

Routine Measurement of Pleural Fluid Amylase Is Not Indicated

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Background: The routine measurement of pleural fluid amylase is frequently recommended, but the cost-effectiveness of this procedure is unknown.

Methods: To assess the utility of routine measurement of pleural fluid amylase in evaluating pleural effusions, we measured amylase, glucose, lactate dehydrogenase, and protein levels and blood cell counts in 379 patients undergoing thoracentesis during a 22-month period from 1997 to 1999. Of these, 199 had effusions after cardiac surgery; 61, malignant; 48, transudative; 28, parapneumonic; 2, chylous; 2, rheumatoid; 1, tuberculous; and 1, from chronic pleuritis. There were 37 exudates of unknown origin.

Results: Measurement of pleural fluid amylase levels did not assist in determining the origin of the effusion

in any of the patients. Amylase levels greater than 100 U/L (normal serum level in our laboratory is 30-110 U/L) were found in 5 (1.3%) of 379 patients: 1 patient with congestive heart failure (amylase, 173 U/L), 2 with post-cardiac surgery effusions (144 U/L and 130 U/L), 1 with pneumonia (109 U/L), and 1 with lung cancer (105 U/L).

Conclusions: The routine measurement of pleural fluid amylase levels is neither clinically indicated nor cost-effective. We suggest that pleural fluid serum amylase levels be measured only if there is a pretest suspicion of acute pancreatitis, chronic pancreatic disease, or esophageal rupture.

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WHEN a patient is diagnosed with a pleural effusion, a timely and systematic evaluation is indicated. A transudative effusion has only a few likely causes. An exudative effusion, however, has an extensive differential diagnosis. There are many useful tests that have been recommended as part of the routine evaluation of exudative effusion, including determining the level of amylase in the pleural fluid.¹⁻⁵ Although an elevated pleural fluid amylase level has been reported in many diseases,^{2,6-10} it is purported to be especially useful in establishing a diagnosis of malignancy, pancreatitis, or esophageal rupture.^{1-3,6}

The purpose of this study was to assess the utility of pleural fluid amylase measurement in the evaluation of pleural effusions. We hypothesized that routine measurement of pleural fluid amylase levels would rarely provide diagnostically useful information.

RESULTS

Of the 379 patients who had pleural fluid amylase levels measured, 199 had effusions after cardiac surgery; 61, malignant; 48, transudative due to congestive heart failure or cirrhosis; 28, parapneumonic; 2, chylous; 2, rheumatoid; 1, tuberculous; and 1, secondary to chronic pleuritis (Table 1). There were 37 exudates of unknown origin. No patient had clinical pancreatitis.

Determining the pleural fluid amylase levels did not assist in making the diagnosis in any of the patients. Of the 379 patients we studied, amylase levels greater than 100 U/L (normal serum level at our hospital, 30-110 U/L) were found in only 5 patients (Table 2). None of these 5 patients had a simultaneous serum amylase level measured. The highest pleural fluid amylase level occurred in patient 1, who was admitted with an acute myocardial infarction. He had a bilateral (right greater than left) transudative effusion, with an amylase level of 173 U/L on the left side

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PATIENTS AND METHODS

PATIENT SELECTION

All patients undergoing thoracentesis in the Interventional Radiology Department at St Thomas Hospital during the 22-month period from August 1997 through May 1999 were eligible for inclusion. We enrolled 416 patients, and amylase levels were measured in pleural fluid samples from 379 patients. Amylase levels were not measured in samples from 37 patients because of various technical reasons and these patients were disqualified from the study. There were no significant differences in the diagnoses of the disqualified patients compared with those in whom pleural fluid amylase levels were measured (**Table 1**). This study was approved by the institutional review board of St Thomas Hospital; all patients gave written informed consent.

PLEURAL FLUID ANALYSIS

At the time of thoracentesis, fluid was collected in a tube with EDTA anticoagulant for white blood cell count and differential, and in a tube with no additives for amylase, glucose, protein, and lactate dehydrogenase analysis. The total white and red blood cell counts were obtained manually by microscopy. The amylase, glucose, protein, and lactate dehydrogenase measurements were made using an automated analyzer (Vitros model 950; Johnson & Johnson; Rochester, NY). These studies were performed according to protocol for all effusions for which consent was obtained, regardless of whether the clinician formally ordered them. Results were provided and patients were billed only for those studies actually ordered by the clinician. The normal range for serum amylase levels in our laboratory is 30 to 110 U/L. Standard definitions were used for identifying the cause of the pleural effusion.¹

COST ANALYSIS

The clinical laboratories of the 4 largest hospitals in Nashville, Tenn (where this study was conducted), were surveyed by telephone to obtain the charge to the patient for measuring pleural fluid amylase levels for both inpatients and outpatients.

