

**Samantha Jill Magier, MD, MEng**

Chief Resident for Quality and Safety, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; Department of Internal Medicine, West Haven Veterans Administration Medical Center, West Haven, CT

Thiruvengadam Muniraj, MD, FRCP

Associate Chief for Endoscopy, Digestive Health, Yale New Haven Health System, New Haven, CT; Director, Yale Center for Pancreatitis; Director, Bariatric Endoscopy, Department of Internal Medicine; Associate Professor of Medicine, Digestive Diseases, Yale School of Medicine, New Haven, CT

Naseema Merchant, MBBS,**FCCP, FACP, FHM**

Physician Lead, High Reliability Organization (HRO) in Health Care; Site Director, Chief Resident Program in Quality Improvement and Patient Safety; Hospital Medicine, Veterans Affairs Connecticut Healthcare System, West Haven, CT; Assistant Professor of Medicine, Section of General Internal Medicine, Yale School of Medicine, New Haven, CT

Q: Serial serum lipase testing after the initial diagnostic workup for inpatients with acute pancreatitis: What is the evidence?

A 35-year-old male with no significant medical history presented to the hospital with acute epigastric pain radiating to his back. Workup revealed a serum lipase of 518 U/L (reference range 0–160 U/L), and computed tomography of the abdomen showed peripancreatic fat-stranding. He does not drink alcohol or take any medications, and the workup was negative for gallstones and hypertriglyceridemia. He was diagnosed with acute idiopathic pancreatitis and admitted to the hospital for management. He received early enteral feeding, intravenous fluid resuscitation, and opioid analgesia for pain control. His pain gradually improved and he was tolerating oral intake. A repeat serum lipase level on hospital day 3 was elevated at 609 U/L. Does this repeat serum lipase value have a role in guiding further clinical decisions?

A: Lipase testing should be ordered for the initial diagnostic workup of patients presenting with concern for acute pancreatitis. Once a diagnosis of acute pancreatitis is established, routine serial lipase testing is recommended against. Subsequent serum lipase testing should be reserved only for rare instances where there is concern for pancreatic duct blockage, pseudocyst formation, or lack of clinical improvement after 1 week, and should be performed in conjunction with repeat cross-sectional imaging.

Thus, for the 35-year-old male in the clinical vignette above, repeat lipase testing is not recommended, and clinically guided management should be utilized.

doi:10.3949/cjcm.90a.22060

DEFINING THE PROBLEM

Acute pancreatitis occurs when the pancreas becomes suddenly inflamed, most commonly related to alcohol use and gallstones, but with a broad differential diagnosis. The condition leads to severe pain and extravasation of pancreatic enzymes, contributing to complications requiring thoughtful management. Acute pancreatitis affects 17 people per 100,000 in the United States annually and is among the most frequent indications for inpatient admission secondary to a gastrointestinal diagnosis.^{1,2} There are roughly 280,000 patient admissions for acute pancreatitis annually, with a median cost of \$6,240 per patient per admission, totaling \$2.6 billion per year.³

KEYS TO EVALUATION

Although upper abdominal pain is the main component of acute pancreatitis, confirmation by objective data is warranted to ensure an accurate diagnosis. Most commonly, the diagnosis is supported by a single measurement of a 3-fold elevation in serum pancreatic enzymes (amylase or lipase, or both) in the setting of characteristic epigastric pain. In the presence of abdominal pain and normal serum pancreatic enzymes or of elevated enzymes in the absence of abdominal pain, imaging is necessary for diagnosis.

The diagnosis of acute pancreatitis is based on the presence of 2 of the following 3 features according to the Atlanta classification: abdominal pain consistent with acute pancreatitis, serum lipase activity (or amylase activity) at least 3 times greater than the upper

limit of normal, and characteristic findings of acute pancreatitis on contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography.⁴

The lipase level increases within 4 to 8 hours after the onset of acute pancreatitis, peaks at 24 hours, and normalizes within 8 to 14 days, with the range encompassing the breadth of etiologies.⁵ After the diagnosis is confirmed, serial lipase measurement has little value in gauging clinical progress or prognosis according to Choosing Wisely,⁶ the American College of Gastroenterology,⁷ and the American Gastroenterology Association.⁸ The evidence for utilizing lipase as a prognostic marker is weak, and far stronger risk-stratification tools exist.⁷⁻⁹

