

SYMPTOMS TO DIAGNOSIS

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Unexplained liver injury: Searching for the cause

A 70-YEAR-OLD MAN presented to the primary care clinic with persistent low back pain, nausea, poor appetite, and an unintentional weight loss of more than 30 lb (13.6 kg) over the previous 6 weeks. He had no history of alcohol use and had not traveled recently or been exposed to infectious agents. He had quit smoking 35 years earlier, with a 32 pack-year history (2 packs per day for 16 years).

His medical history included hypertension, hyperlipidemia, chronic obstructive pulmonary disease, gastroesophageal reflux disease, obstructive sleep apnea, hypothyroidism, type 2 diabetes mellitus, peripheral vascular disease, obesity, and benign prostatic hyperplasia. His medications included metoprolol succinate extended release, hydrochlorothiazide, lisinopril, rosuvastatin, levothyroxine, furosemide, and doxazosin.

Four months earlier, the patient had been treated for an episode of acute sinusitis with amoxicillin-clavulanate for 7 days, along with a short course of oral methylprednisolone. One month before he presented at the clinic, he was hospitalized for acute diverticulitis and dehydration, which was managed with intravenous fluids, cefdinir, and metronidazole. He was readmitted for dizziness and syncope, and during this admission adjustments were made to his diuretic therapy and antihypertensive regimen. There was no evidence of an acute cardiopulmonary process, and repeat imaging showed improvement in his diverticulitis.

During his primary care clinic visit, the patient was fatigued. Vital signs included a blood pressure of 132/78 mm Hg and a heart rate of 86 beats per minute. He was 68 inches (172.7 cm) tall and weighed 183.6 lb (83.3 kg, body mass index 27.9 kg/m²). On physical examination, cardiac and pulmonary findings were unremarkable. The abdomen was soft, non-

tender, and nondistended, with no palpable masses or organomegaly.

Laboratory testing showed marked elevations in alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) and mildly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at the upper end of the reference range (Table 1).

■ EVALUATING OUT-OF-RANGE LABORATORY RESULTS

1 What pattern of liver injury is suggested by the patient's AST, ALT, ALP, and GGT results?

- Hepatocellular
- Cholestatic
- Mixed

Distinguishing between hepatocellular and cholestatic patterns of liver injury is critical for narrowing the differential diagnosis.¹ Hepatocellular injury is characterized by disproportionate elevations in ALT and AST levels, reflecting damage to hepatocytes.² Cholestatic injury manifests with prominent ALP and GGT elevations, indicating biliary dysfunction or obstruction.³

The R value, calculated from ALT and ALP values divided by the upper limit of normal (ULN), helps differentiate between these patterns:

$$R = \frac{ALT \div ULN \text{ of } ALT}{ALP \div ULN \text{ of } ALP}$$

An R value greater than 5 suggests hepatocellular injury; less than 2 indicates cholestasis, and a value from 2 to 5 implies a mixed pattern.² Bilirubin is not included in the R value and should not be used to classify hepatocellular vs cholestatic injury. While hyperbilirubinemia may be present in either type, it does not define the pattern.

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TABLE 1
Key results of laboratory tests ordered at initial presentation

Test	Value ^a	Reference range
Alkaline phosphatase	749 U/L	38–113
Gamma-glutamyl transferase	1,761 U/L	10–70
Aspartate aminotransferase	44 U/L	14–40
Alanine aminotransferase	49 U/L	10–54
Total bilirubin	1.0 mg/dL	0.2–1.3
Albumin	3.3 g/dL	3.9–4.9
Total protein	5.4 g/dL	6.3–8.0
Creatinine	1.30 mg/dL	0.73–1.22
Estimated glomerular filtration rate	59 mL/min/1.73 m²	> 60

^aOut-of-range values are shown in bold.

Our patient's R value of 0.14 (ALT 49/54 ULN ÷ ALP 749/113 ULN) strongly supports a diagnosis of cholestatic injury and aligns with the marked ALP (749 U/L) and GGT (1,761 U/L) elevations and only mildly elevated AST (44 U/L) and ALT at the upper end of the reference range (49 U/L).

■ MORE TESTING IS NEEDED

2 What is the most appropriate next step in evaluating this patient's out-of-range test results?

- Hepatitis viral serologies and autoimmune liver disease markers
- Right upper quadrant abdominal ultrasonography
- Magnetic resonance imaging of the liver
- Monitor ALT, AST, ALP, and GGT levels and repeat testing in 4 to 6 weeks

The patient's test results reflect a cholestatic pattern of liver injury. Total bilirubin is within normal range. With these findings, the first diagnostic priority is to rule out biliary obstruction such as choledocholithiasis, strictures, or mass lesions affecting the biliary tree.