STATISTICAL ANALYSIS

All values are given as mean \pm SD unless otherwise noted.

and 53 U/L on the right side. This effusion resolved with simple diuresis and did not recur. Patient 2 had a loculated hemothorax with an amylase level of 144 U/L that was drained 3 days after coronary artery bypass graft (CABG) surgery. Although this effusion was initially thought to have resolved, he was readmitted 3 months later with dyspnea, recurrent effusion, and weight loss. His symptoms improved after an additional thoracente-

Table 1. Diagnoses of Pleural Effusion of the Patients Enrolled in the Study

Source/Type	Patients, No. (%)	
	Amylase Measured	Amylase Not Measured
After cardiac surgery	199 (52.5)	13 (35.1)
Malignant	61 (16.1)	5 (13.5)
Congestive heart failure	45 (11.9)	6 (16.2)
Parapneumonia	28 (7.4)	6 (16.2)
Cirrhosis	3 (0.8)	0
Chylothorax	2 (0.5)	0
Rheumatoid	2 (0.5)	0
Tuberculous	1 (0.3)	0
Chronic pleuritis	1 (0.3)	0
Unknown	37 (9.8)	7 (18.9)
Total	379 (100.0)	37 (100.0)

sis was performed. The fluid from this second thoracentesis was a lymphocytic transudate with an amylase level of less than 30 U/L. This patient underwent an extensive evaluation for his weight loss, including computed tomographic scanning, bronchoscopy, and thoracoscopy, with normal findings on pleural and lung biopsy, and negative results of flow cytometry of the pleural fluid. The final diagnosis was severe ischemic cardiomyopathy and cardiac cachexia. Patient 3 had a large-volume bloody effusion 6 days following CABG surgery that had an amylase level of 130 U/L. His effusion completely resolved with thoracentesis and did not recur. Patient 4 had a parapneumonic effusion with a borderline elevation of the pleural fluid amylase level (109 U/L). No causative organism was found, and the effusion resolved with antibiotics and a single thoracentesis. Patient 5 had a recurrent large-volume malignant effusion with an amylase level of 105 U/L. She had been receiving palliative chemotherapy for adenocarcinoma of the lung previously diagnosed by bronchoscopy, and had undergone multiple thoracenteses for symptomatic relief.

There were 17 patients who underwent bilateral thoracenteses and 26 patients who had repeated thoracenteses. None of the repeated measurements of serum amylase levels was significantly elevated when the initial level was normal.

A survey of the 4 largest hospitals in Nashville revealed that the average laboratory charge for amylase measurement in pleural fluid was \$36.01 for an outpatient (range, \$21.40-\$50.00) and \$58.76 for an inpatient (range, \$53.95-\$63.00). The total charges for these 379 procedures at our hospital would have been between \$8110.60 and \$20447.05, respectively, and would have ranged from \$13647.79 to \$22270.04 in our community.

COMMENT

In this study of 379 patients with pleural effusions of varying causes, the measurement of pleural fluid amylase was not clinically useful in any patient. Furthermore, the cost of performing all these amylase determinations was substantial. The results of this study suggest that the com-

Table 2. Patients With High Amylase Levels and Pleural Effusions*

Patient No./ Sex/Age, y	Cause	Volume, mL	Side	Amylase, U/L	Protein, g/L	LDH, U/L	Glucose, mmol/L (mg/dL)	RBCs, ×10 ⁹ /L	WBCs, ×10 ⁹ /L	Appearance
1/M/78	Acute MI	150	L	173	28	348	7.3 (131)	0.055	0.300	Straw colored
2/M/76	Post CABG	260	L	144	80	18 065	5.1 (91)	3200	0.048	Bloody
3/M/74	Post CABG	950	L	130	22	1407	4.6 (82)	288.75	1.500	Bloody
4/F/62	Pneumonia	300	L	109	37	381	6.0 (109)	0.985	3.42	Clear yellow
5/F/57	Lung cancer	1200	R	105	41	479	6.0 (108)	

*LDH indicates lactate dehydrogenase; RBCs, red blood cells; WBCs, white blood cells; MI, myocardial infarction; and CABG, coronary artery bypass grafting. Ellipses indicate test not performed.

