Point-of-care Urine Trypsinogen Testing for the Diagnosis of Pancreatitis

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Abstract

Objectives: To assess a point-of-care (POC) urine trypsinogen (UT) test for the diagnosis of pancreatitis in the emergency department (ED).

Methods: This was a prospective cohort study of a convenience sample of patients presenting to the ED with abdominal pain or symptoms suggestive of pancreatitis. A 3-minute POC UT test (Actim Pancreatitis; Medix Biochemica, Kauniainen, Finland) was compared with plasma lipase and amylase measurements, imaging results when performed, and final discharge diagnoses. The criterion standard was a final discharge diagnosis of acute pancreatitis.

Results: Of 191 patients included in this study, 17 patients were diagnosed with either acute or acute-on-chronic pancreatitis. The sensitivity and specificity of UT for acute pancreatitis were, respectively, 100% (95% confidence interval [CI] = 77% to 100%) and 96% (95% CI = 92% to 98%). Seven of the 17 patients with pancreatitis (41%) had diagnostic findings on CT and positive UT tests but had nondiagnostic plasma lipase and amylase levels.

Conclusions: A POC UT screening test for pancreatitis in the ED compared favorably with plasma lipase and amylase levels. Future studies should be performed to explore whether this test in the ED setting has better clinical utility than plasma lipase or amylase.

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Acute pancreatitis is diagnosed in 1% to 8% of patients presenting to the emergency department (ED) with abdominal pain, depending on age and other underlying factors.[1] Among seniors, it is ranked in the top five or six most likely causes of abdominal pain.[2,3] Although most patients with pancreatitis have mild disease that resolves spontaneously, 20% present with severe necrotizing disease, which is associated with increased morbidity and mortality.[1] Unfortunately, clinical signs such as epigastric pain are nonspecific and can be absent in up to 10% of patients with pancreatitis.[4] Many patients with severe disease may not be diagnosed until autopsy.[5]

Accurate diagnosis of pancreatitis in the ED is essential, because early therapy may improve outcome.[6] However, an accepted criterion standard for the diagnosis of pancreatitis other than direct visualization does not exist. Although plasma amylase and lipase historically have been used for the diagnosis of pancreatitis,[1,7] they may be normal in up to 20% of cases,[1,4,6] and although lipase may be a more accurate measure of pancreatitis,[8] neither is considered a definitive test for pancreatitis.[9] Contrast-enhanced abdominal computed tomography (CT) is considered the most accurate noninvasive test for pancreatitis[6,10] but is expensive, not universally available, contraindicated in those with allergies to contrast agents, and carries the risk of ionizing radiation and contrast-induced nephropathy.

Recently, a qualitative, 3-minute point-of-care (POC) test to detect trypsinogen-2 in urine was introduced in Finland to screen patients with abdominal pain for pancreatitis and was shown to be accurate.[6,11] The purpose of this study was to assess the accuracy of the Actim Pancreatitis urine trypsinogen (UT) POC test (Medix Biochemica, Kauniainen, Finland) in the diagnosis of pancreatitis in a non-Finnish ED population.

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METHODS

Study Design

This was a prospective cohort study of a convenience sample of patients with symptoms consistent with acute

