Hepatitis E, a silent food-borne epidemic in Europe

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What is the burden of Hepatitis E Virus?

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis worldwide. Across nine endemic regions, an estimated 3.4 million symptomatic cases have been reported. In developing regions HEV causes large outbreaks amongst young adults. In most cases patients experience an acute self-limiting illness, but in pregnant women and those with pre-existing liver disease there is a significant mortality rate.

In developed countries the picture is quite different. Cases are typically sporadic, and affected patients are generally older than in poorer regions. There are an estimated 100,000 new infections each year in England alone, but confirmed cases account for less than 1% of this number. In large part this is due to our currently incomplete understanding of the clinical phenotype of HEV infection, which leads to many cases going unrecognised or being misdiagnosed. The clinical presentation can range from asymptomatic infection to fulminant liver failure and also includes a variety of extra-hepatic manifestations, most commonly neurological injury.

What are the risk factors?

In poorer countries, HEV genotypes 1 and 2 are predominant. These genotypes are obligate human pathogens which are spread via the faecal-oral route, so the primary risk factor in these areas is poor sanitation. In industrialised nations the endemic HEV genotypes are 3 and 4, which are porcine zoonoses. HEV is found in pig faeces, and it is highly likely that a significant amount of the virus finds its way into watercourses through run-off from pig farms. Additionally, HEV has been found in pork products, and consumption of these products is associated with an increased risk of infection.
What are the treatment algorithms?

In some European countries, national guidelines suggest that all patients presenting with acute hepatitis should be tested for HEV. The precise definition of ‘acute hepatitis’ varies, but elevated alanine aminotransferase (ALT) levels and ALT to alkaline phosphatase (ALKP) ratio levels are commonly used to direct hepatitis investigations. In a recent study our research group found that an ALT cut-off of 300 IU/L is a highly sensitive (98.6%) predictor of a positive HEV test. However, as previously mentioned, a significant proportion of HEV infections do not produce clinically apparent hepatitis so an ALT result less than 300 IU/L cannot preclude HEV testing in all patients. There are three clinical scenarios where HEV testing should be considered regardless of ALT result.

The most common extra-hepatic manifestation of HEV infection is acute neurological injury. There is an especially strong association between HEV and both neuralgic amyotrophy (NA) and Guillain–Barré syndrome (GBS). In cases of HEV-associated neurological injury the neurological signs and symptoms dominate the clinical presentation; hepatic symptoms are mild, ALT results can be normal and the patients are not typically jaundiced. Therefore HEV testing should be considered for all patients which present with acute neurological injury. This is especially important given the observation that patients with HEV-associated neurological conditions are often viraemic at presentation. This raises the possibility that antiviral therapy may have a role in ameliorating disease progression in these patients.

The second group in which clinicians should have a low index of suspicion for HEV infection is patients with chronic liver disease. In these patients acute hepatitis E can result in decompensation, which carries a significant risk of mortality. While a minority of these cases have extremely elevated ALT results (>1000 IU/L), more than 80% do not display any clinical evidence of HEV infection and have ALT results <300 IU/L.

Finally, immunocompromised patients may be chronically infected with HEV. These patients often have only mildly elevated ALT results, so in this group an ALT-based testing algorithm is not appropriate. Immunocompromised patients with any persistent abnormality of ALT result should be tested for HEV to rule out chronic infection. Additionally, serology is unreliable in this cohort so testing of these patients should always include molecular techniques. In solid organ transplant patients with chronic HEV infection immunosuppressant therapy should be reduced; this will allow around a third of patients to achieve clearance of the virus. Anti-viral treatment with ribavirin has also been found to be effective in treating chronic HEV infection in this patient group. In HIV-positive patients and those receiving chemotherapy for haematological conditions both ribavirin and interferon treatment have been shown to be effective.

What are the challenges ahead?

The most immediate challenge in the field is the elucidation of the relationship between HEV infection and its extra-hepatic manifestations. An ever-increasing number of case reports and case series have described linked HEV infection to complications including haematological disorders, glomerulonephritis, pancreatitis and thyroiditis. However, neurological injury is by far the most commonly reported extra-hepatic manifestation. HEV infection has been associated with a range of neurological conditions. These include transverse myelitis, meningoencephalitis, polyradiculopathy and cranial nerve neuritis. The conditions which are most strongly associated with HEV infection are NA and GBS. The next step will be to conduct case-control studies in order to clarify the role of HEV in the natural history of these conditions.
References