Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis

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INTRODUCTION

Acute liver failure is characterized by acute liver injury, hepatic encephalopathy (altered mental status), and an elevated prothrombin time/international normalized ratio (INR). It has also been referred to as fulminant hepatic failure, acute hepatic necrosis, fulminant hepatic necrosis, and fulminant hepatitis. Untreated, the prognosis is poor, so timely recognition and management of patients with acute liver failure is crucial [1]. Whenever possible, patients with acute liver failure should be managed in an intensive care unit at a liver transplantation center.

This topic will review the etiology, clinical manifestations, and diagnosis of acute liver failure in adults. The prognosis and management of patients with acute liver failure is discussed separately. (See "Acute liver failure in adults: Management and prognosis".)

The discussion that follows is consistent with society guidelines from The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) for the management of acute liver failure [2,3].

DEFINITIONS

Acute liver failure refers to the development of severe acute liver injury with impaired synthetic function (INR of ≥1.5) and altered mental status in a patient without cirrhosis or preexisting liver

disease [2-4]. A commonly used cutoff to define acute liver failure is an illness duration of <26 weeks.

Acute liver failure may also be diagnosed in patients with previously undiagnosed Wilson disease, vertically acquired or reactivation of hepatitis B virus, or autoimmune hepatitis, in whom underlying cirrhosis may be present, provided the disease has been recognized for <26 weeks. On the other hand, patients with acute severe alcoholic hepatitis, even if recognized for <26 weeks, are considered to have acute-on-chronic liver failure since most have a long history of heavy alcohol use. The approach to such patients is discussed elsewhere. (See "Management and prognosis of alcoholic hepatitis".)

Acute liver failure can be subcategorized based upon how long the patient has been ill and various cutoffs have been used. We classify acute liver failure as hyperacute (<7 days), acute (7 to 21 days), or subacute (>21 days and <26 weeks). In patients with hyperacute or acute liver failure, cerebral edema is common, whereas it is rare in subacute liver failure [5]. On the other hand, renal failure and portal hypertension are more frequently observed in patients with subacute liver failure. These subcategories have been associated with prognosis, but the associations reflect the underlying causes, which are the true determinants of prognosis. As an example, patients with hyperacute liver failure tend to have a better prognosis than those with subacute liver failure. The better prognosis is related to the fact that these patients often have acetaminophen toxicity or ischemic hepatopathy, diagnoses associated with a better prognosis than many of the disorders that may result in subacute liver failure, such as Wilson disease [2].

ETIOLOGY

Acute liver failure can result from a wide variety of causes, including (table 1 and table 2) [2,6]:

- Acetaminophen (paracetamol)
- Idiosyncratic drug reactions
- Viral hepatitis
- Autoimmune hepatitis
- Wilson disease
- Ischemic hepatopathy
- Budd-Chiari syndrome
- Veno-occlusive disease
- Acute fatty liver of pregnancy/HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome

- Malignant infiltration (most often breast cancer, small cell lung cancer, lymphoma, melanoma, or myeloma)
- Partial hepatectomy
- Toxin exposure, including mushroom poisoning
- Sepsis
- Heat stroke
- Hemophagocytic lymphohistiocytosis (primarily a disorder of children) [7]

Viral and drug-induced hepatitis are the most common causes of acute liver failure in adults. Drug-induced liver injury is the most common cause of acute liver failure in Australia, Europe, the United Kingdom, and the United States, whereas in Asia and Africa, viral hepatitis predominates [3,8,9]:

- In the United States, the US Acute Liver Failure Study Group collected data on 1147 cases of acute liver failure from 23 sites [1]. The most common causes of acute liver failure were acetaminophen overdose (46 percent), indeterminate (14 percent), idiosyncratic drug reactions (12 percent), hepatitis B virus (7 percent), and hepatitis A virus (3 percent).

- Among 856 patients with acute liver failure in Japan, 51 percent of cases were due to viral hepatitis (42 percent hepatitis B), and 10 percent were due to drugs (including acetaminophen) [10].

Viral hepatitis — Several viruses have been associated with acute liver failure, including hepatitis A, B, C, D, and E. In addition, acute liver failure can be seen with herpes simplex virus (HSV), varicella zoster virus, Epstein-Barr virus, adenovirus, and cytomegalovirus [1,8].

Acute liver failure is estimated to develop in 0.35 percent of patients with hepatitis A and in 0.1 to 0.5 percent of patients with acute hepatitis B [11]. However, the incidence of acute liver failure from hepatitis B may be underestimated. Precore or pre-S mutant hepatitis B viruses that are able to produce infection but do not produce hepatitis B e antigen (precore mutants) or surface antigen (pre-S mutants) may be difficult to diagnose by routine serology. Thus, liver failure in such patients may be erroneously attributed to cryptogenic causes [12]. This was illustrated in a study in which evidence of hepatitis B infection was detected by polymerase chain reaction (PCR) in 6 of 17 patients (35 percent) who underwent liver transplantation for what was initially thought to be non-A, non-B hepatitis [13]. (See "Hepatitis A virus infection in adults: Epidemiology, clinical manifestations, and diagnosis" and "Hepatitis B virus: Clinical manifestations and natural history", section on 'Acute hepatitis' and "Clinical significance and molecular characteristics of common hepatitis B virus variants".)

In addition to acute hepatitis B, acute liver failure may also develop in patients who are receiving chemotherapy, immunosuppression, or biologics and have reactivation of previously inactive hepatitis B, highlighting the importance of screening these patients for prior hepatitis B exposure with hepatitis B core IgG antibodies. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Hepatitis C virus alone does not appear to be a significant cause of acute liver failure in the absence of coinfection with hepatitis B. In a study of 109 patients with acute hepatitis C, acute liver failure developed in 11 (10 percent), 9 of whom had concurrent hepatitis B infection [14]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

Infection with hepatitis D virus can lead to acute liver failure in patients with hepatitis B virus infection. Hepatitis D does not cause an infection without hepatitis B. A patient may either acquire both viruses at the same time (coinfection) or acquire hepatitis D in the setting of preexisting chronic hepatitis B (superinfection). The risk of acute liver failure appears to be higher among patients who are coinfected than in those with hepatitis D superinfection or with acute hepatitis B alone. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection".)

Hepatitis E virus is a significant cause of liver failure in countries where it is endemic, such as Russia, Pakistan, Mexico, and India. Overall, the case-fatality rate for hepatitis E is 0.5 to 3 percent. However, among females who are pregnant, the mortality rate increases to 15 to 25 percent. (See "Hepatitis E virus infection", section on 'Acute hepatitis E' and "Overview of coincident acute hepatobiliary disease in pregnant women", section on 'Hepatitis E virus'.)

