

# Hypoxic Hepatitis: A Review and Clinical Update

Najeff Waseem<sup>1,2</sup> and Po-Hung Chen<sup>1\*</sup>

<sup>1</sup>Division of Gastroenterology & Hepatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; <sup>2</sup>George Washington School of Medicine and Health Sciences, Washington, DC, USA

## Abstract

Hypoxic hepatitis (HH), also known as ischemic hepatitis or shock liver, is characterized by a massive, rapid rise in serum aminotransferases resulting from reduced oxygen delivery to the liver. The most common predisposing condition is cardiac failure, followed by circulatory failure as occurs in septic shock and respiratory failure. HH does, however, occur in the absence of a documented hypotensive event or shock state in 50% of patients. In intensive care units, the incidence of HH is near 2.5%, but has been reported as high as 10% in some studies. The pathophysiology is multifactorial, but often involves hepatic congestion from right heart failure along with reduced hepatic blood flow, total body hypoxemia, reduced oxygen uptake by hepatocytes or reperfusion injury following ischemia. The diagnosis is primarily clinical, and typically does not require liver biopsy. The definitive treatment of HH involves correction of the underlying disease state, but successful management includes monitoring for the potential complications such as hypoglycemia, hyperglycemia, hyperammonemia and hepatopulmonary syndrome. Prognosis of HH remains poor, especially for cases in which there was a delay in diagnosis. The in-hospital mortality rate is >50%, and the most frequent cause of death is the predisposing condition and not the liver injury itself.

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## Introduction

Hepatic necrosis around the central veins, a condition now known as centrilobular necrosis, was first described as early as 1901 based upon a series of autopsies in Boston reported by F.B. Mallory.<sup>1</sup> Later, Bynum *et al.*<sup>2</sup> noted the same pattern of necrosis in cardiac failure patients suffering from dramatic rises in serum aminotransferase level. The condition was termed as "ischemic hepatitis," and since then it has also been referred to in the literature as "shock liver" and now, most frequently, as "hypoxic hepatitis" (HH).<sup>3-5</sup>

**Keywords:** Ischemia; Hypoxia; Hepatitis; Liver injury.

**Abbreviations:** HH, hypoxic hepatitis; ICG, indocyanine green; ICU, intensive care unit; INR, international normalized ratio.

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\*Correspondence to: Po-Hung Chen, Division of Gastroenterology & Hepatology, Department of Medicine, Johns Hopkins University School of Medicine, 4940 Eastern Avenue, Suite A-505, Baltimore, MD 21224, USA. Tel: +1-410-550-1793, Fax: +1-410-550-7861, E-mail: pchen37@jhmi.edu

The current diagnosis of HH generally relies on three criteria: a clinical setting resulting in reduced oxygen delivery or utilization by the liver, a significant and often transient increase in serum aminotransferase level, and exclusion of other potential causes of liver injury like drug or viral induced hepatitis. The clinical states that are defined as predisposing to HH include, most commonly, acute cardiac failure, toxic-shock states and respiratory failure;<sup>3-6</sup> however, the condition can occur even without the patient being in shock<sup>7</sup> or without a documented hypotensive event.<sup>8</sup> As such, the majority of cases of HH are diagnosed in the intensive care unit (ICU). For diagnosis, Henrion *et al.*<sup>3</sup> suggested the use of serum aminotransferase level at 20 times the upper limit of normal, but others have used a lower cutoff, ranging from 2.5 to 10 times the upper limit of normal.<sup>9-13</sup> When all three criteria are met, however, the diagnosis of HH can be assumed without the use of liver biopsy, but when in doubt biopsy can provide a definitive diagnosis.<sup>14</sup>