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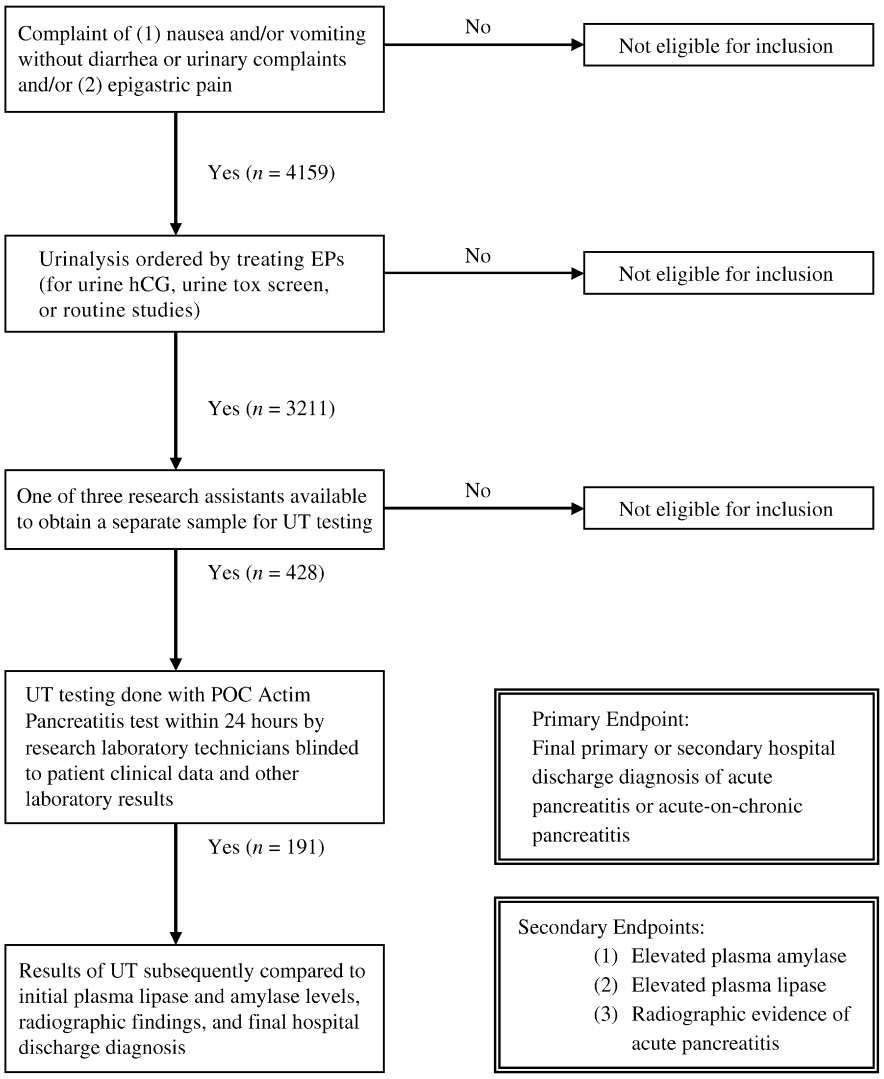

Figure 1. Flow diagram of study participants. EP = emergency physician; hCG = human chorionic gonadotropin; UT = urine trypsinogen; POC = point-of-care.

pancreatitis who had urinalysis ordered as part of their care. This study was approved by our institutional review board for enrollment with a waiver of informed consent because UT samples were obtained from existing urine specimens that were ordered for urine human chorionic gonadotropin, urinalysis, or urine-toxicology testing.

Study Setting and Population

The study was conducted from July 2002 to December 2002 in an urban, academic ED in the Midwest with a postgraduate year 1–4 emergency-medicine residency program and an annual census of 75,000.

Results of a UT POC test were obtained by one of two research laboratory technicians who were blinded to all patient clinical data and other laboratory results. The UT results were compared, by using a predesigned data sheet, with initial plasma amylase and lipase levels, with ultrasound and CT results when available, and with final hospital discharge diagnosis.

In a prior quality-assurance project in our ED, approximately 10% of patients with upper abdominal pain were found to have pancreatitis. Thus, with a presumed sensitivity of approximately 70% for amylase or lipase,[1,7–9] compared with approximately 90% for UT,[1,6,9,12,13] we estimated that an enrollment of 200 patients would give us 20 true positives (patients with actual pancreatitis) and a power of 0.80 for detecting a difference between amylase and lipase and UT.

All patients with symptoms consistent with the diagnosis of pancreatitis as identified by nursing triage and who underwent urinalysis testing that was ordered by their treating clinicians (resident or attending physicians) were eligible for enrollment if at least one of three clinical research assistants was available to obtain another urine sample, separate from the preexisting urine specimen, for UT testing (Figure 1). Patients were considered to have possible acute pancreatitis if the triage nurse noted either 1) nausea or vomiting without diarrhea or urinary symptoms or 2) epigastric pain. Patients were excluded if they were anuric, presented with traumatic abdominal pain, or did not have routine urinalysis ordered. Patients were not excluded for a prior history of pancreatitis.

