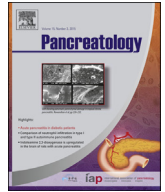




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## Pancreatology

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## Review article

## Frequency and prognosis of acute pancreatitis associated with acute hepatitis E: A systematic review

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## ABSTRACT

**Background:** The association of acute pancreatitis (AP) with viral hepatitis is well known, and is usually attributed to HAV, HBV, or HCV. AP related to acute hepatitis E (AHE) has been rarely described, and the typical profile is that of a young male, residing in an endemic area, presenting with mild to moderate pancreatitis, and improving with conservative management.

**Rationale:** An increasing number of reports describe AP associated with AHE. Some life-threatening complications related to AP may occur, and death has been reported. In addition, it is possible that early diagnosis of these cases may help in reducing the morbidity and mortality.

**Objective:** Perform a systematic review to study cases of AP associated with AHE and to assess their prognosis.

**Data sources:** PubMed, EMBASE, Scopus, and the Cochrane library.

**Study selection:** All available studies discussing AP associated with AHE.

**Data extraction and assessment:** Two blinded independent observers extracted and assessed the studies for diagnosis of AHE based on serological and/or molecular techniques, diagnosis of fulminant hepatitis based on the American Association for the study of Liver Diseases (AASLD) position paper, diagnosis of AP based on the American College of Gastroenterology (ACG) guidelines, diagnosis of AP associated with AHE based on Makharia's association, and diagnosis of AP severity based on the Revision of the Atlanta Classification (RAC).

**Results:** Thirteen case reports and 4 case series were found with 55 patients meeting the inclusion criteria. All patients originated from Southern Asia or had a recent travel to that area. The mean age at diagnosis was 28 years with a male to female ratio of 18:1. The mean interval between the onset of jaundice and the onset of AP pain was 10 days. AP was mild or moderately severe in 45 patients (82%), and severe in 10 patients (18%). Mortality was reported in 2 patients (3.6%).

**Conclusion:** Fifty-five cases of acute pancreatitis associated with AHE are reported in the literature. Acute pancreatitis in this setting is severe in approximately one fifth of patients with an overall mortality rate similar to all other causes of AP.

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## Background

The association of acute pancreatitis (AP) with viral hepatitis is well known. Usually, these cases are attributed to HAV [1], HBV [2],

or HCV [3]. Recently, there have been an increasing number of reports describing AP associated with acute hepatitis E (AHE). The typical profile of the majority of patients is that of a young male residing in an endemic area, and who develops mild to moderate pancreatitis, usually 2–3 weeks after the onset of jaundice, and improves with conservative management [4]. However, some life-threatening complications, such as necrotizing pancreatitis and multiple organ failure, may occur and death has been reported [5]. It is possible that early diagnosis of these cases may help in reducing the morbidity and mortality. The aim of this systematic

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review is to study cases of AP associated with AHE and to assess their prognosis.

### Searching methods

We searched four major databases (PubMed, EMBASE, Scopus, and the Cochrane library) on July 7, 2014 using the terms “hepatitis E” AND “acute pancreatitis”. No language or date restrictions were set. Articles with non-A non-B hepatitis were not included. Reference lists were individually reviewed for additional cases. We wrote to authors in case of missing information.

### Articles inclusion criteria

#### Diagnosis of acute hepatitis E

AHE is diagnosed in immunocompetent individuals based on detection of anti-HEV IgM, increased titers of anti-HEV IgG, or detection of HEV RNA in blood or stool (Fig. 1). AHE is diagnosed in immunocompromised individuals based on detection of HEV RNA in blood or stool [6].

#### Diagnosis of fulminant hepatitis

Fulminant hepatitis is diagnosed based on the American Association for Study of Liver Diseases (AASLD) position paper on acute liver failure [7], and according to the association of coagulation abnormality with (INR)  $\geq 1.5$ , and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks duration.

#### Diagnosis of acute pancreatitis

AP is diagnosed according to the American College of Gastroenterology (ACG) guidelines [8] by the presence of 2 of the 3 following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than three times the upper limit of normal, and (iii) characteristic findings from abdominal imaging.

#### Diagnosis of AP associated with AHE

Association between AHE and AP is best confirmed by the demonstration of HEV RNA in the pancreas which is not applicable in clinical practice. Instead, we use the association proposed by Makharia et al. [9] based on: (i) co-occurrence of AHE and AP, (ii) exclusion of other causes of AP such as gallstones, alcohol, drugs, trauma, hypercalcemia, and hypertriglyceridemia, and (iii) simultaneous resolution of both entities.