Table 3. Summary of Reported Series of High Amylase Pleural Effusions With High Amylase Levels*

	No. of Patients								Total
	Present Study	Light and Ball ⁶	Joseph et al ²	Villena et al ⁸	Buckler and Honeybourne ⁹	Foresti et al ¹⁰	Ende ⁷		
Amylase determinations	379	176	200	380	110	163	29		1437
Effusions with high amylase levels	5	10	25	24	11	9	5		89
Malignant	1	4	13	12	8	9	4		51
Pancreatitis	0	4	4	2	1	0	1		12
Parapneumonic	1	2	5	1	1	0	0		10
Tuberculous	0	0	1	5	0	0	0		6
Cirrhosis	0	0	1	1	0	0	0		2
Esophageal rupture	0	0	0	0	1	0	0		1
Other	3	0	1	3	0	0	0		7
Total malignant effusions, No.	61	50	NR	126	63	77	11		>388

*NR indicates not reported.

mon recommendation¹⁻⁵ that amylase levels be measured routinely in exudative pleural effusion should be reconsidered.

DIFFERENTIAL DIAGNOSIS

Elevated levels of pleural fluid amylase are commonly associated with a diagnosis of pancreatitis, pulmonary malignancy, or esophageal rupture, but have been reported in numerous other diseases.^{2,6-10} **Table 3** summarizes the 7 largest reported series of pleural effusion in which amylase serum levels were measured. Of the 1437 total effusions evaluated, only 89 (6.2%) had elevated amylase levels. The most common causes in these series include malignancy (pulmonary or extrapulmonary) (57.3%), pancreatitis (13.5%), pneumonia (11.2%), tuberculosis (6.7%), cirrhosis (2.2%), and esophageal rupture (1.1%).

ISOENZYMES

There are at least 2 isoenzymes of amylase that separate with electrophoresis. Pancreatic-type amylase originates in the pancreas, and its elevation in serum or in other body fluids is specific for pancreatic inflammation.^{2,11,12} Salivary-type amylase is produced in the salivary glands, lungs, and fallopian tubes and may be secreted ectopically by a variety of tumors.¹²⁻¹⁷ In a prospective study of 200 patients with pleural effusions,

Joseph et al² performed isoenzyme analysis on 18 of 25 amylase-rich effusions, confirming previous case reports that malignant, infectious, and other nonpancreatic effusions have primarily salivary-type amylase.^{2,11,15-18} Case reports and animal experiments have demonstrated consistently that pleural effusions from esophageal ruptures contain high levels of salivary-type amylase,^{1,19} presumably from the passage of amylase-rich saliva through the tear and into the pleural space.

PANCREATITIS

In approximately 10% of patients with pancreatitis, a chest radiograph will show a pleural effusion,²⁰ and in as many as 50%, computed tomography of the chest and abdomen will show a pleural effusion.²¹ The pleural fluid amylase level is often greater than the serum amylase level.^{2,4,6,20} When a pleural effusion complicates pancreatitis, regardless of its size or location, it is a poor prognostic indicator and is associated with increased mortality and increased frequency of pancreatic pseudocysts.²¹ Anatomically, the tail of the pancreas approaches the left hemidiaphragm; when there is pancreatic inflammation, there can be local movement of fluid across the diaphragm. Cases of amylase-rich pleural effusion in patients with clinical pancreatitis but normal levels of serum amylase have been reported,^{4,22} but it is unusual to make this diagnosis on the basis of pleural fluid analysis alone.

