The Incidence and Outcomes of Ischemic Hepatitis: A Systematic Review with Meta-analysis
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ABSTRACT

BACKGROUND: Ischemic hepatitis is a devastating cause of acute liver injury. Data are limited regarding its incidence and outcomes.

METHODS: Systematic review and meta-analysis of studies from PubMed, EMBASE, and Web of Science with specific search terms. Inclusion criteria included case series with >10 patients and clear case definition (especially liver enzyme levels >10 times the upper limit of normal).

RESULTS: Twenty-four papers met inclusion criteria. A total of 1782 cases were identified in these papers (mean 78 per paper, range 12-322). The pooled average age of the included patients was 64.2 years, and their mean peak aspartate aminotransferase level, alanine aminotransferase level, and total bilirubin were 2423 IU/L, 1893 IU/L, and 2.55 mg/dL, respectively. Ischemic hepatitis was present in 2 of every 1000 admissions; including 2.5 of every 100 intensive care unit admissions and 4 of 10 admissions associated with an aminotransferase level >10 times the upper limit of normal. The pooled proportions of patients with ischemic hepatitis who had a predisposing acute cardiac event or sepsis were 78.2% and 23.4%, respectively. The proportion of patients with a documented hypotensive event of any duration was 52.9%. Overall, the pooled rate of survival to discharge was 51% (range 23.1%-85.7%).

CONCLUSIONS: Ischemic hepatitis is a common cause of severe acute liver injury and is associated with a significant risk of in-hospital death. A major opportunity in the management of ischemic hepatitis is recognition of the condition without documented hypotension.

KEYWORDS: Congestive heart failure; Congestive hepatopathy; Hypoxic hepatitis; Liver failure; Shock liver

Massively (>10× the upper limit of normal) elevated liver enzymes generate a limited differential diagnosis, and the most common cause may be ischemic hepatitis.1,2 Also called hypoxic hepatitis or shock liver, ischemic hepatitis is the result of any state wherein hepatic blood-flow is critically insufficient for hepatocyte survival whether by volume or oxygen content.3–5 It is characterized by a (typically) transient, rapid and massive increase in liver enzymes often, but not necessarily, in the context of hypotension.4,6–9 Although ischemic hepatitis may be the cause of the majority of notably elevated liver enzymes,2,10 it is often missed and remains a frequent source of case reports describing the difficulty of diagnosis.11–16

The liver is generally well protected from ischemic injury. Hepatic blood flow accounts for ~25% of cardiac output through 2 sources: the portal vein and hepatic artery.17 While the portal vein supplies 80% of hepatic blood flow, even a marked decrease in portal flow is met by compensatory arteriolar dilation, potentially as a result of the accumulation of adenosine from injured hepatocytes.18 Similarly, arterial hypotension is rarely by itself...
complicated by ischemic hepatitis. Shock due to trauma or hemorrhage is rarely associated with a significant increase in liver enzymes. Ischemic hepatitis, therefore, is the result of simultaneous shortfalls from both vascular sources.

Passive hepatic congestion is a potentially necessary precondition for ischemic hepatitis. Seeto et al, like Killip and Payne, Richman et al, or Henrion et al before them, identified congestive heart failure — particularly elevated right-sided pressures — as a major contributing factor in ischemic hepatitis. As cardiac output diminishes or right-sided pressures increase (or both), the requisite pressure for hepatic sinusoidal perfusion climbs. Eventually, anterograde portal flow fades. We term the result a “functional portal vein occlusion.”

Ischemic hepatitis reflects the extreme of a spectrum of liver injury that begins with passive hepatic congestion. Congestive hepatopathy is a well-described consequence of congestive heart failure (via elevated central venous pressures) typified by congestion of centrilobular sinusoids in mild cases and hepatocyte necrosis if severe. Indeed, mild liver injury is common among, and predictive of, mortality for patients with decompensated heart failure. While systemic hypotension clearly potentiates centrilobular congestion and cellular necrosis, subtle, transient changes in arterial pressure may be sufficient to induce the dramatic presentation reflective of ischemic hepatitis. Accordingly, in patients with preexisting hepatic congestion, as little as 15-20 minutes of transient systemic hypotension is sufficient to produce massive liver cell necrosis.

Herein, we employ a systemic review and meta-analysis to describe the incidence and outcomes of ischemic hepatitis, with an additional focus on the proportion of patients with ischemic hepatitis with documented preceding hypotension, acute cardiac events, or sepsis.

CLINICAL SIGNIFICANCE

- Ischemic hepatitis is present in 2.5% of intensive care unit admissions.
- Fifty-seven percent of patients with liver enzymes >1000 IU/L have ischemic hepatitis.
- Only 1 in 2 patients will have an identifiable hypotensive episode.
- The vast majority of patients have markedly elevated cardiac filling pressures.
- In-hospital mortality associated with ischemic hepatitis is roughly 50%.

METHODS

This systematic review conforms to the guidelines outlined by the Meta-Analysis of Observational Studies in Epidemiology recommendations. As a first step, a broad (free text) search string was used in PubMed, EMBASE, and Web of Science as shown in Figure 1. Potentially relevant papers were accessed in order to review the full text, including those in languages other than English (to be translated). The references within each included manuscript and review were evaluated in order to identify additional papers. All references were managed using EndNote X6 (Thomson Reuters, New York, NY).

We included studies that reported primary data regarding the incidence, outcomes, and associations of ischemic hepatitis first published between January 1965 and April 18, 2015. Reviewed papers were included if the case-definition criteria roughly reflected Henrion’s criteria: 1) A clinical setting of cardiac, circulatory, or respiratory failure; 2) A substantial but transient increase in serum aminotransferase activity; 3) The exclusion of other putative causes of hepatitis, namely viral hepatitis or drug-induced liver injury. The timeframe of liver enzyme elevation resolution was rarely described and thus not required for inclusion.

We excluded all review articles, letters to the editor without primary data, and case reports (<10 patients). Papers unrelated to acute ischemic hepatitis were excluded, including those relating strictly to passive congestion. Papers without inclusion criteria for ischemic hepatitis cases were excluded if attempted contact with the authors could not resolve the problem (eg, ). Three papers included patients with liver enzyme levels significantly below Henrion criteria. If papers met inclusion criteria but were found to be a duplicate analysis of the same cohort, the study with the largest cohort was included.

The range of peak liver enzyme (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) cutoffs varied among studies. We accepted any cutoff of at least 300 IU/L (excluding 2 studies that included low peak values which have been reviewed previously, and another that defined ischemic hepatitis using International Classification of Diseases, Revision codes). We contacted authors of 2 abstracts without defined inclusion criteria, but were unable to determine these data.

Once a study was included, data were extracted and entered into a table that included study-level variables (lead author, year of publication, study site [hospital unit], sample size from which the cases were drawn, and patient-level variables [age, presence of hypotension [arterial pressure <90/60 mm Hg], sepsis [as reported by each author], and acute cardiac events, as well as survival to discharge]. Acute cardiac events included decompensated heart failure, acute myocardial infarction, tamponade, pulmonary embolus, cardiac arrest, and unstable arrhythmia. The proportion with acute cardiac events was pooled, excluding one study were acute cardiac events were required for study enrollment. As many series included a minority of patients...