Measurements

Urine samples were obtained by clinical research assistants and sent to a research laboratory where technicians tested the samples with the Actim Pancreatitis test strip (Medix Biochemica). The test strip is a qualitative, lateral-flow dipstick immunoassay in which the sample and blue latex–labeled anti–trypsinogen 2 monoclonal antibodies migrate up the strip after being dipped into the patient's urine. A second anti–trypsinogen 2 monoclonal antibody is immobilized at a line on the dipstick if trypsinogen 2 is present, forming a blue line in the test zone for a positive result. Technicians reading the UT test were blinded to patient clinical data, the results of other laboratory tests, and patient diagnoses.

Lipase and amylase levels were measured with an enzymatic colorimetric assay by using a Hitachi Modulator System by Roche Diagnostics (Indianapolis, IN). The reference range for both lipase and amylase in our laboratory is 13–100 U/L. A value three times the upper limit of normal (≥300 U/L) was considered diagnostic for pancreatitis, consistent with the standard established elsewhere.[14]

Abdominal CTs and ultrasonography were ordered by clinicians who were blinded to UT results but not to other laboratory or clinical data, and tests were interpreted by board-certified radiologists. Abdominal CTs were performed by using oral and intravenous contrast.

The primary endpoint was the final hospital discharge diagnosis of acute or acute-on-chronic pancreatitis made by physicians who were blinded to the UT results but not to radiographic or other laboratory data. This most often was based on imaging studies (ultrasound or contrast-enhanced CT as read by board-certified radiologists) and on a consistent clinical course (n = 15 [88%] of 17 patients with acute pancreatitis). If imaging was not performed, the primary endpoint of a final hospital discharge diagnosis of pancreatitis had to be supported by plasma lipase or amylase levels of ≥300 U/L and by a consistent clinical course (n = 2 [12%] of 17 patients with pancreatitis).

Data Analysis

Data were kept on an Excel 97 spreadsheet (Microsoft, Redmond, WA), and analysis was performed by using StatView (SAS Institute, Cary, NC) and VassarStats (Richard Lowry, http://faculty.vassar.edu/lowry/vshome.html) to determine sensitivity and specificity with 95% confidence intervals (CIs) rather than with p-values, because CIs allow clinicians to assess both statistical significance and clinical effect.[15]

RESULTS

Four thousand one hundred fifty-nine patients presented with clinical symptoms, and 3,211 had urinalysis. Of those, 428 patients had urinalysis ordered by treating emergency physicians when one of three research assistants was available to obtain a sample separate from the original sample for UT testing. However, 103 patients had their urine samples sent to the main laboratory before research assistants were able to secure a separate sample for UT testing. Of the remaining 325 patients, 134 samples were not run within 24 hours of collection because technicians in the research laboratory were not available. Thus, 191 patients were enrolled in this study and included for analysis (Figure 1).

There were 126 African American (66.0%) and 63 white (33.0%) patients. Seventeen patients were diagnosed with either acute or acute-on-chronic pancreatitis, and all had positive UT tests (Table 1). Seven patients with positive UT tests were not diagnosed with pancreatitis on discharge and thus were considered false positives. The sensitivity and specificity of UT for acute pancreatitis were, respectively, 100% (95% CI = 77% to 100%) and 96% (95% CI = 92% to 98%), compared with 53% (95% CI = 29% to 76%) and 99% (95% CI = 96% to 100%) for

Table 1
Laboratory and Radiographic Findings of Patients Diagnosed with Pancreatitis

Patient*	Medical History	Lipase†	Amylase†	Radiographic Study (Result)
1	Alcoholism	826	425	CT (peripancreatic stranding and fluid with edema)
2	Hypertriglyceridemia	177	54	US (enlarged pancreas with peripancreatic fluid)
3	Alcoholism	210	165	US (enlarged, calcified pancreas)
4	PUD and alcoholism	116	161	CT (pancreatic pseudocyst with stranding and fluid)
5	Hypertriglyceridemia	800	275	CT (peripancreatic stranding and fluid)
6	Alcoholism	57	49	CT (necrosis of pancreas head, stranding, and edema)
7	Gall stones, alcoholism	760	471	US (peripancreatic fluid)
8	None	920	443	None
9	Chronic pancreatitis	55	46	CT (peripancreatic stranding and fluid)
10	Alcoholism	487	313	US (peripancreatic fluid)
11	None	4,860	1,640	CT (peripancreatic stranding and fluid with edema)
12	Alcoholism	645	1,430	US (enlarged, calcified pancreas)
13	Alcoholism	29	56	CT (peripancreatic stranding with edema)
14	Alcoholism	660	203	None
15	1 mo postpartum	5,530	2,230	CT (peripancreatic stranding)
16	Hypertriglyceridemia	149	56	CT (peripancreatic stranding and fluid)
17	Prior pancreatitis	72	37	CT (enlarged pancreas with peripancreatic fluid)

PUD = peptic ulcer disease; CT = computed tomography; US = ultrasound.
* All had positive urine trypsinogen.
† U/L; normal range is 13–100 U/L.

