

Nondirected Testing for Inpatients With Severe Liver Injury

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The “Things We Do for No Reason” series reviews practices which have become common parts of hospital care but which may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent “black and white” conclusions or clinical practice standards, but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CASE REPORT

A 68-year-old woman with ischemic cardiomyopathy was admitted with abdominal cramping, diarrhea, and nausea, which had left her unable to keep food and liquids down for 2 days. She had been taking diuretics and had a remote history of intravenous drug use. On admission, she was afebrile and had blood pressure of 100/60 mm Hg and a heart rate of 100 bpm. Her extremities were cool and clammy. Blood test results showed an alanine aminotransferase (ALT) level of 1510 IU/L and an aspartate aminotransferase (AST) level of 1643 IU/L. The patient’s clinician did not know her baseline ALT and AST levels and thought the best approach was to identify the cause of the transaminase elevation.

Severe acute liver injury (liver enzymes, $>10 \times$ upper limit of normal [ULN], usually 40 IU/L) is a common presentation among hospitalized patients. Between 1997 and 2015, 1.5% of patients admitted to our hospital had severe liver injury. In another large cohort of hospitalized patients,¹ 0.6% had an ALT level higher than 1000 IU/L ($\sim 20 \times$ ULN). A precise diagnosis is often needed to direct appropriate therapy, and serologic tests are available for many conditions, both common and rare (Table). Given the relative ease of bundled blood testing, nondirected testing has emerged as a popular, if reflexive, strategy.²⁻⁵ In this approach, clinicians evaluate each patient for the set of testable diseases all at once—in contrast to taking a directed, stepwise testing approach guided by the patient’s history.

Use of nondirected testing is common in patients with severe acute liver injury. Of the 5795 such patients treated at our hospital between 2000 and 2015, within the same day of service 53% were tested for hepatitis C virus antibody, 38%

for hemochromatosis (ferritin test), 28% for autoimmune hepatitis (antinuclear antibody test), and 15% for primary biliary cholangitis (antimitochondrial antibody test) by our clinical laboratory. Of the 5023 patients who had send-out tests performed for Wilson disease (ceruloplasmin), 81% were queried for hepatitis B virus infection, 76% for hepatitis C virus infection, 75% for autoimmune hepatitis, and 73.1% for hemochromatosis.² Similar trends were found for patients with severe liver injury tested for α_1 -antitrypsin (AAT) deficiency.³ In sum, these data showed that each patient with severe liver injury was tested out of concern about diseases with markedly different epidemiology and clinical presentations (Table).

WHY YOU MIGHT THINK NONDIRECTED TESTING IS HELPFUL

Use of nondirected testing may reflect perceived urgency, convenience, and thoroughness.²⁻⁶ Alternatively, it may simply involve following a consultant’s recommendations.⁴ As severe acute liver injury is often associated with tremendous morbidity, clinicians seeking answers may perceive directed, stepwise testing as inappropriately slow given the urgency of the presentation; they may think that nondirected testing can reduce hospital length of stay.

WHY NONDIRECTED TESTING IS NOT HELPFUL

Nondirected testing is a problem for at least 4 reasons: limited benefit of reflexive testing for rare diseases, no meaningful impact on outcomes, false positives, and financial cost.

First, immediately testing for rare causes of liver disease is unlikely to benefit patients with severe liver injury. The underlying etiologies of severe liver injury are relatively well circumscribed (Table). Overall, 42% of patients with severe liver injury and 57% of those with an ALT level higher than 1000 IU/L have ischemic hepatitis.⁷ Accounting for a significant percentage of severe liver injury cases are acute biliary obstruction (24%), drug-induced injury (10%-13%), and viral hepatitis (4%-7%).^{1,8} Of the small subset of patients with severe liver injury that progresses to acute liver failure (ALF; encephalopathy, coagulopathy), 0.5% have autoimmune hepatitis and 0.1% have Wilson disease.⁹ Furthermore, many patients are tested for AAT deficiency, hemochromatosis, and primary biliary cholangitis, but these are never causes of severe acute liver injury (Table).

Second, diagnosing a rarer cause of acute liver injury modestly earlier has no meaningful impact on outcome. Work-up for more common etiologies can usually be completed

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TABLE. Causes of Severe Acute Liver Injury^a

Disease	Population Estimate	Prevalence Among Those with Severe Liver Injury	Test
Ischemic hepatitis ⁷	Unknown	42%	Physical exam, hemodynamics; if no evidence of hypoperfusion, consider ultrasonography and exclude viral hepatitis
Acute biliary obstruction ^{1,8}	~0.003%	24%	Ultrasonography, cross-sectional imaging
Drug-induced liver injury ⁹	~0.002%	10%-13%	Exclude viral hepatitis, consider biopsy
Viral hepatitis ^{1,3,8}	~1%	4%-7%	Hepatitis C antibody/confirmed with PCR; hepatitis B surface antigen or core immunoglobulin M/confirmed with PCR
Autoimmune hepatitis ^{8,14}	0.001%	<0.5%	Antinuclear antibody, antismooth muscle antibody, immunoglobulin G; consider biopsy
Wilson disease ³	0.03%	<0.1%	Ceruloplasmin <20 mg/dL; confirmed with urine copper concentration
Hemochromatosis ¹⁵	0.1%	0%	Transferrin saturation >45%; confirmed with genetic test
Primary biliary cholangitis ¹⁶	0.01%	0%	Antimitochondrial antibody; consider biopsy
Alpha-1 antitrypsin deficiency ²	0.04%	0%	Alpha-1 antitrypsin level (<80 mg/dL) and confirmatory phenotype