■ SYMPTOMS AND CLINICAL CRITERIA SHOULD GUIDE MANAGEMENT

Symptom-guided and clinical criteria-guided management are the standard of care in acute pancreatitis to facilitate clinical decisions. The use of lipase, a diagnostic test, should not supersede clinical judgment. If there is concern that a patient is not clinically improving, reference to admission risk-stratification scores is recommended, along with consideration of cross-sectional imaging to provide more objective data.^{7,8}

The most notable severity index scores—the Acute Physiology and Chronic Health Evaluation II,¹⁰ the BISAP score,¹¹ and the Ranson criteria¹²—utilize laboratory and clinical data to appropriately predict morbidity at the time of admission. Importantly, none of these scores utilize serum lipase. Despite this knowledge, repeat lipase testing (RLT) is regularly inappropriately performed to guide clinical decisions such as initiation of enteral nutrition and appropriateness of patient discharge.^{13,14}

■ MONETARY AND NON-MONETARY COSTS OF REPEAT LIPASE TESTING

In a retrospective review by Datta et al,¹³ lipase testing was repeated in 203 adult inpatients an average of 2.88 times. In 81.2% of patients, the lipase decreased to below 3 times the upper limit of normal, and 63.6% of these patients had repeat testing despite the downward trend. Importantly, there was no difference in mortality in patients who underwent RLT vs those who did not (1.8% in RLT group vs 0.0% in non-RLT group, $P = .450$), and there was no statistically significant difference in the severity of acute pancreatitis based on age, blood urea nitrogen, and

Systemic Inflammatory Response Syndrome criteria, all of which were surrogate markers of severity.¹³

A study by Ritter et al¹⁴ showed that during an average inpatient stay of 3 days the mean number of lipase tests ordered per patient was $2.4 \pm \text{SD } 2.5$ tests (range 1–25), and there was likewise no difference in disease severity in patients who had repeat testing and those who did not. This highlights that serum lipase was repeated in these patients not solely because they had severe disease, and thus, associated changes in costs cannot be attributed to disease severity. For example, if patients who had repeat serum lipase had more severe disease, then costs could be driven up by use of intensive care unit services. The same severity index for both groups of patients (ie, those who had repeat lipase testing and those who did not) thus reduces a degree of confounding in the cost analysis. While the actual cost of each lipase test was determined to be \$0.88 by bottom-up cost estimation, which approximates costs at the lowest level, the additional attributable cost per test, which reflects the non-value-added cost of an item, was \$3.41, bringing the total cost of each test to \$4.29.¹⁴ Putting together these data, at an approximate total cost of \$4.29 attributed to each lipase test ordered, an excess of 1.4 to 1.88 additional lipase tests performed per patient, and 280,000 annual admissions for acute pancreatitis,³ we estimate that a total range of \$1,681,680 to \$2,258,256 is spent annually as direct costs for RLT in the United States.

Several studies have also shown an association of RLT with increased length of stay and additional cost of admission, even with some statistical adjustment for pancreatitis severity.^{1,13} These studies are limited due to their retrospective nature and may neglect to adjust for variables that may confound the relationship between RLT and reported outcomes. Nonetheless, RLT may add both direct and indirect costs and risks to hospital stays.

■ RISKS ASSOCIATED WITH REPEAT LIPASE TESTING

Although RLT has no diagnostic value, in certain situations when symptoms do not resolve by 1 week or if there is worsening abdominal pain beyond 1 week, RLT may help diagnose complications such as blockage of the pancreatic duct, acute peripancreatic collections, or development of a pseudocyst or necrosis. While all of these complications could cause elevations in lipase, cross-sectional imaging has a higher sensitivity than serum lipase levels for diagnosing locoregional complications of acute pancreatitis.¹⁵

Serum lipase testing should not be performed in the absence of clinical concern for complications, and if symptoms are concerning for such sequelae, imaging should be performed regardless of the serum lipase result.

Serial testing without regard to clinical status can lead to biased interpretation and unnecessary or even harmful downstream interventions. For example, when a patient who is otherwise clinically improving and has a lipase that is abnormal or at a higher level than at admission, this can create a situation where the clinicians caring for the patient incorrectly conclude that the patient is not improving, and such a conclusion can potentially prompt additional investigation.