Acute liver failure is a rare complication of HSV infection. Both HSV-1 and HSV-2 have been implicated as etiologic agents. Those at risk include neonates, patients taking steroids, HIV-infected patients, those with cancer or myelodysplastic syndromes, and pregnant patients. HSV hepatitis has also been reported as an early cause of death after liver transplantation with concomitant lung and gastrointestinal involvement. HSV hepatitis has also been reported rarely in immunocompetent hosts. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Hepatitis'.)

Immunocompromised patients, such as transplant recipients and HIV-infected individuals with advanced disease, are at increased risk for developing complicated herpes zoster infections including acute liver failure. Hepatic involvement may occasionally develop in the absence of coincident rash. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster", section on 'Special considerations in immunocompromised hosts'.)

Epstein-Barr virus can affect virtually any organ system and has been associated with hepatitis and cholestasis. While rare, fatal cases of hepatitis have been described. (See "Infectious mononucleosis", section on 'Other'.)

The more common gastrointestinal manifestation of adenovirus is an acute diarrheal illness. However, hepatitis is a well-described complication of adenovirus infection in immunocompromised hosts, especially with subgroup C type 5. (See "Pathogenesis, epidemiology, and clinical manifestations of adenovirus infection", section on 'Gastrointestinal system'.)

Liver test abnormalities are frequently encountered in patients with symptomatic cytomegalovirus infection. Subclinical transaminitis is the most common finding in immunocompetent patients, but occasionally, patients present with more significant laboratory abnormalities or signs of hepatic dysfunction. (See "Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults", section on 'Hepatic manifestations'.)

Acetaminophen and other hepatotoxins — Acetaminophen is the most common toxin associated with acute liver failure in the United States and other developed countries (table 2) [15]. The hepatotoxicity is dose dependent and rarely occurs at therapeutic doses (up to four grams per day in a patient without preexisting liver disease). (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation" and "Acetaminophen (paracetamol) poisoning in adults: Treatment".)

Most cases occur after ingestion of large doses in an attempt to commit suicide. In addition, some patients unknowingly take large amounts of acetaminophen when multiple acetaminophen-containing medications are taken together or if acetaminophen-containing medications are not taken as directed (a "therapeutic misadventure"). Acute liver failure can also result from normally therapeutic doses in patients who have underlying liver disease (particularly with ongoing alcohol use, which induces the cytochrome P450 system) or who are taking medications known to induce the cytochrome P450 system (particularly CYP2E1), such as anticonvulsants (figure 1). The dosing and safety of acetaminophen for pain management in patients with cirrhosis are discussed separately. (See "Management of pain in patients with advanced chronic liver disease or cirrhosis", section on 'Acetaminophen (paracetamol)'.)

Other toxins associated with acute liver failure include mushroom poisoning (most often *Amanita phalloides*) and carbon tetrachloride. (See "Amatoxin-containing mushroom poisoning (eg, Amanita phalloides): Clinical manifestations, diagnosis, and treatment" and "Acute

hydrocarbon exposure: Clinical toxicity, evaluation, and diagnosis", section on 'Pathophysiology'.)

Idiosyncratic drug reactions — Unlike acute liver failure due to acetaminophen, which is dose related, acute liver failure due to idiosyncratic drug reactions is dose independent. Drug-induced liver injury (DILI) usually occurs within six months of drug initiation [2]. Drugs commonly implicated in cases of DILI include antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants (table 2). Herbal medications and dietary supplements have also been associated with acute liver failure. (See "Drug-induced liver injury" and "Hepatotoxicity due to herbal medications and dietary supplements".)

Hypoperfusion — Hypoperfusion of the liver can result in ischemic hepatitis and acute liver failure. Hypoperfusion may result from systemic hypotension due to causes such as cardiac dysfunction, sepsis, or drugs. Hypoperfusion of the liver may also be seen with Budd-Chiari syndrome (hepatic vein thrombosis), veno-occlusive disease, or the use of vasoconstricting drugs such as cocaine and methamphetamine. (See "Ischemic hepatitis, hepatic infarction, and ischemic cholangiopathy" and "Budd-Chiari syndrome: Epidemiology, clinical manifestations, and diagnosis" and "Hepatic sinusoidal obstruction syndrome (veno-occlusive disease) in adults".)

CLINICAL MANIFESTATIONS

By definition, patients with acute liver failure have severe acute liver injury as demonstrated by an INR ≥1.5 and signs of hepatic encephalopathy (altered mental status or asterixis). Clinical manifestations may include elevated aminotransferases, jaundice, hepatomegaly, and right upper quadrant tenderness. (See 'Diagnosis' below.)

Symptoms — Many of the initial symptoms in patients with acute liver failure are nonspecific [16]. They include:

- Fatigue/malaise
- Lethargy
- Anorexia
- Nausea and/or vomiting
- Right upper quadrant pain
- Pruritus
- Jaundice
- Abdominal distension from ascites

As the liver failure progresses, patients who were initially anicteric may develop jaundice, and those with subtle mental status changes (eg, lethargy, difficulty sleeping) may become confused or eventually comatose.

Physical examination findings

Neurologic examination — The presence of hepatic encephalopathy is one of the defining characteristics of acute liver failure. Recognizing the signs and severity of hepatic encephalopathy is important because it will inform management. Findings in patients with hepatic encephalopathy are variable, ranging from changes in behavior to coma. Hepatic encephalopathy is graded from I to IV (table 3 and figure 2) (see "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis"):

- Grade I: Changes in behavior, mild confusion, slurred speech, disordered sleep, including sleep reversal
- Grade II: Lethargy, moderate confusion
- Grade III: Marked confusion (stupor), incoherent speech, sleeping but wakes with stimulation
- Grade IV: Coma, unresponsive to pain

Patients with grade I encephalopathy may have mild asterixis, whereas pronounced asterixis is typically seen in patients with grade II or III encephalopathy [15]. Asterixis is typically absent in patients with grade IV encephalopathy, who instead may demonstrate decorticate or decerebrate posturing.

Cerebral edema may develop in patients with acute liver failure leading to increased intracranial pressure [15]. Cerebral edema is uncommon in patients with grade I or II encephalopathy, but it is present in 25 to 35 percent of those with grade III encephalopathy and in approximately 75 percent of those with grade IV encephalopathy [16,17]. Pupillary changes are one sign of increased intracranial pressure. The pupils may progress from having a normal response (typical with grade I encephalopathy), to being hyperresponsive (grade II to III encephalopathy), to being slowly responsive (grade III to IV encephalopathy). As the coma worsens, the pupils may become fixed and dilated (a sign typically associated with brainstem herniation).