## Epidemiology

HH has become increasingly recognized in ICUs, where it is now one of the leading causes of dramatic rises in serum aminotransferase levels.<sup>15,16</sup> In a recent meta-analysis of 1782 cases, Tapper *et al.*<sup>8</sup> identified the incidence of HH to be 2 in every 1000 patients for all levels of hospital care, but in ICUs alone the pooled incidence is higher, accounting for 2.5 out of every 100 patients. This finding is consistent with previously reported incidences of 1–2.5% in the ICU.<sup>3-6,12</sup> In patients presenting to the ICU with pre-existing increased serum aminotransferase levels at 10 times above normal, the incidence of HH is reportedly as high as 4 out of every 10 admissions.<sup>8</sup> It is possible that these pooled incidences are too conservative, as the diagnosis is sometimes overlooked clinically;<sup>7</sup> indeed, some estimates have placed the incidence closer to 10% in ICUs.<sup>17</sup>

## Etiology

HH is frequently multifactorial, and one study found more than one underlying risk factor in nearly three-quarters of the patients analyzed.<sup>5</sup> The conditions of cardiac failure resulting in a low output state, sepsis, and respiratory failure together account for >90% of cases,<sup>7</sup> but there are a variety of other documented causes. Once thought to be prerequisites for diagnosis, documented hypotensive events and shock states both have now been shown to occur in only about 50% of patients with HH.<sup>7,8</sup>

The majority of cases described in the literature identify cardiac failure underlying HH, ranging from 39–70%.<sup>3-6,18</sup> In the aforementioned recent meta-analysis, as high as 78% of

HH cases were found to be caused by an acute cardiac event.<sup>8</sup> Patients are **especially at risk when there is passive congestion of the liver related to right-sided heart failure**,<sup>19–21</sup> with some literature asserting that the **passive congestion** may be a **necessary prerequisite** for the development of HH.<sup>22</sup>

Most prevalent among the other risk factors was the condition of septic shock. In one study, **septic shock** was identified in **32%** of patients suffering from HH and was the leading cause of death.<sup>5</sup> Other studies have identified sepsis in **6%**<sup>22</sup> to **33%**<sup>6</sup> of the patients with HH, with a pooled proportion of about **23%**.<sup>8</sup> **Respiratory failure** has also been noted as a **common** predisposing condition, reportedly occurring in nearly **15%** of patients<sup>7</sup> and ranging from as low as **7%**<sup>6</sup> to as high as **34%**<sup>23</sup> in the studies. Other documented preconditions include hypovolemic shock, anemia, extensive burns and sleep apnea.<sup>5,23–25</sup>

**Pre-existing liver pathologies**, especially **cirrhosis**, can also lead to **poorer outcomes** in HH.<sup>5,9</sup> **Cirrhotic** livers have **porto-systemic shunting** and **impaired functional blood flow**,<sup>26</sup> which thereby **exacerbate** the hypoxic damage suffered from a shock state or upon respiratory failure. The association between HH and other chronic liver diseases, such as viral hepatitis or alcoholic liver disease, has not yet been explicitly studied. Nonetheless, given the natural history of chronic hepatitis B and C infections, cases that have progressed to cirrhosis are at increased risk for HH.

## Pathophysiology

Regardless of the underlying etiology, in order to sustain anoxic injury, the **normally robust defense mechanisms of the liver must be overcome**. The liver is **protected** from **ischemic injury** by a **dual blood flow system**, in which the near **25%** of **cardiac output** that the liver receives is split between the **portal vein** and the **hepatic artery**.<sup>27,28</sup> In addition, the highly permeable **sinusoids** of the liver allow for **increased oxygen diffusion to the hepatocytes**, facilitating **oxygen extraction to levels near 90%**.<sup>29</sup> Finally, the liver is normally able to respond to **decreases** in cardiac blood flow by **releasing adenosine** and **dilating** the hepatic **vasculature** to **increase hepatic blood flow**.<sup>30</sup>