Right upper quadrant abdominal ultrasonography is the most appropriate initial imaging modality⁴ because it is noninvasive, widely available, cost-effective, and sensitive for detecting bile duct dilatation, gallstones, and intrahepatic or extrahepatic biliary obstruction. It has limitations, however. It may not reliably detect early or subtle obstruction, and it cannot exclude disorders such as primary sclerosing cholangitis. If clinical suspicion remains despite normal study results, further testing with magnetic resonance imaging or

magnetic resonance cholangiopancreatography may be warranted.⁵

Observation with repeat testing in 4 to 6 weeks is inappropriate given the marked cholestatic pattern.

■ CASE CONTINUED: LIVER INJURY PROGRESSES

The patient was prescribed amoxicillin-clavulanate for 7 days for his persistent diverticulitis pain. As part of his initial evaluation, the following tests were ordered:

- Right upper quadrant abdominal ultrasonography
- Repeat measurement of ALP, GGT, ALT, and AST
- Pancreatic tumor marker carbohydrate antigen 19-9
- Tumor marker carcinoembryonic antigen
- Inflammatory markers (C-reactive protein and erythrocyte sedimentation rate).

Abdominal ultrasonography showed no biliary dilatation, gallstones, or hepatic masses. Repeat laboratory evaluation showed further elevation of ALP, GGT, ALT, and AST (**Table 2**). This evolving pattern of liver injury, now marked by a significant rise in ALP, GGT, ALT, AST, and total bilirubin, continued to suggest a cholestatic process, while the increasing transaminase levels raised concern for a possible mixed pattern or progressive hepatic injury.

In addition, elevated carbohydrate antigen 19-9 (174 U/mL) and carcinoembryonic antigen (8.6 ng/mL) raised suspicion for potential underlying malignancy or infiltrative liver disease, although these markers may also be elevated in benign cholestasis.⁶ Given the absence of structural abnormalities on ultrasonography and the patient's progressive symptoms, further workup was considered.

TABLE 2
Results of laboratory tests ordered after initial evaluation

Test	Value ^a	Reference range
Alkaline phosphatase	1,620 U/L	38–113
Gamma-glutamyl transferase	1,676 U/L	10–70
Aspartate aminotransferase	205 U/L	14–40
Alanine aminotransferase	222 U/L	10–54
Total bilirubin	8.9 mg/dL	0.2–1.3
Creatinine	1.45 mg/dL	0.73–1.22
Albumin-to-creatinine ratio	29 mg/g	< 30
Carbohydrate antigen 19-9	174 U/mL	< 37
Carcinoembryonic antigen	8.6 ng/mL	< 5

^aOut-of-range values are shown in bold.

■ NO OBSTRUCTION, NOW WHAT?

3 Which is the most likely explanation for this patient's apparent cholestatic disease?

- Obstructing common bile duct stone
- Pancreaticobiliary malignancy
- Metastatic infiltration of the liver
- Drug-induced liver injury
- Primary sclerosing cholangitis
- Viral hepatitis

The patient's laboratory results show a cholestatic pattern without evidence of biliary obstruction or hepatic mass on imaging. Notably, a normal ultrasonography examination does not reliably exclude most of the diagnostic possibilities listed, such as choledocholithiasis, malignancy, metastatic disease, drug-induced liver injury, primary biliary cholangitis, or primary sclerosing cholangitis. Ultrasonography is mainly useful to detect bile duct dilatation or gallstones; its ability to detect early or subtle disease is limited. Viral hepatitis is less likely to present with such a markedly cholestatic pattern, but additional testing is needed to distinguish among the remaining causes.

■ NARROWING THE DIAGNOSIS

4 What is the most appropriate next step in the evaluation?

- Liver biopsy
- Observation and repeat ALT, AST, ALP, and GGT in 4 weeks

- Serologic workup for viral and autoimmune liver disease
- Magnetic resonance imaging of the liver with and without contrast
- Endoscopic retrograde cholangiopancreatography

The differential at this point leans toward nonobstructive causes such as drug-induced liver injury, autoimmune cholangiopathies, infiltrative liver disease, and malignancy. Serologic testing may help narrow the diagnosis, but magnetic resonance imaging of the liver provides a detailed evaluation of the hepatic parenchyma and biliary tree and is the most appropriate next imaging study to assess for subtle intrahepatic or extrahepatic abnormalities not seen on ultrasonography, including early infiltrative disease or biliary strictures.