Other clinical features of increased intracranial pressure can include systemic hypertension, bradycardia, respiratory depression (Cushing's triad), seizures, and abnormal brainstem reflexes (eg, oculocephalic reflex, corneal reflex, jaw reflex, cough response to tracheobronchial suctioning). (See "Evaluation and management of elevated intracranial pressure in adults", section on 'Clinical manifestations'.)

Seizure activity in patients with acute liver failure is common but may be difficult to detect if patients are intubated and receiving paralytics. In the control arm of one trial, 7 of 22 patients (32 percent) had subclinical seizure activity detected by electroencephalogram [18].

Other physical examination findings — Other findings on physical examination in patients with acute liver failure may include:

- Jaundice, which is a common finding in patients with acute liver failure but may be absent early in the course of acetaminophen poisoning or herpes simplex virus (HSV) infection [2]
- Vesicular skin lesions suggestive of HSV (present in 30 to 50 percent of patients with acute liver failure due to HSV) [2,19]
- Fever in patients with HSV (reported in 82 percent of patients in one review) [19]
- Right upper quadrant tenderness and hepatomegaly
- Ascites
- Signs of intravascular volume depletion, such as orthostatic hypotension

Laboratory test abnormalities — Laboratory test abnormalities typically seen in patients with acute liver failure include:

- Prolonged prothrombin time, resulting in an INR ≥1.5 (this finding is part of the definition of acute liver failure and thus must be present); hemostasis when measured by thromboelastography is normal [20,21].
- Elevated aminotransferase levels (often markedly elevated).
- Elevated bilirubin level.
- Low platelet count (≤150,000/microL), but this is variable and has been associated with clinically significant portal hypertension. (See "Hemostatic abnormalities in patients with liver disease", section on 'Physiologic effects of hepatic dysfunction'.)

Decreasing aminotransferase levels may indicate spontaneous recovery but could also signal worsening of the liver failure with loss of hepatocyte mass. In patients who are improving, the bilirubin and prothrombin time/INR will decline, whereas in those with worsening liver failure, the bilirubin and prothrombin time/INR will continue to rise. Elevations in bilirubin with associated jaundice can take weeks to months to resolve. Hypophosphatemia may represent liver regeneration [22]. Because of the prognostic importance of the prothrombin time/INR, it is recommended that products such as plasma only be used when there is a clear indication [2]. In addition, despite an abnormal INR, patients may not be hypocoagulable. In a study of 20 patients with acute liver failure, thromboelastography suggested a hypocoagulable state in 20

percent, normal coagulation in 45 percent, and a hypercoagulable state in 35 percent [23]. (See "Acute liver failure in adults: Management and prognosis", section on 'Bleeding prevention' and "Hemostatic abnormalities in patients with liver disease", section on 'Bleeding' and "Hemostatic abnormalities in patients with liver disease", section on 'Invasive procedures'.)

Other laboratory findings that may be seen in patients with acute liver failure include [15]:

- Hemolytic anemia
- Elevated serum creatinine and blood urea nitrogen
- Elevated amylase and lipase
- Hypoglycemia
- Hypomagnesemia
- Hypokalemia
- Acidosis or alkalosis
- Elevated ammonia level
- Elevated lactate dehydrogenase (LDH) level

Acute kidney injury complicates acute liver failure in approximately 30 to 70 percent of patients [17,24-26]. The frequency of renal injury is higher (up to 75 percent) for etiologies of acute liver failure that are known to independently damage the kidneys, such as acetaminophen intoxication [12,26,27]. In one series of 1604 patients with acute liver failure, some degree of acute kidney injury developed in 70 percent of the patients, with 30 percent receiving renal replacement therapy [26].

The pathogenesis of renal injury in patients with acute liver failure is incompletely understood but may be related to systemic and intrarenal hemodynamic changes similar to those seen in hepatorenal syndrome. The clinical picture is similar in that the urine sodium concentration and fractional excretion are very low in the absence of diuretic therapy or tubular injury (as might be induced by acetaminophen), and the urine sediment shows few or no cells or casts in the absence of marked hyperbilirubinemia. The blood urea nitrogen concentration may not be a sensitive test to follow renal function in patients with acute liver failure since hepatic production of urea is decreased. (See "Hepatorenal syndrome".)

Laboratory findings associated with specific diagnoses — Laboratory test findings often vary depending upon the specific cause of acute liver failure. Patterns seen on laboratory testing may suggest a diagnosis, but additional history, laboratory and imaging testing is required prior to making a diagnosis. These patterns should not be used to rule in or rule out a given diagnosis. (See 'Diagnosis' below.)

Some patterns that may be seen include [2]:

- Acetaminophen – Very high aminotransferase levels (>3500 international units/L), low bilirubin, high INR (see "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation", section on 'Clinical manifestations')

- Ischemic hepatic injury – Very high aminotransferase levels (25 to 250 times the upper limit of normal), elevated serum LDH levels (see "Ischemic hepatitis, hepatic infarction, and ischemic cholangiopathy", section on 'Clinical manifestations')

- Hepatitis B virus – Aminotransferase levels of to 1000 to 2000 international units/L are common, alanine aminotransferase (ALT) level that is higher than the aspartate aminotransferase (AST) level (see "Hepatitis B virus: Clinical manifestations and natural history", section on 'Acute hepatitis')

- Wilson disease – Coombs-negative hemolytic anemia, aminotransferase levels <2000 international units/L, AST to ALT ratio of >2, normal or markedly subnormal alkaline phosphatase (<40 international units/L), alkaline phosphatase (international units/L) to total bilirubin (mg/dL) ratio <4, rapidly progressive renal failure, low uric acid levels (see "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Acute liver injury/failure')

- Acute fatty liver of pregnancy/HELLP syndrome – Aminotransferase levels <1000 international units/L, elevated bilirubin, low platelet count (see "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)" and "Acute fatty liver of pregnancy")

- Herpes simplex virus – Markedly elevated aminotransferases, leukopenia, low bilirubin (anicteric hepatitis)

- Reye syndrome, valproate toxicity, or tetracycline toxicity – Minor to moderate elevations in aminotransferase and bilirubin levels [15]

Imaging and other studies — Abdominal computed tomography (CT) in a patient with acute liver failure often reveals a liver that appears less dense than skeletal muscle [28]. Other findings may include heterogenous liver parenchyma, hepatomegaly, ascites, evidence of malignant infiltration, and evidence of hepatic vein occlusion. Cirrhosis may be present in patients with acute liver failure due to Wilson disease, vertically transmitted hepatitis B, or autoimmune hepatitis and may result in a nodular-appearing liver on imaging. However, a massively necrotic liver may also appear nodular due to parenchymal collapse [29]. However, because of the risk of renal failure with the intravenous contrast used for CT, ultrasound with Doppler imaging is often the preferred initial modality for the evaluation of acute liver failure. (See 'Imaging studies' below.)