The pathophysiology of HH is often multifactorial, as displayed in Figure 1, but the predominating mechanism of damage to the liver can be different depending on the underlying condition. As mentioned previously, **passive congestion of the liver related to right-sided heart failure** has been the most studied, and is likely the most contributory, of all the pathophysiologic mechanisms. In a case-control study, Seeto *et al.*<sup>22</sup> found that underlying heart disease is a major predictor for the development of ischemic hepatitis among patients with at least 15 minutes of documented hypotension; moreover, of these patients, **94% had right-sided heart failure**. These findings were confirmed by Henrion *et al.*<sup>3</sup> and Birrer *et al.*<sup>4</sup>, with both groups demonstrating **elevated central venous pressures**, **reduced delivery of oxygen** and **reduced hepatic blood flow** in patients suffering from HH caused by cardiac failure. Additionally, Birrer *et al.*<sup>4</sup> showed that mean pulmonary capillary wedge pressure and systemic vascular resistance were elevated in all patient groups suffering from HH. Therefore, the **combination** of pre-existing **hepatic congestion** and any **acute** event resulting in **reduced hepatic blood flow** greatly predisposes the liver to **hypoxic injury**.<sup>19</sup>

Oxygen delivery is a function of both cardiac output and oxygen saturation. In addition to reduced hepatic blood flow, total body hypoxemia can also result in hypoxic damage to the liver, as evidenced in an exacerbation of chronic respiratory failure. During these times, very low levels of arterial pressure of oxygen (less than 40 mmHg) serve to predispose the liver to hypoxic damage, as the **hypoxemia** causes a severe reduction in delivery of oxygen to the hepatocytes.<sup>31,32</sup> Henrion *et al.*<sup>3</sup> and Birrer *et al.*<sup>4</sup> reported that their cohorts of patients with respiratory failure and HH had low average levels of arterial oxygen (34 and 32 mmHg respectively), but also showed elevated central venous pressures in these patients, suggesting an element of hepatic venous congestion.

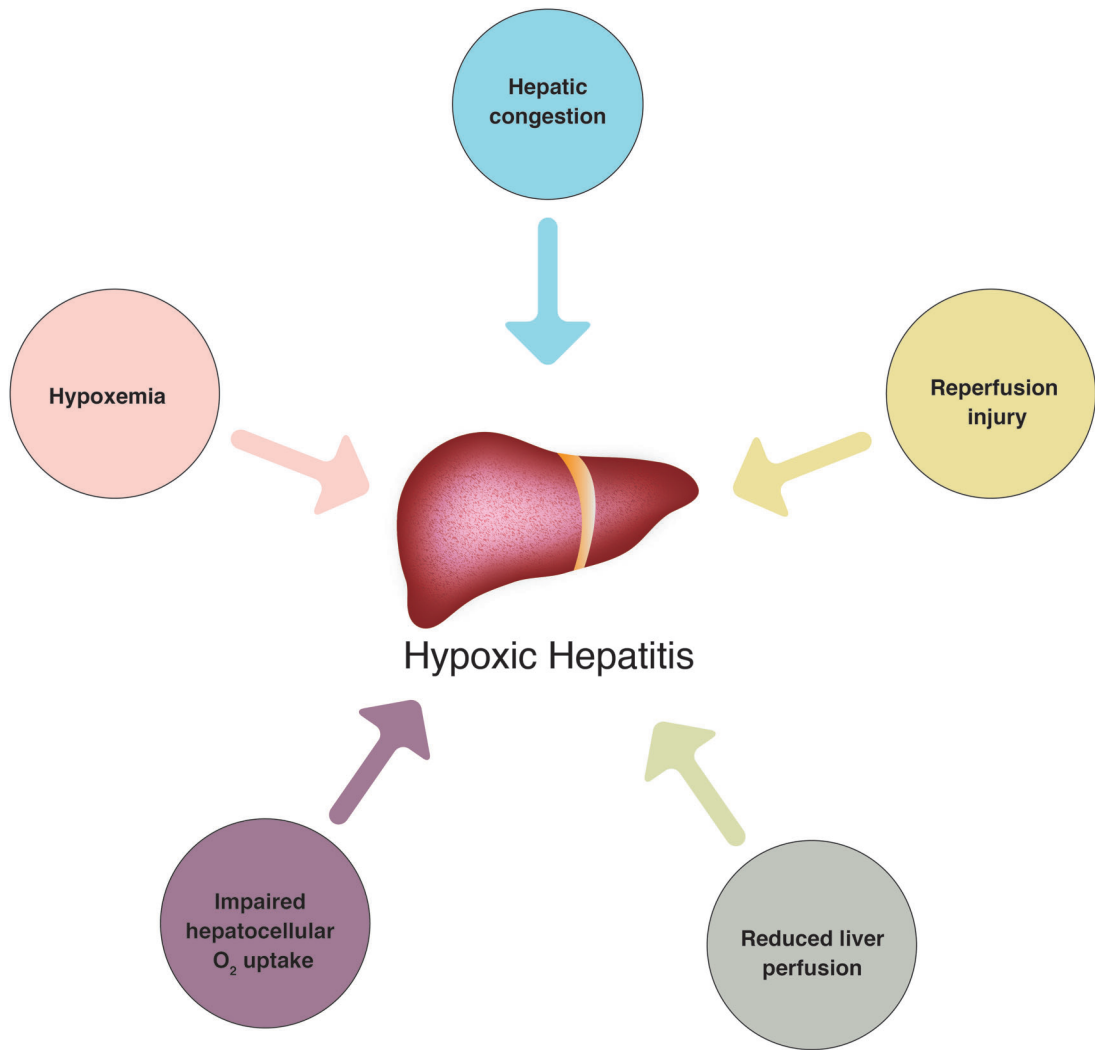
In **septic shock**, the proposed mechanism of hypoxic injury is not a failure to deliver oxygen but rather an **inability of hepatocytes to utilize oxygen**. **Splanchnic blood flow is increased in septic shock**,<sup>33</sup> but **inflammatory** mediators and the release of **endotoxin** likely **reduce** the capability of hepatocytes to **extract oxygen** from blood.<sup>34,35</sup> When coupled with states of reduced cardiac output, the effect is yet again multiplied, making hypoxic damage to the liver more likely.

