# Aerospace Medicine Clinic

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You're the flight surgeon consulted to assess a search and rescue (SAR) technician applicant. SAR technicians are highly trained pararescue specialists, extensively screened and trained to respond to land and sea rescue and distress situations and render life-sustaining medical care in otherwise inaccessible areas. Individuals are required to be as fit as aircrew and divers. The medical selection process involves an initial medical screening prior to a physically demanding remote wilderness survival exercise. Those successful following the initial selection then require subsequent detailed medical evaluation.

The applicant is a 25-yr-old man with no significant past medical history and no prescribed or over-the-counter medications. A social history reveals alcohol use on only a few occasions per year. Of note, there is no personal or family history of gastrointestinal disease. A physical exam is unremarkable. Prior to the selection exercise, a full battery of laboratory tests, including liver chemistries, are within normal limits.

The applicant returns to your office 2 wk after the selection exercise for an additional detailed exam. He describes the selection process as intensively rigorous, involving activities such as carrying heavy loads in freezing temperatures and long strenuous hiking with limited food intake. He endorses up to 12 lb of recent weight loss but is feeling otherwise well.

You fill a lab requisition to repeat bloodwork, which returns as follows (**Table I**): you note that the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are above normal limits. You review your records for bloodwork performed several months ago and note that previous values were within normal range.

1. What is the next best step in investigating this lab result?
   A. Abdominal ultrasound.
   B. Evaluate serum creatine kinase and lactate dehydrogenase.
   C. Assess liver synthetic function: albumin, international normalized ratio, and platelets.
   D. Check serum ceruplasmin and evaluate for Kayser-Fleischer rings.
   E. Conservative management; repeat abnormal values in 1–2 wk.

## ANSWER/DISCUSSION

**1. E.** In the absence of risk factors, stigmata, or known history of liver disease, mild-moderate elevations in ALT and AST, in most situations, can be followed conservatively and managed expectantly. In this case, an extensive work-up was initiated for this patient, including imaging, which was normal. Serum liver enzymes were repeated and a significant, expected decrease was confirmed, as noted in **Table II**.

2. What is the most likely cause for this individual's abnormal liver chemistry values?
   A. Nonalcoholic fatty liver disease given the AST:ALT < 1 pattern.
   B. Viral hepatitis.
   C. Wilson's disease.
   D. Strenuous exercise-induced liver chemistry elevation.
   E. Drug-induced liver injury.

## ANSWER/DISCUSSION

**2. D.** The history and clinical context suggest a subacute process to explain the rise in liver chemistries. The patient previously presented with a normal liver profile prior to a period of strenuous exercise. Exercise-induced liver chemistry elevation is a common phenomenon that has been reported in the literature among otherwise healthy patients. In a study of 14 young, healthy men following a 1-h intensive weight-lifting exercise, all but one subject had elevations in both AST and ALT greater than the upper limit of normal. Other liver chemistries, including gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and total bilirubin remained unchanged for the study


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**Table I.** Liver Chemistries Before and After the Selection Process.

| CHEMISTRY | NORMAL RANGE | 10/2019 | 1/2020 | 2/2020 |
|---|---|---|---|---|
| ALT | 5-35 IU/L | 33 | 2 wk training | 376 |
| AST | 7-40 IU/L | 28 | exercise | 182 |
| ALP | 35-100 IU/L | 81 | | 71 |
| CK | 5-130 IU/L | – | | 111 |
| T-bilirubin | <26 nmol · $L^{-1}$ | 3 | | 4 |
| GGT | 8-61 U · $L^{-1}$ | 15 | | 26 |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; CK: creatine kinase; GGT: gamma-glutamyl transferase.