Neuroimaging (head CT or magnetic resonance imaging [MRI]) in patients with acute liver failure may reveal evidence of cerebral edema, including a decrease in the size of the ventricles, flattening of cerebral convolutions, and attenuation of the signal intensity of brain parenchyma [30]. An electroencephalogram may reveal seizure activity, even in the absence of clinical signs of seizures [18].

Pulmonary edema and pulmonary infections develop in approximately 30 percent of patients with acute liver failure and may be seen on chest radiographs [17]. (See "Clinical evaluation and diagnostic testing for community-acquired pneumonia in adults", section on 'Chest imaging findings' and "Clinical manifestations and evaluation of edema in adults", section on 'Isolated pulmonary edema'.)

DIAGNOSIS

Diagnosing acute liver failure — Acute liver failure should be in the differential diagnosis of patients with the recent onset (<26 weeks) of mental status changes, jaundice, or right upper quadrant pain. It should also be considered in patients with nonspecific symptoms such as nausea, vomiting, and malaise. The evaluation of such patients should include serum liver tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, gamma-glutamyl transpeptidase [GGT], total and direct bilirubin, albumin). If the liver tests are abnormal, the patient's prothrombin time/INR should also be measured. (See 'Symptoms' above.)

Acute liver failure is diagnosed by demonstrating all of the following:

- Altered mental status (hepatic encephalopathy) (see 'Neurologic examination' above)
- Prolonged prothrombin time (INR ≥1.5) (see 'Laboratory test abnormalities' above)

Determining the cause of acute liver failure — A cause for acute liver failure can be established in approximately 60 to 80 percent of patients [5]. Identifying the underlying cause of the liver failure is important because it influences the approach to management and provides prognostic information. A diagnosis is typically made with a combination of history-taking, laboratory tests, and imaging studies. If the initial evaluation fails to identify an etiology, a liver biopsy may be a subsequent option that must be balanced with the risk of life-threatening bleeding. (See 'Liver biopsy' below.)

Empiric therapy is often started along with the diagnostic workup if a particular cause is likely based upon history or examination findings. This is especially true in patients with suspected acetaminophen-associated acute liver failure since the treatment, N-acetylcysteine (NAC),

significantly improves outcomes if started early and has few side effects. NAC has also been used for adult patients with nonacetaminophen-induced liver failure. Once the cause of the liver failure is confirmed, therapy can be adjusted as needed. (See 'Laboratory findings associated with specific diagnoses' above and "Acute liver failure in adults: Management and prognosis", section on 'Treatment of the underlying cause'.)

Timing of the evaluation — The evaluation of a patient with acute liver failure should begin at the time of diagnosis to establish the cause and initiate empiric therapy. This is crucial because in some cases, early diagnosis and treatment may improve the patient's prognosis. In addition, timely evaluation is required to identify patients who may require urgent evaluation for liver transplantation. (See "Acute liver failure in adults: Management and prognosis", section on 'Treatment of the underlying cause'.)

The initial transplantation evaluation should **not** be delayed for patients who are being transferred to a liver transplant center. Laboratory tests and abdominal imaging should be ordered as soon as acute liver failure is recognized and should not be delayed while the history and physical examination are being performed. Likewise, because patients with grade I or II encephalopathy may progress to higher grade encephalopathy and lose their ability to communicate, a history should be obtained as soon as possible from such patients. In addition, patient transfer should not be delayed because test results are still pending, because some patients (particularly those with cerebral edema) will quickly become too unstable. If an etiology such as acetaminophen toxicity is identified during the initial evaluation, therapy should be initiated immediately.

History — A thorough history may identify potential causes for a patient's acute liver failure, but in patients with severe encephalopathy, the history may be limited or unavailable. In some cases, the patient's caregivers may be able to provide useful information even if the patient is not able to.

Patients and/or their caregivers should be asked about:

- Timing of symptom onset (eg, malaise, nausea, vomiting, jaundice, mental status changes).
- History of alcohol use.
- History of prior episodes of jaundice.
- Medication use, including all medications used, the amounts ingested, and the durations of use. Medication use is not limited to prescription medications, but also includes over-

the-counter medications, herbal and dietary supplements, and illicit drug use.

- Risk factors for intentional drug overdose, such as a history of depression or prior suicide attempts.
- Toxin exposure, including occupational toxin exposures or wild mushroom ingestion.
- Risk factors for acute viral hepatitis, including travel to areas endemic for hepatitis A or E, intravenous drug use, occupational exposure, sexual exposure, chronic or inactive hepatitis B infection, history of blood transfusion, and immunosuppression.
- Risk factors for hepatic ischemia, including hypotension, cardiac failure, a hypercoagulable disorder, oral contraceptive use, or malignancy.
- Family history of liver disease such as Wilson disease.

In patients who develop acute liver failure while hospitalized, the patient's records should be reviewed for possible causes including medications the patient has received (including anesthetics, antibiotics, and immunosuppressants) and episodes of hypotension or cardiac dysfunction.

Physical examination — Physical examination findings may help identify a cause of a patient's acute liver failure, but in many cases the findings, such as jaundice or hepatomegaly, are nonspecific. The physical examination may also help identify complications of acute liver failure, such as cerebral edema and infection. (See 'Physical examination findings' above.)

All patients should have a routine physical examination, including a complete skin examination. In addition, patients suspected of having Wilson disease should undergo an ocular slit lamp examination. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'When to suspect Wilson disease'.)

Physical examination findings that may point to a specific cause of acute liver failure include:

- Vesicular skin lesions (herpes simplex virus [HSV])
- Kayser-Fleisher rings (Wilson disease) (picture 1)
- Features of preeclampsia, such as hypertension (HELLP syndrome) (table 4 and table 5)

Laboratory evaluation — An extensive laboratory evaluation is required in patients with acute liver failure to determine the cause, assess the severity, and prepare for possible liver

transplantation. Because patients with acute liver failure may decompensate rapidly, testing should not be delayed. (See 'Timing of the evaluation' above.)