While the previously described mechanisms outline how reduced oxygen delivery and utilization lead to hepatocyte necrosis, it has been theorized that the initial lack of oxygen may not be the only source of injury and rather that the hepatocytes suffer **damage upon re-oxygenation**. **Ischemia/reperfusion** injury has been described since the early time of HH study,<sup>36,37</sup> but the exact mechanism remains unknown. Detailed discussion of the mechanism that has been proposed is beyond the scope of this review, but it is appropriate to note that it generally includes the formation of reactive oxygen species; the details can be found in various reviews published in the literature.<sup>7,23,38</sup> Regardless of the exact timing and mechanism of injury, however, the aforementioned pathological pathways all ultimately lead to the same clinical syndrome of HH.

## Clinical presentation

HH often affects **elderly men**, with mean reported ages between 64 and 70 years-old,<sup>3–6,8</sup> who suffer from medical **co-morbidities including heart failure or chronic respiratory failure**.<sup>11</sup> Patients presenting to the ICU usually have **pre-existing increased serum aminotransferases**,<sup>3</sup> and generally show signs and symptoms of the underlying precondition, such as ankle edema, **hepatojugular reflux** or shortness of breath as a result of **cardiac insufficiency**.<sup>39</sup> Patients can, however, develop **right-upper quadrant abdominal pain**, **hepatomegaly** (**50% of patients**),<sup>3,38</sup> or elevated **serum bilirubin >3 mg/dL** (**36% of patients**).<sup>40</sup> Sequelae of liver disease, including **encephalopathy** and **hyperammonemia**, can also occur; **encephalopathy**, however, **usually** results from the **predisposing** condition such as **sepsis** or hypoxic injury to the brain, **rather** than being a **direct result of the liver damage**.<sup>41</sup> In addition, both **hypoglycemia**<sup>12</sup> and **hyperglycemia**<sup>42</sup> have been reported in patients with HH.