^aSevere acute liver injury = liver enzymes >10 times the upper limit of normal.
NOTE: Abbreviation: PCR, polymerase chain reaction.

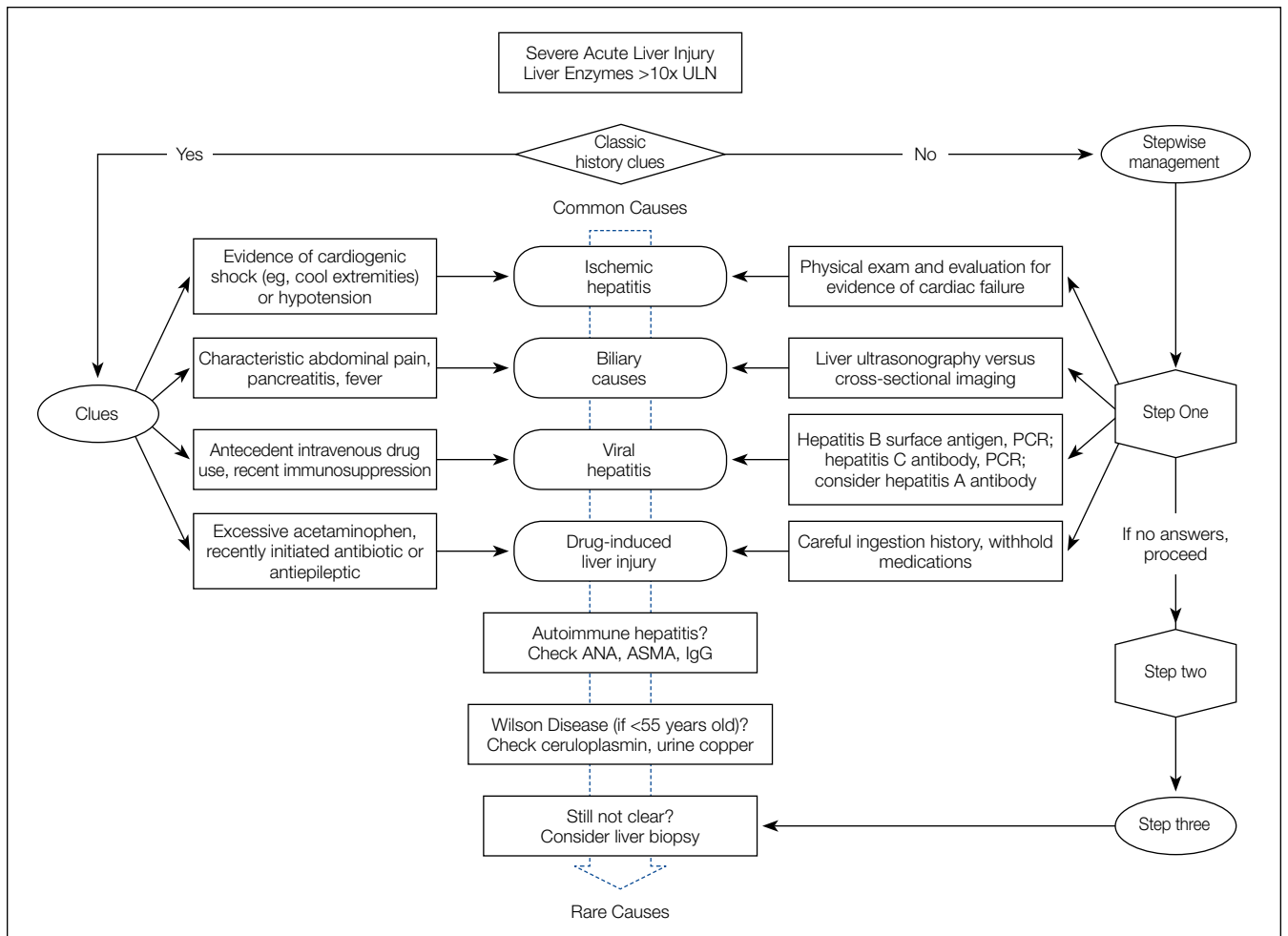


FIG. Pathway for evaluation of severe acute liver injury.

