COMMENTARY

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International outbreak of acute pediatric hepatitis: Was acetaminophen the missing link?

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During the outbreak of acute pediatric hepatitis, two centers reported a threefold increase in cases.[1] In their report, the hepatitis was preceded by an acute viral infection with a period of fasting. Patients ranged in age from 3 months to 5 years. One notable finding was that all patients had received acetaminophen therapeutically at least two days before onset. Despite receiving normal doses, the authors asserted that "the potential for this injury may have been augmented by ingestion of therapeutic doses of acetaminophen while patients were in a fasted state". One might be surprised to learn that this was not a report from the well-known outbreak of acute childhood hepatitis that occurred in the winter and spring of 2021–2022, but an outbreak that was reported 30 years earlier.

Both this past outbreak, and the current international outbreak, however, have some things in common. First, while all patients in the former outbreak used acetaminophen, the majority (three-quarters) in the current outbreak did as well – as determined by the comprehensive UK Health Security Agency (UKHSA) investigation of cases in the United Kingdom.[2] Similarly, the other large epidemiological study on the outbreak in the USA also noted that acetaminophen was the "most frequently reported medication used".[3] Secondly, in the outbreak that occurred 30 years ago, although acetaminophen was considered a factor, it was never further investigated. This parallels the current outbreak, where acetaminophen has also not been investigated – in fact, the UKHSA simply concluded that "detection of paracetamol is likely to be related to appropriate therapeutic use…which would not be a concern"[2] – and thus further queries along these lines have come to an end.

Adenovirus has been a key suspect in many investigations into this outbreak. In addition, further studies have suggested adenovirus in combination with other infections such as adenovirus-associated virus type 2, human herpesvirus type 6, etc. may work synergistically to induce hepatitis.[4] While it may be tempting to conclude that adenovirus was a key link in all these cases, it does require one to overlook the fact that while adenovirus was detected in 68% of cases in the UK study,[5] for other studies on this outbreak it was much less frequent.[3,6–9] In this light, it may be worth reconsidering the often-discussed hypothesis that children in this outbreak may have been more sensitive to infections following removal of lockdown measures, due to a lack of previous exposure during pandemic restrictions.[10] Unlike adenovirus, acetaminophen, used to reduce fever and treat infectious symptoms, would have been common to all regions. Were these young children, naïve to many acute infections, more susceptible to hepatitis from the synergistic action of an acute infection plus acetaminophen?

Both animal and human studies demonstrate that infections can augment acetaminophen hepatoxicity. A study by Lopes et al.[11] measured the mortality rate in mice injected intravenously with a low dose of *Escherichia coli*

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without or with acetaminophen. All mice without acetaminophen administration survived after *E. coli* infection; however, there was liver injury and a 40% mortality rate in mice in the latter group, with evidence of impaired liver Kupffer cell function. In another study examining liver injury in hepatitis C virus (HCV) transgenic mice,[12] they found that in fed mice exposed to acetaminophen, liver toxicity increased, but was not markedly exaggerated as compared to the wild-type mice; however, in fasted mice, significantly greater liver injury was observed in HCV transgenic mice exposed to acetaminophen. Finally, in a mouse model infected with influenza B, investigators observed that compared to infected controls without acetaminophen, "concomitant infection with influenza B virus has a significant enhancing effect on the hepatic toxicity of acetaminophen in mice."[13]

Several studies in humans with acute viral infections also observed worse hepatic outcomes for patients who had used acetaminophen therapeutically. Garfein et al.[14] reported on an outbreak of acute hepatitis B among injection drug users. Patients were divided into those with and without fulminant hepatitis, with 100% of the former exposed to acetaminophen *vs*. 44% of the latter. No patient had evidence of chronic liver disease. Renzende et al.[15] reviewed 40 consecutive cases of acute hepatitis A where there was precise documentation of drug intake prior to admission. Those with hepatitis-associated encephalopathy were significantly more likely to have taken acetaminophen than those without (odds ratio = 6.9, $P = 0.03$). Acetaminophen use was also associated with elevated alanine aminotransferase (ALT) and bilirubin levels. Polson et al.[16] reported on 26 patients who presented with acute hepatitis A or B and had acetaminophen levels measured. Median ALT levels were 5400 U/L for those with detectable acetaminophen *vs.* 1367 U/L with no acetaminophen detected. The odds of death were 2.4 times higher in the acetaminophen group *vs.* the non-acetaminophen group. The authors concluded that "a few grams of acetaminophen taken in response to viral symptoms could potentially tip the balance toward the development of fulminant hepatic failure".