Patients with HH have **rapid, transient rises in serum aminotransferase levels** (aspartate and alanine aminotransferase) as well as a **dramatic rise in lactate dehydrogenase** levels. This sharp **rise in lactate dehydrogenase can sometimes point to HH** as the cause of liver **injury** as opposed to **viral hepatitis**.<sup>43</sup> These liver enzymes **typically peak** early in the course of the disease, often **within 24 hours**, but **after 24 to 72 hours the enzyme levels drop to nearly half** of their



**Fig. 1. Multifactorial contributors to hypoxic hepatitis.** The pathophysiological mechanisms leading to hypoxic hepatitis are presented. These can occur alone or in concert, depending on the underlying condition. Abbreviation: O<sub>2</sub>, oxygen.

peaks,<sup>7,23</sup> with normalization typically occurring within 1 to 2 weeks.<sup>7,23</sup>

Other abnormal laboratory findings can be found in HH patients, but they are non-specific and not considered sufficiently reliable for diagnosis. Patients typically have reduced prothrombin activity, and can show increases in serum creatinine (>2 mg/dL in 65% of patients)<sup>3,4</sup> as well as serum bilirubin (>3 mg/dL in 36% of patients).<sup>40</sup> Serum lactate levels can also be elevated, due to impaired hepatic clearance.<sup>44</sup> Finally, elevations in the international normalized ratio (INR) can occur, with levels >1.5 supporting the diagnosis of acute liver failure.<sup>45</sup>

**Diagnosis**

The diagnosis of HH is largely clinical, using the three widely accepted criteria listed in Table 1.<sup>3</sup> The differential diagnosis of liver conditions leading to massively and rapidly elevated liver enzymes is limited, and HH is one of the leading causes

(Table 2).<sup>15,23</sup> In predisposed patients who fulfill the criteria, the diagnosis of HH can be assumed without liver biopsy. Nonetheless, the use of liver biopsy to demonstrate centrilobular necrosis may be necessary when the diagnosis is unclear, such as when aminotransferase levels are <20 times the upper limit of normal.<sup>14</sup> Otherwise, biopsy is generally inadvisable in HH patients with multiple co-morbidities, especially those with coagulopathy.

**Table 1. Criteria for diagnosing hypoxic hepatitis\***

1. A clinical setting of cardiac, circulatory or respiratory failure
2. A dramatic, but transient, rise in serum aminotransferase activity
3. Exclusion of other causes of liver cell necrosis, especially viral or drug-induced hepatitis

\*Adapted from Henrion et al. 2003.

**Table 2. Liver differential diagnosis for serum aminotransferase levels >10 times the upper limit of normal**

Hypoxic hepatitis
Acute viral hepatitis
Toxin- or drug-induced liver injury
Autoimmune hepatitis
Liver trauma

Non-invasive imaging options like abdominal ultrasonography can be supportive in diagnosis of HH. Dilation of the inferior vena cava and suprahepatic veins due to passive congestion is suggestive of HH.<sup>46</sup> However, the diagnostic utility of ultrasonography in HH has not yet been validated. Other imaging techniques, like computed tomography or magnetic resonance imaging, are not required for diagnosis but may help exclude other causes of liver injury. The specific pattern of lab test abnormalities can also help to exclude other diagnoses. For example, viral hepatitis typically has lower peaks in serum lactate dehydrogenase than does HH.<sup>23</sup> In addition, the pattern of liver injury in HH is hepatocellular rather than cholestatic, so large increases in alkaline phosphatase are atypical.

Specific measures of hepatic blood flow and function using non-invasive methods such as clearance of galactose or indocyanine green (ICG) have also been proposed to support diagnosis of HH. Although galactose clearance has been used in previous studies to characterize hepatic blood flow,<sup>3,4</sup> it has not been well-established clinically for diagnosis of HH. Additionally, galactose is not solely cleared by the liver<sup>47</sup> and the clearance can be unpredictable in acute liver injury.<sup>48</sup> ICG is more reliably cleared by hepatocytes, whereupon it enters bile circulation, and has been increasingly demonstrated as an accurate measure of hepatic function, even in cases of cirrhosis and HH.<sup>49</sup> ICG is a generally non-toxic, water soluble dye that binds tightly to plasma proteins;<sup>50</sup> its plasma disappearance rate can be measured conveniently using the transcutaneous method of pulse densitometry.<sup>51</sup> Given these advantages, there is increasing interest in ICG plasma disappearance rate as a diagnostic or even prognostic tool for HH;<sup>49,50</sup> however, further studies are needed to firmly establish its clinical role.<sup>52</sup> Finally, invasive hepatic hemodynamic monitoring, including measurement of hepatic venous pressure, can be used to evaluate the impact of congestive hepatopathy in acute liver injury,<sup>53</sup> but presently it does not have a clearly defined role in HH.