period of 12 d.[11] In a similar study of 20 young male subjects, elevations in AST and ALT were apparent 12-h following intensive boxing exercise.[14] Similar increases were noted in two separate studies involving a more rigorous and sustained period of exercise. In a study of 87 military cadets undergoing a 30-km march, AST and ALT levels increased by 418% and 256%, respectively, 12–24 h after completion of the march.[5] Nagel et al. studied 55 subjects during a long-distance 1000-km race spanning 20 d. Subjects were noted to have a fivefold increase in AST levels from days 0–3 and a threefold increase in ALT up to day 6. Unlike other studies, concomitant rises in other liver chemistries such as GGT and ALP were also noted, likely owing to the longer study duration.[9]

The cause for such elevations in liver chemistries is thought to be multifactorial, as both AST and ALT are found in sources outside of the liver, such as in skeletal muscle. In the setting of strenuous muscle activity, a significant proportion of AST and ALT elevation is likely accounted for by damage to skeletal muscle. Other biochemical markers that are more specific to liver injury, such as GGT, can be key to understanding the extent of concurrent damage to hepatocytes. Elevations in GGT raise greater concern for a liver specific cause. In the case of the SAR applicant, the GGT was 26 (normal range 8–61) at 2 wk postactivity and 22 after 4 wk. Elevations in GGT have been reported in the literature following exhaustive exercise, and

**Table II.** Repeated Liver Chemistries Demonstrating a Trend Toward Normalization with Conservative Management.

| PARAMETER | RANGE (MALE) | DAY 0 | DAY 3 | DAY 14 | DAY 28 |
|---|---|---|---|---|---|
| ALT | 5–35 IU/L | Final day | 412 | 376 | 129 |
| AST | 7–40 IU/L | of 2 wk | 489 | 182 | 46 |
| ALP | 35–100 IU/L | training | | 71 | 66 |
| Total bilirubin | <26 nmol · $L^{-1}$ | exercise | | 4 | 4 |
| GGT | 8–61 U · $L^{-1}$ | | | 26 | 22 |
| Albumin | 35–50 g · $L^{-1}$ | | | 46 | |
| INR | 1.0 | | | 1.0 | |
| Ferritin | 12–30 µg · $L^{-1}$ | | | 142 | |
| TSH | 0.4–4 µU · $L^{-1}$ | | | 1.20 | |
| Hemoglobin | 140–180 g · $L^{-1}$ | | | 155 | |
| Platelets | 150–400 × $10^9$/L | | | 301 | |
| White blood cells | 4–10 × $10^9$/L | | | 5.7 | |
| HBsAg | | | | Negative | |
| Anti-HBs | | | | Positive | |
| Hep A IgM | | | | Negative | |
| Anti-HCV | | | | Negative | |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; CK: creatine kinase; GGT: gamma-glutamyl transferase; INR: international normalized ratio; TSH: thyroid-stimulating hormone; HBsAg: hepatitis B surface antigen; HBs: hepatitis B surface; Hep A IgM: hepatitis A immunoglobulin M; HCV: hepatitis C virus.

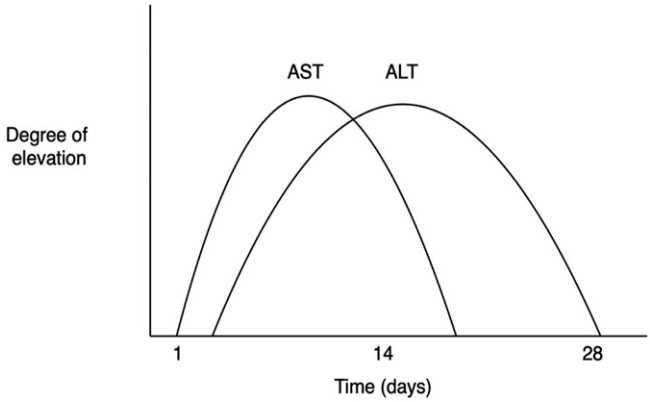


**Fig. 1.** Increases in serum AST may be detectable within 24 h of strenuous muscular activity, followed by ALT. AST is cleared more rapidly than ALT; as such, the measured serum AST:ALT ratio varies depending on the time of measurement.

though these elevations are usually mild, they have been reported to increase up to sixfold.[2,9] However, the frequency and time course of these elevations remain unclear. As such, it is possible that our patient's GGT would have been elevated if measured earlier, immediately following his selection exercise.