NOTE: Abbreviations: ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; IgG, immunoglobulin G; PCR, polymerase chain reaction; ULN, upper limit of normal.

within 2 or 3 days. This is true even for patients with ALF. Specific therapies generally are lacking for ALF, save for use of N-acetylcysteine for acetaminophen overdose and anti-

viral therapy for hepatitis B virus infection.^{9,10} Furthermore, although effective therapies are available for both autoimmune hepatitis and Wilson disease, the potential benefit

stems from altering the longer term course of disease. Initial management, even for these rare conditions, is no different from that for other etiologies. Conversely, acute liver injury caused by ischemic hepatitis, biliary disease, or drug-induced liver injury requires swift corrective action. Even if normotensive, patients with ischemic hepatitis are often in cardiogenic shock and benefit from careful monitoring and critical care.⁷ Patients with acute biliary obstruction may need therapeutic endoscopy. Last, patients with drug-induced liver injury benefit from immediate discontinuation of the offending drug.

Third, in the testing of patients with low pretest probabilities, false positives are common. For example, at our institution and at an institution in Austria, severe liver injury patients with a low ceruloplasmin level have a 95.1% to 98.1% chance of a false-positive result (they have a low ceruloplasmin level but do not have Wilson disease).^{3,4} Furthermore, 91% of positive tests are never confirmed,³ indicating either that clinicians never valued the initial test or that other diagnoses were much more likely. Even worse, as was the case in 65% of patients with low AAT levels,^{2,3} genetic diagnoses were based on unconfirmed, potentially false-positive serologic tests.

Fourth, although the financial cost for each individual test is small, at the population level the cost of nondirected testing is significant. For example, although each reflects testing for conditions that do not cause acute liver injury, the costs of ferritin, AAT, and antimitochondrial antibody tests are \$13, \$16, and \$37, respectively (Medicare/Medicaid reimbursements in 2016 \$US).¹¹ About 1.5% of admitted patients are found to have severe liver injury. If this proportion holds true for the roughly 40 million discharges from US hospitals each year, then there would be an annual cost of about \$40 million if all 3 tests were performed for each patient with severe liver injury. In addition, although nondirected testing may seem clinically expedient, there are no data suggesting it reduces length of stay. In fact, ceruloplasmin, AAT, and many other tests are sent to external laboratories and are unlikely to be returned before discharge. If clinicians delay discharge for results, then nondirected testing would increase rather than decrease length of stay.

WHAT YOU SHOULD DO INSTEAD

In this era of increasing cost-consciousness, nondirected testing has escaped relatively unscathed. Indeed, nondirected testing is prevalent, yet has pitfalls similar to those of serologic testing (eg, vasculitis or arthritis,⁶ acute renal injury, infectious disease¹²). The alternative is deliberate, empirical, patient-centered testing that is attentive to the patient's presentation and the harms of false positives. The idea is to select tests for each patient with acute liver injury according to presentation and the most likely corresponding diagnoses (Table, Figure).

The patient in our case report had a history suggestive of ischemic hepatitis, which requires urgent evaluation, and management of potential decompensated heart failure.

However, given her history of intravenous drug use, viral hepatitis must be excluded. In addition, a careful history of medication and ingestion should be obtained. Testing should start with physical examination (assessing for hypoperfusion), consideration of abdominal ultrasonography with Doppler evaluation, and serologic testing for viral hepatitis. Testing for rare diseases should be performed only after these more common diseases have been excluded.

The "one-stop shopping" in providers' electronic order entry systems makes it too easy to over-order tests. Fortunately, these systems' simple and effective decision supports can force pauses in the ordering process, create barriers to waste, and provide education about test characteristics and costs.^{4,5,13} Our medical center's volume of ceruloplasmin orders decreased by 80% after a change was made to its ordering system; the ordering of a ceruloplasmin test is now interrupted by a pop-up screen that displays test characteristics and an option to continue or cancel the order.^{4,5} Hospitals should consider implementing clinical decision supports in this area. Successful interventions provide electronic rather than paper-based support as part of the clinical workflow, during the ordering process, and recommendations rather than assessments.¹³

RECOMMENDATIONS

- For each patient with severe acute liver injury, select tests on the basis of the presentation (Figure). Testing for rare diseases should be performed only after common diseases have been excluded.
- Avoid testing for hemochromatosis (iron indices, genetic tests), AAT deficiency (AAT levels or phenotypes), and primary biliary cholangitis (antimitochondrial antibodies) in patients with severe acute liver injury.
- Consider implementing decision supports that can curb nondirected testing in areas in which it is common.

CONCLUSION

Nondirected testing is associated with false positives and increased costs in the evaluation and management of severe acute liver injury. The alternative is deliberate, epidemiologically and clinically driven directed testing. Electronic ordering system decision supports can be useful in curtailing nondirected testing.

Disclosure: Nothing to report.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason"? Let us know what you do in your practice and propose ideas for other "Things We Do for No Reason" topics. Please join in the conversation online at Twitter (#TWDENR)/Facebook and don't forget to "Like It" on Facebook or retweet it on Twitter.

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