#### Determination of acute pancreatitis severity

AP is classified into mild, moderately severe or severe based on Revision of the Atlanta classification (RAC) [10]. Mild AP is

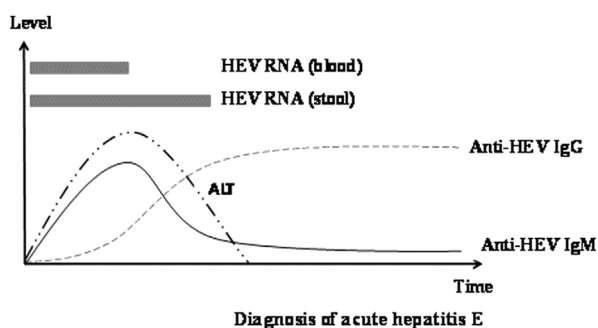


Fig. 1. Diagnosis of acute hepatitis E (Modified from: Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis E virus infection. Gastroenterology 2012; 142:1388–1397).

characterized by the absence of organ failure and the absence of local or systemic complications. Moderately severe AP is characterized by the presence of transient organ failure (<48 h) of the respiratory, renal or cardiovascular system, or local or systemic complications. Severe AP (SAP) is characterized by single or multiple persistent organ failure for more than 48 h.

### Data extraction and assessment

Two independent reviewers (HS, BF) blinded to names of authors, institutions, journal names, funding, and acknowledgments evaluated the included studies, and extracted the relevant data. These parameters were presented in the following predefined tables: diagnosis of AHE and AP (Table 1), exclusion of other common causes of AP (Table 2), severity of AP related to non-fulminant AHE (Table 3), and overall results of included patients (Table 4). Disagreements between the two reviewers were resolved by discussion and analysis of the data.

## Results

The flow diagram of the study selection is shown in Fig. 2. Seventeen studies meeting the selection criteria were examined. Thirteen studies were case reports [4,5,9,11–22], 2 were prospective case series [23,24], and 2 were retrospective case series [4,25,26]. One study was in an abstract form [26], and all others were original articles. There were a total of 56 patients. One patient did not meet the selection criteria because of other plausible causes of AP (including medications) [15].

Fifty-three patients were from South Asia (India and Nepal), and the remaining 2 were from western countries with a recent travel to South Asia [16,17]. The mean age of patients at diagnosis was 28 years (range: 7–54) with a male to female ratio of 18:1. The diagnosis of AHE was based on anti-HEV IgM in 51 patients, anti-HEV IgG and anti-HEV IgM in 1 patient, and anti-HEV IgM and HEV RNA in 3 patients (Table 1). Genotype testing was performed in one patient, and was type 1a [17]. Two patients have fulminant hepatitis E according to AASLD position paper on acute liver failure [7].

The diagnosis of AP was based on the ACG guideline in all patients. The diagnosis of AP associated with AHE based on Makharia's association was obtained in all but 2 patients who had SAP leading to death without excluding them from the study. The mean interval between the onset of jaundice and the onset of abdominal pain related to AP was 10 days (range: 0–35). The mean hospital stay for AP was 9 days (range: 2–35). Acute pancreatitis was mild in 19 cases, moderately severe in 9 cases, and severe in 10 cases. In 17 cases, it was not possible to classify patients due to incomplete data.

Conservative management resulted in the improvement of 50/55 patients (91%). Surgery was undertaken in 2 patients (cystojejunostomy for a large pancreatic pseudocyst in one patient [12], and therapeutic drainage of left-sided pleural effusion in a second patient [25]). The overall mortality rate was 3.6% as 2/55 perished due to SAP complications, whereas the mortality rate in patients with SAP was 20% (2 of 10 patients). Death was due to acute renal failure, severe metabolic acidosis, hemorrhagic pseudocyst, and hemodynamic instability in one patient [5]; and complications secondary to shock in a second patient [24].

## Discussion

In non-endemic regions, HEV-associated diseases have been increasingly described among immigrants, and immunosuppressed individuals such as transplant recipients, and HIV-infected patients. This has resulted in an increased clinical interest in HEV course and its pathogenesis and prevention, considering that it has been

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