It is important to note that this patient's ratio of ALT:AST is < 1, conflicting with the aforementioned studies demonstrating a ratio of AST:ALT > 1 following physical activity. However, this can be explained by the time which they are measured. AST levels have been noted to rise and decrease at a faster rate than ALT owing to a shorter half-life. Had the flight surgeon measured the patient's liver chemistries within 72 h after the training exercise, an AST:ALT > 1 pattern would have likely been present (**Fig. 1**). Beyond 7 d, the ratio of these two values approaches 1 and reverses thereafter, with ALT remaining elevated for a sustained period of time.[5,9,14] The causes of liver chemistry elevation have been conventionally grouped into ALT or AST dominant; as such, it is important to note that this pattern of elevation is dependent on the time of measurement. After 14 d when the patient's AST and ALT levels were measured, AST levels had likely already peaked and a greater proportion of the AST was cleared.

Elevated liver chemistries in previously healthy individuals are commonly seen among SAR tech applicants following selection exercises. Some flight surgeons have opted to delay repeat bloodwork if liver chemistries are previously normal, as this may impart a misrepresentative picture of liver disease, leading to unnecessary and costly investigations. Furthermore, it may lead to unnecessary patient anxiety in a population that is undergoing competitive selection and screening processes for limited training positions.

3. Which process(es) is/are involved in the pathophysiology of exercise induced liver injury?
   A. Reduced hepatic blood flow.
   B. Ischemia-reperfusion phenomenon.
   C. Production of reactive oxygen species (ROS).
   D. Increased hepatocyte permeability.
   E. All of the above.

## ANSWER/DISCUSSION

**3. E.** Intensive exercise is associated with a physiological shift in blood circulation toward skeletal muscle and away from other organs, such as the liver.[12] There are several theorized mechanisms by which a reduction in hepatic circulation may be responsible for the elevation in liver chemistries noted. The ischemia-reperfusion phenomenon is a process by which a return of circulation to cells previously in a state of ischemia promotes the production of ROS. An imbalance in the production and clearance of ROS leads to a state of oxidative stress, which can lead to cellular damage. ROS can impart direct damage onto hepatocytes and result in the release of biochemical markers of liver injury, such as AST, ALT, and GGT, among others.[4,12]

Anatomically, the liver is divided into lobules that are subdivided further into various zones. Certain zones receive less oxygenation from the oxygen-carrying hepatic arterioles than others, particularly the pericentral hepatocytes closest to the central vein. Exhaustive exercise has been noted to induce the swelling of these pericentral hepatocytes and the subsequent transient ischemia is thought to increase the permeability of the cellular membrane, thus facilitating the release of biomarkers from these pericentral hepatocytes.[12]

The SAR tech applicant in our case described a several-day history of minimal caloric intake during the exercise training. Studies examining the effect of energy intake on exercise induced liver injury in rats found that the hepatocytes of fasting rats are more prone to ischemic injury than those in the feeding state. This is likely related to reduced levels of glutathione and glycogen in liver cells when exposed to lower energy intake, which are important in counteracting the effects of ROS and preventing oxidative stress.[4] Taken together, exercise-induced liver injury to hepatocytes may explain your patient's elevated enzyme levels in addition to skeletal muscle damage.

4. If the applicant presented to you prior to the selection exercise with elevated serum aminotransferases (AST and ALT) that remain persistently elevated on repeat bloodwork, and with no recorded history of normal values, what would be the next step in management?
   A. Advise against participation in the training exercise.
   B. Hepatitis B and C serology.
   C. Perform a more detailed medication review, including herbal and over-the-counter medications.
   D. Check an iron and total-iron binding capacity level.
   E. Right-upper quadrant ultrasonography.
   F. All of the above.