■ CASE CONTINUED: IMAGING STUDIES AND LIVER BIOPSY

Abdominal magnetic resonance imaging with magnetic resonance cholangiopancreatography sequences was performed after a 4-week delay due to patient scheduling. The procedure revealed no evidence of biliary ductal dilatation or filling defects, and no suspicious hepatic or pancreatic masses were identified. A small amount of gallbladder sludge was noted without cholelithiasis or signs of cholecystitis. The pancreas showed atrophy without ductal dilatation. No lymphadenopathy or other significant abnormalities were seen. Esophagogastroduodenoscopy was normal and colonoscopy was deferred until the diverticulitis symptoms resolved. Results of laboratory testing for

TABLE 3
Results of laboratory workup for autoimmune, metabolic, and infectious causes

Test	Value ^a	Reference range
Alpha-1 antitrypsin	210 mg/dL	90–200
Mitochondrial M2 immunoglobulin (Ig) G	3.3 U	≤ 20.0
Anti-gp210 antibody IgG	0.6 U	0–24.9
Anti-sp100 antibody IgG	1.6 U	0–24.9
Actin smooth muscle IgG	3 U	< 20
Antinuclear antibody	Negative	
Ferritin	823.0 ng/mL	30.3–565.7
Iron	146 µg/dL	41–186
Total iron-binding capacity	< 201 µg/dL	232–386
Transferrin saturation	72.6%	15%–57%
Total hepatitis B core antibody	Negative	
Hemoglobin	15.8 g/dL	13.0–17.0
White blood cell count	8.28 × 10 ⁹ /L	3.70–11.00
Platelet count	333 × 10 ⁹ /L	150–400

^aOut-of-range values are shown in bold.

viral, metabolic, and autoimmune liver diseases are shown in **Table 3**.

Given the ongoing cholestatic liver injury and inconclusive imaging, a liver biopsy was performed. Histopathology revealed a cholestatic pattern of injury characterized by portal edema, mixed portal inflammation, and a prominent ductular reaction. There was no evidence of fibrosis, cirrhosis, or malignancy. This pattern is consistent with drug-induced liver injury or bile outflow obstruction; small-duct primary sclerosing cholangitis cannot be ruled out based on available data.

Ferritin was elevated at 823 ng/mL, likely reflecting an acute phase response to hepatic inflammation rather than iron overload.

Drug-induced liver injury

Based on the timing of symptom onset and medication history, amoxicillin-clavulanate was identified as the most likely culprit (the patient had recently completed a course of this antibiotic for diverticulitis). Serial ALP, GGT, ALT, and AST monitoring was started to assess recovery. At 3 months, the patient's laboratory evaluation showed marked improvement: ALP decreased to 138 U/L, GGT to 188 U/L, and both AST and ALT normalized to 14 U/L, supporting the diagnosis of amoxicillin-clavulanate-induced liver injury.

A **Roussel Uclaf Causality Assessment Method (RUCAM) score** was calculated to further support the diagnosis.⁷ RUCAM is a validated, structured scoring system used in hepatology to assess the likelihood that a specific drug caused liver injury. It incorporates factors such as the timing of symptom onset relative to drug exposure, the course of transaminases and other relevant enzymes after drug cessation, known risk factors (eg, age, alcohol use), concomitant medications, exclusion of alternative causes, and response to rechallenge. However, while a positive rechallenge can increase diagnostic confidence, intentional reexposure to a suspected hepatotoxic drug is strongly discouraged because it carries a significant risk of severe liver injury.⁸

RUCAM scores are categorized as *unlikely* (1–2 points), *possible* (3–5 points), *probable* (6–8 points), or *highly probable* (≥ 9 points); web-based calculators⁹ are available. The patient's total RUCAM score was 8, indicating a probable likelihood of drug-induced liver injury due to amoxicillin-clavulanate.

Ideally, RUCAM is applied prospectively, but it is often used retrospectively in clinical practice, as in this case. Limitations include subjectivity in scoring and reliance on complete prior workup. RUCAM provides a standardized framework, but clinical judgment and cross-checking medications with resources such as LiverTox remain essential.¹⁰

■ CASE CONCLUSION: IMPROVEMENT AFTER DRUG DISCONTINUATION

In this patient, the pattern of liver injury was cholestatic (R ratio < 2), and the timing of ALP, GGT, ALT, and AST elevations correlated with repeated courses of amoxicillin-clavulanate. Other causes, including viral, autoimmune, and obstructive etiologies, were excluded. The patient was older than 55 (a known risk factor) and had no history of alcohol use. After discontinuation of the drug, ALP, GGT, AST, and ALT levels gradually declined over the following month, consistent with a drug-related injury.