Laboratory tests that should be obtained at presentation include [2]:

- Prothrombin time/INR
- Serum chemistries (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphate, lactate dehydrogenase)
- Liver blood tests (AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin, albumin)
- Complete blood count with differential
- Acetaminophen level
- Blood and urine toxicology screen including **phosphatidylethanol testing** (see "Alcohol use disorder: Treatment overview", section on 'Evaluating response to treatment')
- Viral hepatitis serologies (anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, anti-hepatitis C virus antibodies, hepatitis C RNA, HSV type 1 and type 2 DNA polymerase chain reaction (PCR), varicella zoster virus DNA PCR, Epstein-Barr virus (EBV) DNA PCR, anti-viral capsid antigen IgM, anti-viral capsid antigen IgG, anti-EBV nuclear antigen, cytomegalovirus (CMV) DNA PCR, anti-CMV virus antibodies; anti-hepatitis E IgM in patients who are pregnant)
- Serum pregnancy test in females of childbearing potential who are not already known to be pregnant
- Autoimmune markers (antinuclear antibody, antismooth muscle antibody, anti-liver/kidney microsomal antibody type 1, anti-liver soluble antigen, immunoglobulin levels)
- Arterial blood gas
- Arterial lactate
- Arterial ammonia
- Blood type and screen
- Serologic testing for HIV
- Amylase and lipase

Additional tests that are indicated in specific circumstances include:

- Ceruloplasmin level in patients suspected of having Wilson disease. However, serum ceruloplasmin may be normal or elevated in the setting of acute liver failure.

  We obtain testing for Wilson disease in patients with acute liver failure who are under the age of 40 years or who have any of the following:

  - A Coombs-negative hemolytic anemia
  - Neurologic symptoms prior to the onset of acute liver failure
  - Kayser-Fleisher rings
  - A ratio of AST to ALT of greater than two
  - Low alkaline phosphatase
  - A ratio of alkaline phosphatase (international units/L) to total bilirubin (mg/dL) of less than four

  If these studies are nondiagnostic, then a liver biopsy may be a subsequent option. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Diagnostic evaluation'.)

- Anti-hepatitis D virus antibodies in patients with acute or chronic hepatitis B. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Diagnosis of HDV infection'.)

- Anti-hepatitis E virus antibodies for patients who are pregnant, immunosuppressed, or with travel to endemic areas such as Russia, Pakistan, Mexico, India, or Africa. (See "Hepatitis E virus infection", section on 'Diagnosis'.)

- Urinalysis to look for proteinuria in patients who are pregnant.

Imaging studies — Imaging with abdominal Doppler ultrasonography should be obtained to look for evidence of Budd-Chiari syndrome, portal hypertension, hepatic steatosis, hepatic congestion, and underlying cirrhosis. Ultrasonography is readily available, inexpensive, and noninvasive. Hepatic imaging may also reveal evidence of malignant infiltration. As noted above, a massively necrotic liver may appear nodular and does not necessarily indicate underlying cirrhosis. (See "Budd-Chiari syndrome: Epidemiology, clinical manifestations, and diagnosis", section on 'Diagnosis' and 'Imaging and other studies' above.)

Alternatives to ultrasound include abdominal CT scan, venography, or MRI with magnetic resonance venography (MRV). In addition to being able to detect Budd-Chiari syndrome, CT and MRI are more sensitive than ultrasound for diagnosing hepatic malignancies. However, prior to

obtaining a CT scan, venogram, or MRI/MRV, the risk of kidney injury associated with the contrast agents should be weighed against the need for the examination, especially since patients with acute liver failure may also have kidney failure. We reserve the use of these imaging techniques for patients with a negative ultrasound in whom the suspicion for Budd-Chiari syndrome or malignancy remains high. For patients who are being evaluated for liver transplantation, contrast-enhanced, cross-sectional imaging with either a CT scan or an MRI of the liver is performed to assess for thrombosis or malignancy. The patient's hemodynamic status should be stabilized prior to obtaining advanced imaging studies. In general, a CT is preferred rather than MRI. (See "Contrast-associated and contrast-induced acute kidney injury: Clinical features, diagnosis, and management" and "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging", section on 'Approach to preventing nephrogenic systemic fibrosis'.)

An echocardiogram to look for cardiac dysfunction should be considered in patients suspected of having acute hepatic ischemia without a known cause (eg, in a patient with markedly elevated transaminases without a cause identified from the patient's history, laboratory examination, or abdominal imaging). Additionally, patients who are being considered for liver transplantation should undergo institution-specific protocols for pretransplant cardiac evaluation. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation", section on 'Cardiopulmonary evaluation'.)

Liver biopsy — If laboratory and imaging tests fail to identify an etiology, a liver biopsy may aid with the diagnosis, but we recommend caution given the bleeding risk associated with liver biopsy. A transjugular approach is preferred in the setting of acute liver failure to minimize the risk of bleeding. Portal pressure measurements can help determine the chronicity of the patient's underlying disease. Our practice is to obtain a liver biopsy in patients with acute liver failure of indeterminate etiology who are hemodynamically stable with low bleeding risk. However, if the patient has progressed to the point of requiring liver transplantation, histologic evaluation can instead be performed on the explanted liver. (See "Transjugular liver biopsy".)

Prior to proceeding with a liver biopsy, we obtain contrast-enhanced, cross-sectional liver imaging (eg, CT scan) to exclude malignancy. If malignancy is identified on imaging, a discussion with the institution's multidisciplinary hepatobiliary tumor board should take place to assess if liver biopsy is necessary for guiding further management.

Liver biopsy may help with the diagnosis of:

- Malignant infiltration.
- Autoimmune hepatitis. (See "Overview of autoimmune hepatitis", section on 'Histology'.)

- Wilson disease. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Diagnostic evaluation'.)
- Hepatitis due to HSV infection.
- Acute fatty liver of pregnancy. However, because liver biopsy is invasive, it should be approached with caution during pregnancy and reserved for cases in which a diagnosis of acute fatty liver of pregnancy is in doubt and the appropriate treatment (delivery) is being delayed. (See "Acute fatty liver of pregnancy", section on 'Histologic findings'.)

DIFFERENTIAL DIAGNOSIS

The primary entity in the differential diagnosis of acute liver failure is severe acute hepatitis. Patients with severe acute hepatitis have jaundice and coagulopathy but lack signs of hepatic encephalopathy. Distinguishing the two is important because patients with severe acute hepatitis generally have a good prognosis, whereas those who progress to acute liver failure have a high mortality rate and often require liver transplantation [15].

Differentiating severe acute hepatitis from acute liver failure in a patient with Wilson disease may be difficult because neurologic Wilson disease may be confused with hepatic encephalopathy. Features that suggest neurologic Wilson disease rather than hepatic encephalopathy include the presence of dysarthria, dystonia, tremors, or parkinsonism. In addition, neurologic symptoms in a patient with Wilson disease may have been present prior to the onset of the hepatic manifestations. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Neurologic involvement'.)

