat the infection did not differ between centers with low and high rates of CMV infection. The management of CMV infection did not differ significantly between surgeons or gastroenterologists/hepatologists; seven out of seven surgeons test for CMV infection, and three out of seven surgeons would treat the infection. Out of 28 gastroenterologists/hepatologists, 20 test for CMV infection, and 15 of those 20 would treat the infection. One center responded “other” as responsible for workup and follow-up and was therefore not included in this analysis of differences between surgeons and gastroenterologists/hepatologists.

Ten centers answered that they use both/either intravenous ganciclovir or oral valganciclovir. Six centers answered that they use oral valganciclovir, and only two centers answered that they use intravenous ganciclovir.

### 3.7 | Interest in future prospective study

Clinicians from 33 centers expressed an interest in a future prospective study.



**FIGURE 2** Graph of different rates of cytomegalovirus infection in patients with biliary atresia in 26 pediatric centers. CMV, cytomegalovirus.

## 4 | DISCUSSION

The results of this survey are consistent with the results of the smaller European study from 2019.<sup>23</sup> We could confirm in a larger and globally spread group of centers that there is no international consensus about testing for or treating CMV infection in patients with BA. Thus, 25% of the centers are not testing the patients for CMV infection, which implies that it is not included in their standard work-up for neonatal cholestasis and that they do not believe that CMV infection would affect the outcome after surgery. On the other hand, 50% of the centers use AVT for CMV infection in patients with BA, suggesting that they believe it is beneficial for the outcome. Since 50% of the centers use AVT for CMV-infected patients, and 50% do not, it could be considered a randomly chosen treatment. Therefore, we propose the need for a prospective, randomized, multicenter study on CMV infection treatment in patients with BA.

It seems that CMV-infected patients are older at the time of Kasai portoenterostomy<sup>11,13,20</sup> which is a well-known factor for worse outcome after surgery. Some studies show that the infected patients have lower jaundice clearance,<sup>9,13,20</sup> but not many studies have convincingly shown that CMV infection negatively affects native liver survival. In a small study from the UK,<sup>12</sup> CMV-infected patients seemed to benefit from AVT regarding clearance of jaundice, and in another study from UK,<sup>20</sup> untreated CMV positive patients had lower rate of native liver survival than patients receiving AVT. The authors of the previously mentioned, and recently published, North American multicenter study on this topic reported that none of the participating centers used AVT for CMV in BA patients.<sup>11,24,25</sup>

Even though CMV-associated BA has been suggested to be one of four clinical subgroups of BA,<sup>8</sup> studies showing that CMV, in fact, causes BA are lacking.

If indeed CMV-associated BA would be a separate etiological entity, CMV-positive patients with other kinds of BA might also be included in this subgroup. A question could then be raised about the risk of wrongfully treating these particular patients with AVT. Furthermore, the question remains whether any patients with BA and CMV infection will benefit from AVT.

A study on the effect of AVT in patients with BA and CMV infection in a randomized setting requires a sufficient number of CMV-positive patients. We calculated the sample size for a future study using numbers from a recent Swedish study<sup>10</sup> where the CMV-infected patients received AVT and had a 1-year native liver survival of 47%. To show a 25% effect of AVT with 80% power, using two independent study groups, at least 122 patients need to be included. The mean yearly number of patients with BA in the 36 responding centers from this survey is approximately 300

((208 + 380)/2 = 294). The median rate of CMV infection could be 10%–20% if all centers would use both IgM and PCR for screening. The yearly number of potentially infected patients would consequently be 45 (300 × 0.15 = 45). Participation from all these centers would make it possible to include 135 patients in a randomized study within 3 years.

The questionnaire was designed to be as non-demanding as possible to maximize the number of responses. Answering in estimated intervals was presumed to be easier than answering with precise numbers, but the ranges made it challenging to calculate statistics, especially when the range included the number zero. Also, for simplicity, the questionnaire was not designed to get detailed information about AVT, follow-up or outcome. The strengths of this study are that it includes both small and large centers from different parts of the world and explores a subject that is increasingly discussed but not sufficiently researched. However, since the questionnaire was offered to participants at a conference in Europe there is a relative under-representation of non-European centers.

## 5 | CONCLUSION

Most centers test for CMV infection, and a considerable proportion use AVT despite the lack of solid evidence of its benefits. Our data suggest that a prospective, randomized, multicenter study on the treatment of CMV infection in patients with BA is necessary. Such a study would be feasible if close collaboration could be established between tertiary centers responding to this survey, utilizing expertise from ERN Rare Liver, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the network of North American collaborators.<sup>11,24</sup>

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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