Table 2
Test Characteristics of UT, Plasma Lipase, and Plasma Amylase for the Final Hospital Diagnosis of Pancreatitis

Characteristic	UT (95% CI)	Plasma Lipase (95% CI)	Plasma Amylase (95% CI)
Sensitivity (%)	100 (77.1, 100)	53 (28.5, 76.1)	41 (19.4, 66.5)
Specificity (%)	96 (91.6, 98.2)	99 (96.1, 100)	95 (89.3, 98.3)
LR+	2.43 (1.51, 3.91)	9 (4.7, 17.3)	1.4 (0.67, 2.94)
LR−	0	0.05 (0.023, 0.10)	0.09 (0.052, 0.17)

UT = urine trypsinogen.
Likelihood ratios (LRs) weighted for prevalence.

plasma lipase and with 41% (95% CI = 19% to 67%) and 95% (95% CI = 89% to 98%) for plasma amylase (Table 2).

The diagnoses of those with a negative UT are shown in Table 3, and the false positives are shown in Table 4. Seven of the 17 patients with pancreatitis (41%) had diagnostic radiographic findings and positive UT tests but had plasma amylase and lipase levels of <300 U/L. Chart review for patients with clinical diagnoses without radiographic imaging (Table 3; peptic ulcer disease or gastritis, nonspecific abdominal pain, urinary tract infection, and atypical chest pain) did not reveal any new cases of pancreatitis after six months.

DISCUSSION

The test characteristics of the Actim Pancreatitis test for acute pancreatitis in our sample were comparable to those found previously in a Finnish population.[6,11] The test was accurate in our sample (sensitivity, 100% [95% CI = 77.1% to 100%]; specificity, 96% [95% CI = 91.6% to 98.2%]), with a better negative likelihood ratio than either plasma amylase or plasma lipase (Table 2), consistent with prior work,[16] suggesting that the Actim Pancreatitis UT test may be useful as an ED screening test for pancreatitis.

The sensitivity in our study differs from that of more recent studies among non-Scandinavian patients, but this may be explained by the time course of testing. Saez et al. found UT to be comparable to amylase and lipase, with a sensitivity of 68%, but performed UT within 48 hours of symptom onset.[12] Likewise, Chen et al. also showed that UT was comparable to amylase/lipase but performed immediate UT testing in patients who presented within 24 hours of symptom onset.[13] However, Hwang et al. found that delayed measurement of UT was associated with increased sensitivity for pancreatitis.[17] In our study, we did not control for the time of UT testing relative to the duration of symptoms and may have included a more heterogeneous population. This further suggests the utility of UT testing, given that patients with pancreatitis may not always present within 24 or 48 hours of symptom onset.

The seven false-positive UT results (Table 4) all occurred in patients requiring admission for life-threatening illness, consistent with results of a study published elsewhere.[9] Two of these false positives (patients 1 and 2) occurred in patients who could reasonably have been diagnosed with pancreatitis as a secondary diagnosis and who thus may not have been true false positives. Four occurred in patients with acute renal failure (Table 4; patients 3, 4, 5, and 7), which may be explained by the decreased excretion of trypsinogen in renal failure and should be explored further.

It is noteworthy that six patients with CT scans and one with ultrasound (US)-documented acute pancreatitis (41%) had nondiagnostic plasma lipase and amylase levels but tested positive on the UT test. This suggests that UT may have utility in identifying acute pancreatitis in patients with pancreatic insufficiency who would not be able to manifest elevated plasma lipase or amylase levels. This should be studied further. If shown to be accurate in a larger sample, UT may decrease the need for CT in evaluation of these patients.

Previous studies have evaluated UT in non–African American populations (from Finland and Asia). Our study evaluates the characteristics of this test in a more racially mixed population, including African Americans, but was not designed to study the effect of race. This should be considered in determining how the findings of this study may apply to other patient populations.