Patients with severe acute alcoholic hepatitis may present with liver failure that appears to have developed over the course of weeks to months [31]. However, patients with alcoholic hepatitis typically have a history of heavy drinking for many years and are thus thought to have acute-on-chronic liver failure [32]. Patients with a diagnosis of alcoholic hepatitis without another cause of liver injury (ie, acetaminophen toxicity) are not eligible for priority listing for liver transplant because this is regarded as a chronic disease. Differentiating alcoholic hepatitis from acute liver failure is important because the two entities are managed differently (eg, there is a role for corticosteroids in the treatment of alcoholic hepatitis, but not in acute liver failure). (See "Management of alcohol-associated steatosis and alcohol-associated cirrhosis".)

Alcoholic hepatitis should be considered in patients with a history of heavy alcohol use or who have an aspartate aminotransferase to alanine aminotransferase ratio of approximately 2:1. However, a history of heavy alcohol use does not exclude other causes of acute liver failure (and

in the case of acetaminophen toxicity may predispose to it), so a patient presenting with acute liver failure in the setting of heavy alcohol use still requires a thorough evaluation. (See "Alcoholic hepatitis: Clinical manifestations and diagnosis", section on 'Introduction'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute liver failure".)

SUMMARY AND RECOMMENDATIONS

- **Definitions** – Acute liver failure refers to the development of severe acute liver injury with encephalopathy (altered mental status) and impaired synthetic function (international normalized ratio [INR] of ≥1.5) in a patient without cirrhosis or preexisting liver disease. While the time course that differentiates acute liver failure from chronic liver failure varies between reports, a commonly used cutoff is an illness duration of <26 weeks. (See 'Definitions' above.)

- **Etiology** – Acute liver failure can result from a wide variety of causes, including (table 1 and table 2) [2,15] (see 'Etiology' above):

  - Acetaminophen (paracetamol)
  - Idiosyncratic drug reactions
  - Viral hepatitis
  - Autoimmune hepatitis
  - Wilson disease
  - Ischemic hepatopathy
  - Budd-Chiari syndrome
  - Veno-occlusive disease
  - Acute fatty liver of pregnancy/HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome
  - Malignant infiltration
  - Partial hepatectomy
  - Mushroom poisoning
  - Sepsis
  - Heat stroke

Viral and drug-induced hepatitis are the most common causes of acute liver failure in adults. (See 'Etiology' above.)

- **Clinical manifestations** – Clinical manifestations of acute liver failure include hepatic encephalopathy and an INR ≥1.5 (all of which are required for the diagnosis), and may include jaundice, hepatomegaly, right upper quadrant tenderness, elevated liver enzymes, and thrombocytopenia. (See 'Clinical manifestations' above.)

- **Diagnostic evaluation** – Determining the etiology of acute liver failure requires a combination of history-taking, laboratory tests, and imaging studies. If the initial evaluation fails to identify an etiology, a liver biopsy may be required. (See 'Diagnosis' above.)

  Because patients may decompensate rapidly, the initial evaluation should be broad, even in patients with a presumed cause for their acute liver failure. A broad evaluation is required to identify a cause of the acute liver failure and to prepare for possible liver transplantation.

  - **Laboratory testing** – Laboratory tests that should be obtained at presentation include (see 'Laboratory evaluation' above):

    - Prothrombin time/INR.
    - Serum chemistries (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphate, lactate dehydrogenase).
    - Liver blood tests (AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin, albumin).
    - Complete blood count with differential.
    - Acetaminophen level.
    - Blood and urine toxicology screen including **phosphatidylethanol testing.**
    - Viral hepatitis serologies (anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, anti-hepatitis C virus antibodies, hepatitis C RNA, HSV type 1 and type 2 DNA polymerase chain reaction [PCR], varicella zoster virus DNA PCR, Epstein-Barr virus [EBV] DNA PCR, anti-viral capsid antigen IgM, antiviral capsid antigen IgG, anti-EBV nuclear antigen, cytomegalovirus [CMV] DNA PCR, anti-CMV virus antibodies; anti-hepatitis E IgM in patients who are pregnant).

- Serum pregnancy test in females of childbearing potential who are not already known to be pregnant.
- Autoimmune markers (antinuclear antibody, antismooth muscle antibody, anti-liver/kidney microsomal antibody type 1, anti-liver soluble antigen, immunoglobulin levels).
- Arterial blood gas.
- Arterial lactate.
- Arterial ammonia.
- Blood type and screen.
- Serologic testing for HIV.
- Amylase and lipase.

Additional laboratory tests that are indicated in specific circumstances include:

- Ceruloplasmin level in patients suspected of having Wilson disease. However, serum ceruloplasmin may be normal or elevated in the setting of acute liver failure, so if there is significant concern for Wilson disease, a liver biopsy may be required. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Diagnostic evaluation'.)
- Anti-hepatitis D virus antibodies in patients with acute or chronic hepatitis B. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Diagnosis of HDV infection'.)
- Anti-hepatitis E virus antibodies for pregnant patients or patients with travel to endemic areas such as Russia, Pakistan, Mexico, Africa, or India. (See "Hepatitis E virus infection", section on 'Diagnosis'.)
- Urinalysis to look for proteinuria in females who are pregnant.

- **Imaging** – Imaging with abdominal Doppler ultrasonography, CT scanning, venography, or MRI and magnetic resonance venography (MRV) should be obtained to look for evidence of Budd-Chiari syndrome. Hepatic imaging may also reveal evidence of malignant infiltration. However, CT scanning, venography, and MRI/MRV should be used with caution because the contrast agents used are associated with renal injury.

Additionally, the patient should be hemodynamically stable prior to obtaining imaging. (See 'Imaging studies' above.)

We reserve the use of CT, venography, and MRI/MRV for patients with a negative ultrasound in whom the suspicion for Budd-Chiari syndrome or malignancy remains high. In addition, for patients who are being considered for liver transplantation, contrast-enhanced, cross-sectional imaging with either a CT scan or an MRI of the liver is performed to assess for thrombosis and malignancy.

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Topic 3574 Version 38.0

GRAPHICS

Mnemonic for causes of acute liver failure: The ABCs

A	Acetaminophen, hepatitis A, autoimmune hepatitis, *Amanita phalloides* (mushroom poisoning), adenovirus
B	Hepatitis B, Budd-Chiari syndrome
C	Cryptogenic, hepatitis C, CMV
D	Hepatitis D, drugs and toxins
E	Hepatitis E, EBV
F	Fatty infiltration - acute fatty liver of pregnancy, Reye's syndrome
G	Genetic - Wilson disease
H	Hypoperfusion (ischemic hepatitis, SOS, sepsis), HELLP syndrome, HSV, heat stroke, hepatectomy, hemophagocytic lymphohistiocytosis
I	Infiltration by tumor

CMV: cytomegalovirus; EBV: Epstein-Barr virus; SOS: sinusoidal obstruction syndrome (veno-occlusive disease); HELLP: hemolysis, elevated liver enzymes, low platelets; HSV: herpes simplex virus.