## ANSWER/DISCUSSION

**4. F.** All of the above. Evaluation of elevated aminotransferases must first begin with consideration of a general approach to abnormal liver chemistries. There have been a variety of approaches to describe abnormal liver chemistries, with the most common classification being: 1) hepatocellular (disproportionate elevations of AST and ALT); 2) cholestatic (disproportionate elevation of ALP); 3) mixed; and 4) isolated hyperbilirubinemia. These classifications highlight the most notable enzyme elevation. The R ratio can be used to categorize a liver enzyme elevation into these categories, where an R ratio of > 5 represents a hepatocellular pattern, 2–5 mixed, and < 2 cholestatic.[7]

$$R = \frac{\text{ALT value / ALT upper limit of normal (ULN)}}{\text{ALP value / ALP ULN}} \qquad \text{Eq. 1}$$

The differential diagnosis for mild-moderately elevated transaminases is broad and the evaluation should be guided by the risk factors. Referring back to question 4, the evaluation of mild and moderately elevated transaminases (AST and/or ALT)—defined as AST/ALT being elevated 2–5× and 5–15× the ULN, respectively—must first begin with clinical assessment, which includes comprehensive history and physical examination to assess pretest probability of underlying liver disease and evidence suggesting a specific etiology. History must include careful medication review and screening for alcohol use; hepatotoxic medications should be discontinued and alcohol cessation should be advised. Next, investigations should include routine bloodwork, general work-up for underlying liver disease, and those guided by pretest probability of various etiologies. Practically, in addition to routine bloodwork (complete blood count with differential, AST/ALT, ALP, albumin, prothrombin time/international normalized ratio), a general liver disease work-up should assess for important underlying pathologies, including viral hepatitis (hepatis B surface antigen, antibody to surface antigen, and core antibody; antibody to hepatitis C virus with PCR if positive), hereditary hemochromatosis (iron panel), and imaging (right upper quadrant ultrasound) for nonalcoholic fatty liver disease.[7,13]

If this work-up is negative, observation is a reasonable next step, with repeat liver panel and consideration of thorough investigation of other underlying causes. Persistently elevated liver chemistries may warrant further investigation for rarer causes such as autoimmune liver disease (antinuclear antibody, anti-smooth muscle antibody, gamma-globulin), Wilson's Disease (ceruloplasmin), alpha-1 antitrypsin deficiency, *Mycobacterium tuberculosis*, celiac sprue, tick-borne disease, thyroid disease, and myopathies. Liver biopsy is the definitive test that can be pursued if these investigations are nondiagnostic.[13] In a study of almost 20,000 military recruits who voluntarily donated blood over a 1-yr period, 99 were found to have an asymptomatic elevation in aminotransferases during routine serological screen of donated blood. Of those, only 12 received a confirmatory diagnosis, which included hepatitis B, hepatitis C, autoimmune hepatitis, and gallbladder disease.[6]

5. Patients may present with an isolated, asymptomatic elevation in ALP. Which of the following is the best method for determining whether the elevation in ALP represents a hepatic process?
   A. Measure serum GGT.
   B. Perform a liver biopsy.

C. Ask the laboratory to fractionate the ALP into iso-enzymes.
D. Right upper quadrant ultrasonography.
E. Observe and investigate only if symptoms or stigmata of liver disease manifest.

## ANSWER/DISCUSSION

**5. A.** ALP is an enzyme that is commonly measured in association with other liver chemistries in the work-up of liver disease and is useful in diagnosing hepatobiliary disease such as cholestasis. However, ALP is present within the biliary ducts and in other sources, such as in bone, intestine, and placenta. As such, ALP can also be mildly elevated as part of a normal physiological response to pregnancy and after meals. An efficient way to determine whether an elevation in ALP is of hepatic origin is to check GGT, which should also be elevated in the setting of liver disease.[8]

When ALP is confirmed to be of hepatic origin, an ultrasound should be performed to assess for biliary duct dilation, and a positive finding could require further investigation with magnetic resonance cholangiopancreatography, intervention with endoscopic retrograde cholangiopancreatography, or both. The absence of radiological findings would require further investigation for primary biliary cholangitis through serum antimitochondrial antibody levels, and expert consultation from a gastroenterologist or hepatologist should be sought.[3]