## Management

The only established strategy for treating HH is to correct the underlying disease state. Prompt diagnosis and initiation of treatment is crucial, as delay in diagnosis has been shown to worsen mortality risk.<sup>5</sup> Treatments directed at the predisposing condition include optimization of whole body circulation, maintenance of adequate mean arterial pressure, and preservation of liver microcirculation and oxygenation through the use of inotropes, vasodilators and diuretics. That being said, an ideal inotropic agent has not yet been identified, and the existing studies have reported only limited benefit in specific clinical circumstances. For example, dopamine may offer a survival benefit for patients with normotensive cardiogenic shock and kidney injury,<sup>54</sup> and dobutamine has been proposed

to augment splanchnic blood flow to the liver in patients with low cardiac index.<sup>55</sup> The findings from these small studies are not widely generalizable, however.

Among the more experimental treatments, some have advocated for the use of N-acetylcysteine or other antioxidants, but evidence is lacking that demonstrates their effectiveness.<sup>38</sup> Another approach uses a modified dialysis system targeting substances bound to serum albumin, namely the molecular adsorbent recirculating system (MARS). It is theorized to remove small hydrophobic toxins that are normally detoxified by the healthy liver. While MARS showed some early promise in increasing liver circulation<sup>56</sup> and providing survival benefit in acute liver failure,<sup>57</sup> there is not yet sufficient evidence to recommend its regular use. Finally, it should be noted that liver transplantation is rarely indicated for the treatment of HH.<sup>58</sup>

As HH is a consequence of cardiogenic, circulatory or respiratory failure, it often coincides with other organ system failures, including that of the lungs and kidneys. Specifically, the incidence of hepatopulmonary syndrome with HH has been shown to be as high as 46%.<sup>59</sup> In these instances, it is often difficult to determine whether the lung or kidney injury preceded the liver injury, or vice versa, but adequate management relies on determining the extent of multi-system failure.<sup>5</sup> Additionally, glycemic control is paramount in managing HH, as both hypoglycemia and hyperglycemia are possible. As in other forms of liver failure, a target blood glucose level of <150 mg/dL is advisable.<sup>45</sup>

## Prognosis

As a result of the life-threatening conditions underlying HH, the prognosis is generally poor. The rates of in-hospital mortality from two large-pooled reviews were 56% and 59%.<sup>7,8</sup> Other reports put 1-year survival at near 25%.<sup>3,4</sup> The cause of death is usually not liver failure, however, but rather the predisposing condition. In a study of a large European cohort, the risk of in-hospital mortality was found to be significantly greater among patients with higher peak levels of aspartate aminotransferase (mean: 5.129 U/L), lactate dehydrogenase (mean: 5.047 U/L), INR (mean: 2.9) and lactate (mean: 10.4 mmol/L).<sup>5</sup> In addition, prolonged durations of HH (defined as >24 hours of rising aspartate aminotransferase levels) were found to be associated with significantly poorer overall survival.<sup>5</sup> Other biochemical and clinical abnormalities are associated with increased risk of in-hospital mortality as well, including increased phosphate levels, encephalopathy,<sup>60</sup> jaundice,<sup>40</sup> and, in a recent prospective study, ICG plasma disappearance rate.<sup>49</sup> The long-term outcome, however, is still largely determined by the overall cardiovascular morbidity and mortality.<sup>60</sup>

## Conclusions

In ICU settings, HH is one of the most common and lethal causes of massively elevated serum aminotransferase levels. It usually results as a consequence of a severe underlying illness state, such as cardiac, circulatory or respiratory failure, leading to a rate of in-hospital mortality of >50%. Prompt recognition is vital, as delays in diagnosis and prolonged HH can worsen outcomes. The only recognized treatment is to correct the predisposing condition; the newest therapies directed at the liver still require further investigation before they can be widely recommended.

## Conflict of interest

None

## Author contributions

Jointly performed the manuscript writing (NW, PHC), critically revised the manuscript and administered the literature review (PHC).

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