Graphic 67925 Version 6.0

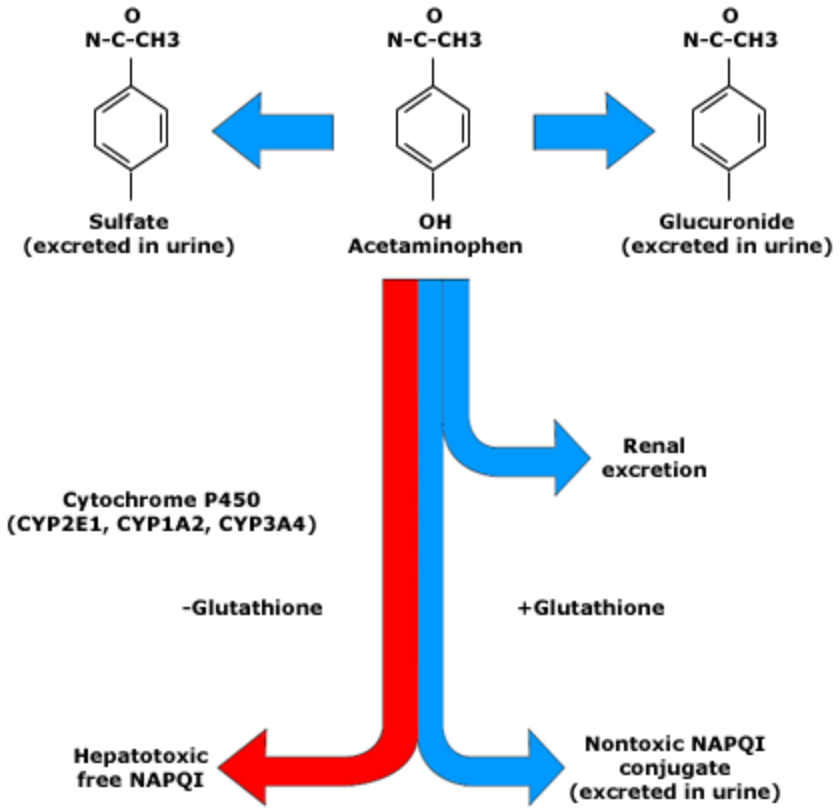
Some drugs, herbal products, and toxins associated with acute liver failure

Abacavir
Acetaminophen (paracetamol)
Allopurinol
Amiodarone
Amoxicillin
Aspirin
Carbamazepine
Carbon tetrachloride
Ciprofloxacin
Cocaine
Comfrey
Dapsone
Didanosine
Dideoxyinosine
Disulfiram
Doxycycline
Efavirenz
Gemtuzumab
Gold
Greater celandine
Halothane
He Shou Wu
Herbalife®
Hydroxycut®
Isoflurane
Isoniazid
Itraconazole
Kava Kava
Ketoconazole
Labetalol

LipoKinetix®
Ma Huang
MDMA (Ecstasy)
Methamphetamine
Monoamine oxidase inhibitors
Methyldopa
Nicotinic acid
Nitrofurantoin
Nonsteroidal anti-inflammatory drugs
Phenprocoumon
Phenytoin
Poison mushrooms (*Amanita phalloides*)
Propylthiouracil
Pyrazinamide
Rifampin
Senecio
Statins
Sulfonamides
Terbinafine
Tetracycline
Tolcapone
Tricyclic antidepressants
Valproic acid

Graphic 79913 Version 7.0

Acetaminophen metabolism



At therapeutic doses, 90 percent of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine. One-half of the remaining acetaminophen is excreted unchanged in the urine and one-half is metabolized via the hepatic cytochrome P450 (CYP2E1, CYP1A2, CYP3A4 subfamilies) mixed function oxidase pathway to N-acetyl-p-benzoquinoneimine (NAPQI), which is hepatotoxic. With normal doses (blue arrows), NAPQI is rapidly conjugated to hepatic glutathione, forming nontoxic cysteine and mercaptate compounds that are excreted in the urine. With toxic doses (red arrow), the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by cytochrome P450 enzymes. Once glutathione stores are depleted, NAPQI begins to accumulate and hepatic injury ensues.

Graphic 68213 Version 2.0

Grading system for hepatic encephalopathy

Grade	Mental status	Asterixis	EEG
I	Euphoria/depression	Yes/no	Usually normal
	Mild confusion		
	Slurred speech		
	Disordered sleep		
II	Lethargy	Yes	Abnormal
	Moderate confusion		
III	Marked confusion	Yes	Abnormal
	Incoherent		
	Sleeping but arousable		
IV	Coma	No	Abnormal

EEG: electroencephalogram.