Even when there are no clinical signs or symptoms of hepatitis, acetaminophen exposure may still lead to liver injury. A notable human study was undertaken during a measles outbreak in Israel.[17] All patients received therapeutic doses of acetaminophen or dipyrone to reduce fever; however, those patients who received acetaminophen, had a significantly higher elevation of liver enzymes. In another study, Jiang et al.[18] examined acetaminophen protein adduct levels (markers for hepatoxicity) in hospitalized children who received therapeutic doses of acetaminophen. They noted patients with infections had "remarkably higher adduct concentrations than those observed for patients admitted for noninfectious diseases" and multiple doses were correlated with higher levels. Amongst the 181 children receiving acetaminophen, 2% had excessive levels (signaling acetaminophen-induced liver injury) – not a trivial number when considering all received doses within the therapeutic range. Similarly, in a study of patients hospitalized with acute viral hepatitis, therapeutic doses of acetaminophen were associated with greater alterations of surrogate markers of the severity of acute viral hepatitis.[19] These studies highlight the fact that even when there are no overt symptoms, there still may be underlying injury to the liver.

In the past, aspirin was one of the most commonly used antipyretics, and therapeutic doses of aspirin were long assumed to be safe for children; however, epidemiological data countered this assumption, showing that a rare adverse effect (i.e. Reye syndrome) was more likely to occur in those using aspirin – nearly all within the therapeutic range. Similarly, the safety of acetaminophen is too often assumed, rather than determined by evidence. For example, studies examining causes of acute hepatitis, generally divide probable factors into distinct categories. For example, a study[20] examining pediatric patients with acute liver failure (ALF) categorized causes as: acetaminophen overdose (18%), mushroom poisoning (15%), viral infections (9%), and indeterminate (59%) – but are these mutually exclusive categories? Did the patient with mushroom poisoning take acetaminophen for abdominal pain or did the patient with a viral infection use acetaminophen to reduce fever? How many in the indeterminate category had taken acetaminophen? Would they be statistically more likely to have used acetaminophen (at therapeutic doses of course) than comparable patients without ALF? This is not even considered, but animal and human data support that a pathological synergism between these two factors may be enough to trigger hepatitis in rare cases.

Considering that acetaminophen was the most common drug used in the two largest outbreaks reported,[2,3] we should at least do more than assume it was not a factor. Despite being one of the most common causes of pediatric hepatitis, acetaminophen was never ruled out in this outbreak of acute hepatitis. Could this possible suspect be the missing link between all these cases in children who were immunologically naïve due to pandemic restrictions? While it is well known that an overdose of acetaminophen can lead to hepatitis, why is it not possible in rare cases that normal doses (maybe multiple normal doses) can cause hepatitis? While many have ruled out acetaminophen theoretically, it has yet to be ruled out epidemiologically and should remain a possible suspect until there is evidence to exclude it.

From the preceding data reviewed, several issues remain unresolved: normal doses are generally not recorded or reported,[4] beyond this outbreak, reports of acute hepatitis should determine the role therapeutic doses may play in this condition; other co-factors need to be explored as well, such as the role of multiple doses and fasting on liver

injury; animal and human data support hazardous synergism with infections, and further studies need to be carried out in animal models to elucidate risks. One of the recommendations of the UKHSA has been to establish an ongoing surveillance scheme for non-A–non-E hepatitis. While a valid idea, the one shortfall for such a surveillance program is that the use of acetaminophen will likely not be recorded in cases where it represents "appropriate therapeutic use". Much of the presumed safety of acetaminophen depends on our assumption that uncommon occurrences of hepatitis are not related to use within the normal range. This has never been systematically studied and thus critical data to support the safety of this drug related to these rare adverse events does not exist.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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