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Children's Hepatitis Outbreak Still Lacks Definitive Answers

As new cases of acute hepatitis among kids have declined, questions remain unanswered.

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Cases of unexplained acute hepatitis among children have declined from their peak in early summer, but a small number of cases are still being reported, and a singular definitive cause has not yet been identified, according to a presentation at the AASLD Liver Meeting.

As previously reported, the cluster was first detected in the United Kingdom in April. At that time, 73 cases of severe acute hepatitis of unknown cause were under investigation, mostly among children ages two to five years old. Once health officials and doctors knew what to look for, more reports began flooding in from around the world.

By the time cases began to decline in July, more than 1,000 probable cases had been identified dating back to the fall of 2021, according to the World Health Organization. Most children recovered, but some developed liver failure, required liver transplants or died. But after the initial burst, case reports began to level off. It is still unclear whether pediatric acute hepatitis actually became more common over the past year or whether it is truly a new medical condition.

Multiple possible causes were proposed—and mostly dismissed—including well-known hepatitis viruses (the children tested negative for hepatitis A, B, C, D and E), current SARS-CoV-2 infection (most tested negative) and COVID-19 vaccines (most were too young to be eligible). Some early evidence pointed to an adenovirus (in particular, adenovirus type 41). Some experts suspected kids might be more susceptible to adenoviruses due to "immunity debt" from reduced exposure during COVID lockdowns. Others blamed the coronavirus more directly, suggesting it might damage the liver, trigger inflammation or impair immune defenses in kids who no longer tested positive.

In July, research teams in England and Scotland independently reported that a different virus, adeno-associated virus type 2 (AAV2), might be the cause, but it appeared to require the help of another virus, which might be adenovirus 41, SARS-CoV-2 or something else.

Case Characteristics

In an effort to learn more, the Severe Hepatitis in Pediatric Patients (SHIPP) international registry

was created to characterize the clinical features and outcomes of pediatric acute hepatitis. Pediatric gastroenterologists from around the world were invited to contribute, and 25 sites responded. Most of the responding sites were in the United States and Canada, so the registry does not offer a full picture of the outbreak, which has included nearly 500 cases in the United Kingdom and Europe. The registry was started in July and data were included through the end of October.

As Rohit Kohli, MBBS, of Children's Hospital Los Angeles reported, the registry included children (under age 18) with an ALT liver enzyme level above 500—indicating significant liver injury—with no known chronic liver disease or ingestion of acetaminophen (Tylenol), which can cause acute liver damage.

A total of 151 cases had been reported at the time of the Liver Meeting presentation—roughly one third of the cases in the Americas included in the July WHO tally. Cases peaked at around 20 per month in May and June, with 10 or fewer cases reported in July, August and September. Most of the children were young, with a median age of 41 months. Just over half were boys and 40% were Latino.

At they presented with acute hepatitis, 80% of the children had gastrointestinal symptoms, followed by fever (27%) and respiratory symptoms (23%). Some 15% were taking medications for chronic conditions, including nearly 3% on immunosuppressant drugs. Fifteen children (10%) had had SARS-CoV-2 infection during the past year, and 20 (13%) had received COVID-19 vaccines. Laboratory values, including ALT, AST and bilirubin, were elevated, and 36 children (24%) had evidence of autoimmune biomarkers.

Testing revealed the presence of a range of viruses, but none were observed in a majority of the children. Just over 40% tested positive on a respiratory infection panel, with common cold viruses being most frequent. About one in five (22%) tested positive for adenoviruses, 13% for Epstein-Barr virus (EBV) and 4% for cytomegalovirus (CMV). Kohli noted that there was "a lot of overlap with multiple positive viruses in many patients."

Less than half of the children (42%) received liver biopsies. Pathology descriptions emphasized portal and lobular inflammation with infiltration of CD8 T cells, according to Kohli. Three children developed hemophagocytic lymphohistiocytosis, a build-up of white blood cells that can be triggered by viral infections. However, none of the biopsy samples showed a definitive viral cause of hepatitis.

More than a quarter of the children (27%) required treatment in an intensive care unit. Eight (5%) underwent liver transplantation. About a third (32%) received steroids, and this group was more likely to require transplantation. Three of the children died.

The good news, Kohli said, is that more than 90% of the children survived with their original liver intact. Most of the recovered children at his center returned to normal liver function, he noted, but the registry does not include long-term follow-up data.

In this large international dataset of pediatric patients, “the majority did not have a singular definitive etiology,” Kohli concluded. He added that continued community surveillance and close cooperation through the registry are needed to further investigate the indeterminate causes of hepatitis in children. “This is a call to arms to all of us,” he said.

Adenovirus Treatment

These findings raise the question of how best to prevent and treat acute pediatric hepatitis. Given that adenoviruses were commonly detected in affected children, some clinicians have attempted to treat the infection. Although there are no approved drugs for adenovirus, cidofovir—a broad-spectrum nucleotide analogue antiviral best known as a treatment for CMV retinitis in people with AIDS—was shown to be active against multiple types of human adenovirus in laboratory studies.

Sunitha Vimalesvaran, MBBS, of King’s College Hospital in London, reported on the safety and efficacy of cidofovir for this indication. Among the 258 children with acute hepatitis who were tested for adenovirus in the United Kingdom, two thirds tested positive—considerably higher than the proportion in the SHIPP registry.

Nine children with acute hepatitis who tested positive for adenovirus received cidofovir. All were treated with the standard 5 milligrams per kilogram dose of cidofovir once weekly for two weeks and then every two weeks.

The median age of the treated children was approximately three years old. Most had evidence of prior SARS-CoV-2 infection, including two within six weeks prior to hepatitis presentation. Six had received liver transplants.

Four children experienced complete adenovirus clearance and four others showed significant viral load reduction. All showed improvement in clinical and biochemical parameters, the researchers reported. None of the transplant recipients experienced a recurrence of adenovirus-associated hepatitis in their new liver, despite immunosuppression.

Kidney toxicity is a major side effect of cidofovir, and the children also received probenecid, a medication that protects the kidneys, and other therapies to reduce adverse effects. The liver transplant recipients received the immunosuppressant drug tacrolimus, which can also cause kidney toxicity. Although all children initially had normal kidney function, five required kidney dialysis as part of acute liver failure management. Four children developed kidney dysfunction after the first or second dose of cidofovir, but all except one had normalized kidney function at the time of hospital discharge.

“Whilst we continue to understand the precise etiology and pathophysiology of this condition, interim use of cidofovir in children with acute liver failure and adenoviremia [detectable adenovirus in the blood] appears to be safe, well tolerated and effective in reducing adenoviremia,” the researchers concluded.

Click here to read the SHIPP registry abstract.

Click here to read the cidofovir abstract.

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