Graphic 62922 Version 2.0

Clinical features of hepatic encephalopathy in adults

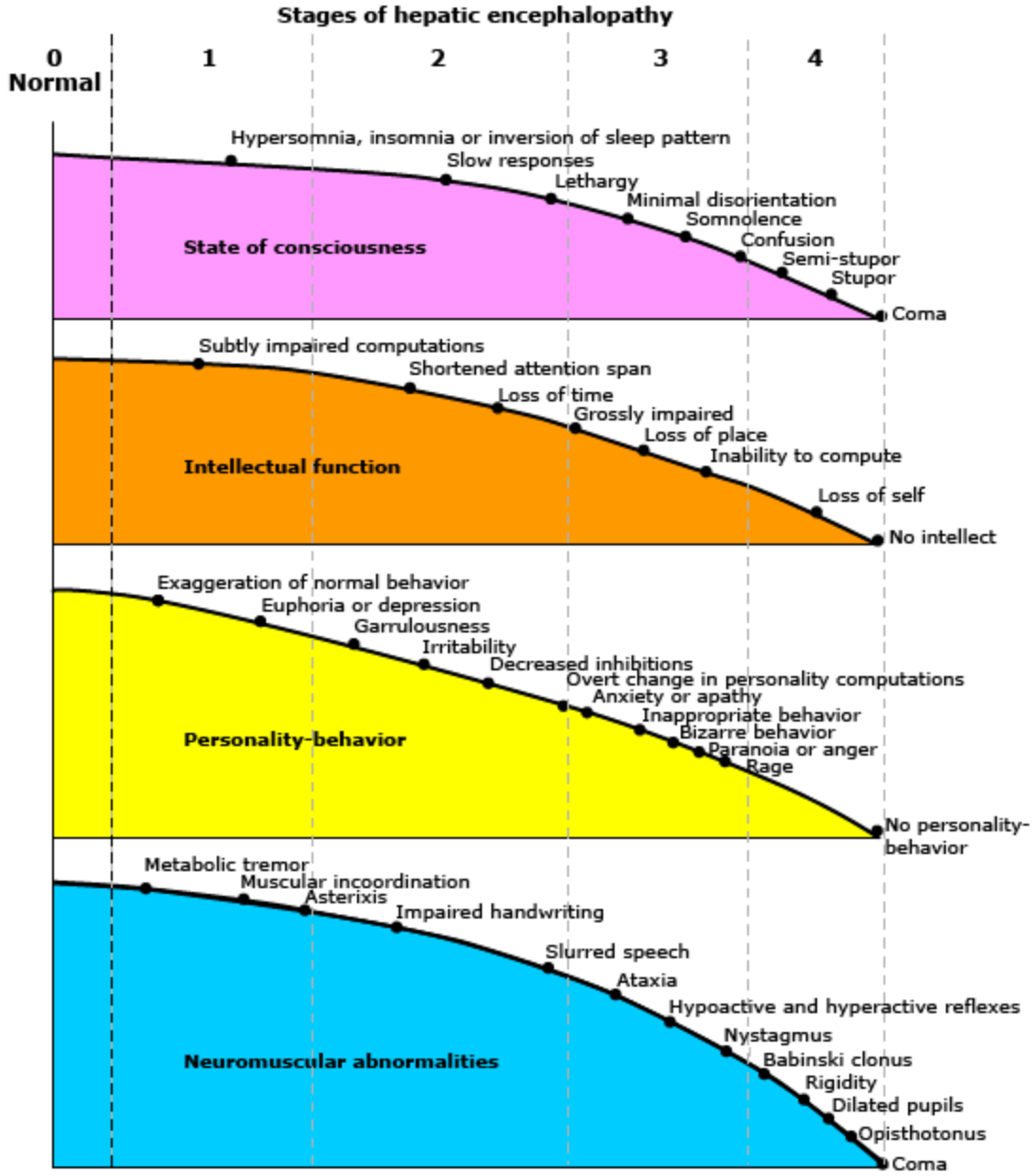
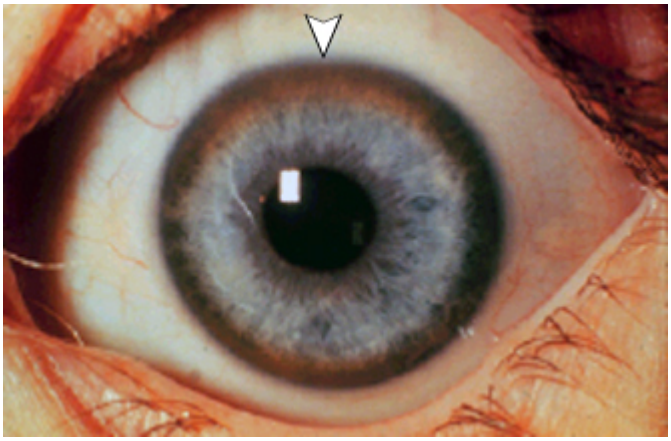


Diagram depicting the grade of hepatic encephalopathy in adults and the clinical features associated with advancing stages.

Data from: Conn HO, Lieberthal MM. The hepatic coma syndromes and lactulose. Lippincott Williams & Wilkins, Baltimore 1979.

Graphic 70740 Version 6.0

Kayser-Fleischer ring



Kayser-Fleischer ring (arrowhead) in a patient with advanced neuropsychiatric Wilson disease. The dense brown copper deposits encircle the iris. It is rare to see Kayser-Fleischer rings without the aid of a slit lamp examination because Wilson disease is usually recognized at an earlier stage when the rings are not as prominent.

Courtesy of Marshall M Kaplan, MD.

Graphic 65925 Version 3.0

Diagnostic criteria for preeclampsia

Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of 1 or more of the following*:
▪ Proteinuria ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (30 mg/mmol) in a random urine specimen or dipstick ≥2+ if a quantitative measurement is unavailable
▪ Platelet count <100,000/microL
▪ Serum creatinine >1.1 mg/dL (97.2 micromol/L) or doubling of the creatinine concentration in the absence of other kidney disease
▪ Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
▪ Pulmonary edema
▪ New-onset and persistent headache not accounted for by alternative diagnoses and not responding to usual doses of analgesics¶
▪ Visual symptoms (eg, blurred vision, flashing lights or sparks, scotomata)

Preeclampsia is considered superimposed when it occurs in a patient with chronic hypertension. Superimposed preeclampsia is characterized by worsening or resistant hypertension (especially acutely), the new onset of proteinuria or a sudden increase in proteinuria, and/or significant new end-organ dysfunction in a patient with chronic hypertension. It typically occurs after 20 weeks of gestation or postpartum.

Definitions/diagnostic criteria for preeclampsia are generally similar worldwide except the International Society for the Study of Hypertension in Pregnancy definition also includes signs of uteroplacental dysfunction (eg, fetal growth restriction, abnormal angiogenic markers, abnormal umbilical artery Doppler, abruption, fetal demise).

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* If systolic blood pressure is ≥160 mmHg and/or diastolic blood pressure is ≥110 mmHg, confirmation within minutes is sufficient.

¶ Response to analgesia does not exclude the possibility of preeclampsia.

Adapted from:

1. *American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2020; 135:e237.*
2. *Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2022; 27:148.*

Graphic 79977 Version 39.0

Findings which increase the certainty of the diagnosis of preeclampsia

Systolic blood pressure ≥160 mm Hg
Diastolic blood pressure ≥110 mm Hg
Proteinuria occurring for the first time during pregnancy, especially if ≥2 g in 24 hours. A qualitative result of 2+ or 3+ is also suggestive.
Serum creatinine >1.2 mg/dL (106 mmol/L)
Platelet count <100,000 cells per cubic millimeter
Evidence of microangiopathic hemolytic anemia (eg, elevated indirect bilirubin or lactic acid dehydrogenase)
Elevated liver chemistries (eg, alanine aminotransferase or aspartate aminotransferase)
Persistent headache or other cerebral or visual disturbances
Persistent epigastric pain

Working group report on high blood pressure in pregnancy. National Instititutes of Health, Washington, DC 2000.

Graphic 60502 Version 3.0

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