Amoxicillin-clavulanate is a well-established cause of cholestatic liver injury. Although this patient was exposed to the drug multiple times, a formal challenge was not documented.

■ AMOXICILLIN-CLAVULANATE-INDUCED LIVER INJURY

The global annual incidence of drug-induced liver injury is estimated to range from 13.9 to 24.0 cases per 100,000 people.¹¹ Amoxicillin-clavulanate is one of the most commonly prescribed antibiotics worldwide, and is often used to treat respiratory, urinary tract, and skin infections.¹² Amoxicillin-clavulanate causes drug-induced liver injury in approximately 1 of every 2,300 patients who take it.¹³ While generally considered safe, it is a leading cause of idiosyncratic drug-induced liver injury, accounting for a significant proportion of reported cases.¹⁴

Idiosyncratic drug-induced liver injury occurs unpredictably in a small subset of patients and is unrelated to the dose or duration of therapy.¹⁵ These reactions typically reflect complex interactions between the host immune system and drug metabolism and are not reproducible in animal models.^{16,17} Most patients tolerate amoxicillin-clavulanate, but liver injury may develop unexpectedly, sometimes even after short courses of treatment.¹⁸

Epidemiology and risk factors

Amoxicillin-clavulanate-induced liver injury typically occurs in older adults, with a higher incidence reported in men and individuals older than 60. Risk factors include prolonged or repeated courses of the drug, underlying liver disease, and genetic predispositions affecting drug metabolism and immune response.¹⁹ The latency period between drug exposure and onset of liver injury usually ranges from 1 to 6 weeks but can be longer.^{18–20}

Clinical presentation and biochemical pattern

Its clinical presentation is variable, ranging from asymptomatic elevations in ALP, GGT, ALT, and AST to jaundice, fatigue, nausea, and pruritus. The biochemical pattern is predominantly cholestatic or mixed hepatocellular-cholestatic, characterized by marked elevations in ALP and GGT, with mild to moderate increases in ALT and AST. Hyperbilirubinemia is common and may be severe.²¹

Pathogenesis

The pathogenesis of amoxicillin-clavulanate-induced liver injury is believed to be immune-mediated idiosyncratic hepatotoxicity.^{21,22} Genetic factors, such as certain human leukocyte antigen alleles (eg, *DRB1*1501*), have been associated with increased susceptibility.^{21–23}

Diagnosis

The diagnosis of amoxicillin-clavulanate-induced liver injury relies on a thorough medication history, temporal correlation between drug exposure and liver injury, exclusion of other causes (viral hepatitis, autoimmune liver disease, biliary obstruction), and supportive laboratory and imaging studies.²⁴ RUCAM is used to assess the likelihood of drug-induced liver injury.⁷ Liver biopsy may be helpful in atypical or severe cases, showing cholestasis with portal inflammation and ductular reaction.²⁵

Management and prognosis

Primary treatment is immediate cessation of the offending drug.²⁶ Most patients experience gradual biochemical and clinical improvement over weeks to months.¹⁹ Severe injuries with acute liver failure are rare but may require liver transplantation.²⁶ Reexposure to amoxicillin-clavulanate should be avoided due to the risk of recurrence and more severe reactions.²⁷

■ TAKE-HOME POINTS

- Drug-induced liver injury is a diagnosis of exclusion, particularly in older adults with complex medication regimens and subtle or delayed symptom onset.
- Amoxicillin-clavulanate is a leading cause of idiosyncratic drug-induced liver injury, most often presenting with a cholestatic or mixed injury pattern.
- Idiosyncratic drug-induced liver injury is unpredictable, is not dose dependent, and is more common in older adults, particularly after repeated or prolonged exposure.

- Cholestatic injury is suggested by a low R ratio (< 2) and disproportionate elevations in ALP and GGT compared with transaminases.
- Initial imaging with right upper quadrant ultrasonography is essential to rule out biliary obstruction, with magnetic resonance imaging or magnetic resonance cholangiopancreatography and serologic testing to follow if initial studies are nondiagnostic.
- Liver biopsy can help differentiate drug-induced liver injury from infiltrative or autoimmune processes when the diagnosis remains uncertain.
- The RUCAM score is a validated tool for assessing

the likelihood of drug-induced liver injury and should be used when the cause of liver injury is unclear.

- Timely recognition and withdrawal of the offending agent is the cornerstone of management. Most patients experience gradual biochemical recovery, though the course may be prolonged. ■

DISCLOSURES

Dr. Carey has disclosed ownership interest (stock in a publicly traded company) in Pfizer, Inc. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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