Conversely, a patient with a normal lipase level or a level lower than at admission on serial testing who is clinically not showing signs of improvement is at risk for the incorrect conclusion that pancreatitis is getting better, and these interpretations may delay additional workup that the patient may actually need.

Overall, overutilization of RLT to monitor the disease course is common in nonselected groups of patients admitted with acute pancreatitis. It poses monetary and nonmonetary costs to the health system,¹⁴ affords no mortality benefit, does not aid in prognostication, leads to unnecessary increased length of stay for patients in many cases, can potentially lead

to inaccurate interpretation of clinical status, and can potentially delay care in patients who otherwise show signs of unresolving pancreatitis.

■ TAKE-HOME MESSAGES

The evidence to support serum lipase testing beyond the initial diagnostic workup in patients presenting with suspicion of acute pancreatitis is weak, and the results of serial testing may be misleading and lead to adverse effects on patient care and increases in healthcare spending. Lipase testing should be ordered in the initial diagnostic workup, but serial or follow-up testing should be reserved for the rare instances where there is concern for pancreatic duct blockage, pseudocyst formation, or lack of clinical improvement after 1 week, and should be done in conjunction with repeat cross-sectional imaging, which is of higher diagnostic yield.

Routine serial testing of serum lipase in patients who are admitted to the hospital with acute pancreatitis contributes to increased monetary and nonmonetary costs to the health system and should be avoided. ■

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

■ REFERENCES

- Mandalia A, Wamsteker EJ, DiMaggio MJ. Recent advances in understanding and managing acute pancreatitis. *F1000Res* 2018; 7:F1000 Faculty Rev-959. doi:10.12688/f1000research.14244.2
- Brown A, Young B, Morton J, Behrens K, Shaheen N. Are health related outcomes in acute pancreatitis improving? An analysis of national trends in the US from 1997 to 2003. *JOP* 2008; 9(4):408-414. pmid:18648131
- Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018 [published correction appears in *Gastroenterology* 2019; 156(6):1936]. *Gastroenterology* 2019; 156(1):254-272.e11. doi:10.1053/j.gastro.2018.08.063
- Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62(1):102-111. doi:10.1136/gutjnl-2012-302779
- Tietz NW, Shuey DF. Lipase in serum—the elusive enzyme: an overview. *Clin Chem* 1993; 39(5):746-756. pmid:8485865
- American Society for Clinical Pathology. Do not test for amylase in cases of suspected acute pancreatitis. Instead, test for lipase. <https://www.choosingwisely.org/clinician-lists/american-society-clinical-pathology-testing-for-amylase>. Accessed May 16, 2023.
- Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis [published correction appears in *Am J Gastroenterol* 2014; 109(2):302]. *Am J Gastroenterol* 2013; 108(9):1400-1416. doi:10.1038/ajg.2013.218
- Forsmark CE, Baillie J; AGA Institute Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. *Gastroenterology* 2007; 132(5): 2022-2044. doi:10.1053/j.gastro.2007.03.065
- Pathmarajah T, Idrees M, Nasim S, Weber DG. Serial lipase for pancreatitis: not enough evidence. *ANZ J Surg* 2018; 88(6):E491-E497. doi:10.1111/ans.14312
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13(10):818-829. pmid:3928249
- Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut* 2008; 57(12):1698-1703. doi:10.1136/gut.2008.152702
- Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974; 139(1):69-81.
- Datta SK, Inaganti A, Nguyen MT, Singh M, Affi A. 48: An overused lab test? Evaluating repeat lipase in the management of acute pancreatitis and its impact on patient outcomes. *Am J Gastroenterol* 2019; 114(1):S28. doi:10.14309/01.ajg.0000589724.85010.ef
- Ritter JP, Ghirimoldi FM, Manuel LSM, et al. Cost of unnecessary amylase and lipase testing at multiple academic health systems. *Am J Clin Pathol* 2020; 153(3):346-352. doi:10.1093/ajcp/aqz170
- Jasdanwala S, Babyatsky M. A critical evaluation of serum lipase and amylase as diagnostic tests for acute pancreatitis. *Integr Mol Med* 2015; 2(3):189-195. doi:10.14309/01.ajg.0000589724.85010.ef

Address: Samantha Magier, MD, MEng, Chief Resident for Quality and Safety, Yale School of Medicine, 330 Cedar Street, New Haven, CT 06510; Samantha.Magier@yale.edu