Occasionally a pancreatic pseudocyst will decompress into the mediastinum or into the pleural space, with relief of abdominal pain, but often with the onset of pulmonary symptoms or symptoms of chronic illness.^{1,23} When this occurs, the patient will frequently have an invasive evaluation for an occult malignancy. Under these circumstances, demonstrating a markedly elevated pancreatic isoamylase level in the pleural fluid can help establish the diagnosis.^{1,3,4,23}

ESOPHAGEAL RUPTURE

Any patient with a pleural effusion who appears acutely ill should have esophageal rupture included in the differential diagnosis.¹ It is imperative that this diagnosis be made as quickly as possible, given the rapidly progressive nature of esophageal ruptures and their potential for surgical treatment if discovered early. Symptoms include severe chest pain, dyspnea, and, occasionally, hematemesis, and they usually occur after vomiting or an invasive esophageal procedure. Low pH, the presence of particulate matter, and an elevated level of salivary amylase in the pleural fluid of a patient with this constellation of symptoms constitute good evidence of esophageal rupture.^{1,19,23}

MALIGNANCY

Amylase-rich malignant effusions are not necessarily related to pancreatic tumors. These effusions can occur with primary or metastatic lung cancer (often adenocarcinoma) as well as other nonpancreatic tumors. In Table 3, there are data for 388 patients with cancer and malignant effusions; of these, 38 (9.8%) had an increased amylase level. Previous reports have demonstrated that approximately 50% of patients with amylase-rich malignant effusions will also have an increased serum amylase level.¹ When malignant effusions have elevated amylase levels the amylase is usually of the salivary type^{2,11-13,15-17} and is produced ectopically by the tumor cells.¹²⁻¹⁶ It is also possible for amylase to accumulate in the pleural space due to tumor obstruction of the pleural lymphatics.²

Malignancy is often unsuspected at the time of thoracentesis, and it has been suggested that elevated pleural fluid amylase levels (especially of the salivary type) in the absence of pancreatic disease or esophageal rupture should prompt a search for occult malignancy.^{1,2,11} However, since only about 10% of patients with malignancy have an elevated pleural fluid amylase level, this is certainly an inefficient means to screen for this disease

AFTER CABG

Elevated pleural fluid amylase levels have been reported in association with postoperative cardiac surgery.¹⁸ In our series, 2 patients had an elevated pleural fluid amylase level following CABG. In 1988, Kazmierczak et al¹⁸ reported that the serum amylase levels were elevated in 49.5% of 101 patients following cardiac surgery and the amylase was usually of the salivary type. They showed a significant correlation between postoperative hyperamylasemia and the size of the pleural effusions and hypoth-

esized that saliva, with its high amylase level, was aspirated during anesthesia and subsequently absorbed systemically. They did not measure pleural fluid amylase levels. The present study documents that the vast majority of effusions after CABG do not have a high amylase level.

ROUTINE MEASUREMENT

Several authors recommend routinely measuring pleural fluid amylase levels in all exudative effusions.¹⁻⁵ This study suggests problems with this diagnostic approach. Elevated pleural fluid amylase levels are most common in, and therefore most potentially helpful with, the diagnosis of pancreatitis, esophageal rupture, and malignant disease. The history, physical examination, and serologic studies associated with acute pancreatitis usually suggest this diagnosis without further confirmatory studies. Pleural effusion complicating chronic pancreatitis can be more difficult to identify, however, and the finding of elevated pancreatic amylase level in this fluid can therefore be helpful. This test lacks the sensitivity to serve as a screening study for malignancy. Therefore, apart from a pretest suspicion of pancreatic disease or esophageal rupture, it is difficult to justify the routine measurement of pleural fluid amylase levels.

LIMITATIONS OF THE STUDY

The current study is limited by several factors. The prevalence of amylase-rich effusion is lower than in previous series, which may reflect either a selection bias because our population had a disproportionate number of post-CABG pleural effusions, or some systematic error in measurement of amylase levels. We did not routinely measure serum amylase levels to determine pleural fluid to serum amylase ratios, nor did we determine amylase isoenzymes levels in the samples with elevated levels.

In conclusion, the present study, along with the previous studies on the measurement of pleural fluid amylase levels, suggests that the routine measurement of pleural fluid amylase levels is not indicated. Certainly, a pleural fluid amylase level should be obtained for patients with pleural effusions who are suspected of having esophageal rupture, because an elevated pleural fluid amylase level is a sensitive test for this diagnosis. In like manner, patients with chronic pleural effusions with high lactate dehydrogenase levels or who appear to have a malignancy but who have negative pleural fluid cytologic findings should have their pleural fluid amylase level measured to rule out a chronic pancreatic pleural effusion before an invasive diagnostic procedure such as thoracoscopy is undertaken.

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