Common practice previously involved 'fractionating' ALP into its unique iso-enzyme components (i.e., placental, intestinal, and hepatocytic) to determine the site of origin; however, this is no longer commonly practiced and may not be offered by commercial or hospital laboratories.[10] If GGT is normal and physiological causes have been ruled out, a persistently elevated isolated ALP should prompt investigation for bone disorders such as Paget's disease.[1]

## AEROMEDICAL DISPOSITION

In conclusion, the differential diagnosis for elevated liver chemistries is broad and requires an organized approach with an understanding of the patient's risk factors. The severity and temporality (acute or chronic) of each elevation must be considered. In this case, a 25-yr-old otherwise healthy SAR tech applicant presented with a moderate, acute transaminase elevation in the context of recently returning from a 14-d wilderness exercise. Bloodwork and physical exam revealed no other abnormalities or cause for the elevation and repeat liver chemistries demonstrated a trend toward normalization. The applicant's presentation was in keeping with strenuous exercise-induced liver chemistry elevation. No further follow-up was required.

**Danho S, Partridge ACR, Saary J.** ***Aerospace medicine clinic: evaluation of abnormal liver chemistries in the setting of strenuous physical activity.*** **Aerosp Med Hum Perform. 2022; 93(2):129–132.**

## REFERENCES

1. Al Nofal AA, Altayar O, BenKhadra K, Agha OQ, Asi N, et al. Bone turnover markers in Paget's disease of the bone: a systematic review and meta-analysis. Osteoporos Int. 2015; 26(7):1875–1891.
2. Fallon KE, Sivyer G, Sivyer K, Dare A. The biochemistry of runners in a 1600 km ultramarathon. Br J Sports Med. 1999; 33(4):264–269.
3. Friedman LS, Chopra S, Travis AC. Approach to the patient with abnormal liver biochemical and function tests. Waltham (MA): UpToDate; 2017. [Accessed March 8, 2021]. Available from: http://pgnrc.sbmu.ac.ir/uploads/Approach_to_the_patient_with_abnormal_liver_biochemical_and_function_tests.pdf.
4. Kinoshita S, Yano H, Tsuji E. An increase in damaged hepatocytes in rats after high intensity exercise. Acta Physiol Scand. 2003; 178(3):225–230.
5. Koury JC, Daleprane JB, Pitaluga-Filho MV, de Oliveira CF, Gonçalves MC, Passos MC. Aerobic conditioning might protect against liver and muscle injury caused by short-term military training. J Strength Cond Res. 2016; 30(2):454–460.
6. Kundrotas LW, Clement DJ. Serum alanine aminotransferase (ALT) elevation in asymptomatic US Air Force basic trainee blood donors. Dig Dis Sci. 1993; 38(12):2145–2150.
7. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017; 112(1):18–35.
8. Musana KA, Yale SH, Abdulkarim AS. Tests of liver injury. Clin Med Res. 2004; 2(2):129–131.
9. Nagel D, Seiler D, Franz H, Jung K. Ultra-long-distance running and the liver. Int J Sports Med. 1990; 11(6):441–445.
10. PetitClerc C. Quantitative fractionation of alkaline phosphatase isoenzymes according to their thermostability. Clin Chem. 1976; 22(1):42–48.
11. Pettersson J, Hindorf U, Persson P, Bengtsson T, Malmqvist U, et al. Muscular exercise can cause highly pathological liver function tests in healthy men. Br J Clin Pharmacol. 2008; 65(2):253–259.
12. Praphatsorn P, Thong-Ngam D, Kulaputana O, Klaikeaw N. Effects of intense exercise on biochemical and histological changes in rat liver and pancreas. Asian Biomed. 2010; 4(4):619–625.
13. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med. 2000; 342(17):1266–1271.
14. Saengsirisuwan V, Phadungkij S, Pholpramool C. Renal and liver functions and muscle injuries during training and after competition in Thai boxers. Br J Sports Med. 1998; 32(4):304–308.