Table 3
Final Diagnoses of Patients Who Presented with Abdominal Pain with a Negative Urine Trypsinogen

Diagnosis	*n* (*N* = 174 total)	Follow-up Studies
Peptic ulcer disease or gastritis	40	10 patients had normal US; 11 patients had normal abdominal CT
Nonspecific abdominal pain	37	21 patients had normal abdominal CT
Cholelithiasis or cholecystitis	32	32/32 had US demonstrating biliary pathology without evidence of pancreatic pathology
UTI or pyelonephritis	24	8 patients had confirming abdominal CT showing pyelonephritis
Atypical chest pain	14	
Small-bowel obstruction	13	13/13 had CT showing small-bowel obstruction with a normal pancreas
Gastroenteritis	9	9/9 without pancreatitis by 1-yr computer chart review
Appendicitis	3	3/3 had CT showing appendicitis and correlating pathology
Cholangitis	2	2/2 with CT showing cholangitis but a normal pancreas

UTI = urinary tract infection, CT = computed tomography, US = ultrasound.

Table 4
Final Diagnoses, Laboratory, and Radiological Results of Patients with False-positive (FP) Urine Trypsinogen

FP Number	Laboratory and Radiographic Data	Final Diagnosis
1	Lipase 48,* CT: multiple intra-abdominal abscesses and peripancreatic fluid	Multiple abdominal abscesses
2	Lipase 416, amylase 120, CT: multiple masses consistent with metastatic small-cell cancer, including a mass in the head of the pancreas	Metastatic small-cell cancer
3	Lipase 28, amylase 68, CT: normal pancreas, West Nile CSF PCR positive	ARF caused by West Nile encephalitis and subsequent GI bleed
4	Lipase 44, amylase 114, Cr 5.8	HIV with ARF caused by dehydration
5	Lipase 23, amylase 51, calcium 14.6, Cr 3.7	Idiopathic hypercalcemia with ARF
6	Lipase 24, Cr 1.8, CT: esophageal tear	DKA and Mallory-Weiss tear
7	Lipase 51, calcium 10.9, Cr 3.4	Idiopathic hypercalcemia with ARF

CSF, cerebrospinal fluid; PCR, polymerase chain reaction; ARF, acute renal failure; GI, gastrointestinal; Cr, creatine; DKA, diabetic ketoacidosis.
* Normal range is 13 to 100 U/L; Cr and calcium are measured in mg/dL.

This study suggests that the 3-minute POC Actim Pancreatitis test compares favorably with plasma amylase and lipase values and may be useful as a screening test for pancreatitis in racially diverse patient populations. Future studies could assess the impact of UT testing on ED throughput and patient outcomes, possible cost benefits of UT testing in the ED, and its use in the pediatric and pregnant populations.

LIMITATIONS

This study had several limitations. First, it was a single-center study, and the small number of patients with pancreatitis resulted in wide confidence intervals, precluding demonstration of superiority of UT to plasma amylase or lipase values.

Second, there is no accepted criterion standard in the medical literature for the diagnosis of pancreatitis other than direct visualization. Thus, the primary criterion standard was the final hospital discharge diagnosis of pancreatitis, supported either by consistent radiographic findings on CT or US or by a plasma amylase or lipase result of $\geq$300 U/L, which is more rigorous than the standard used in clinical practice.[1,7,8] The use of amylase and lipase values to diagnose pancreatitis may have produced an incorporation bias that would have improved the apparent sensitivity and specificity of lipase and amylase for pancreatitis. However, this incorporation bias would not favorably have biased the results of the UT test, further suggesting the utility of UT for the diagnosis of pancreatitis. Likewise, abdominal radiography was not used in every case to exclude or confirm the diagnosis of pancreatitis, thus introducing the possibility of workup bias. Fifteen of the 17 patients with a final diagnosis of pancreatitis had confirmatory radiographic imaging, compared with 109 of 174 patients who had an alternative diagnosis for their abdominal pain. Although performing abdominal imaging on every patient would have avoided workup bias, that would not have reflected clinical practice[1,7,8] and might have raised ethical concerns, given the associated radiation exposure and contrast risks for patients whose ED management was not likely to change on the basis of the results of abdominal imaging (e.g., patients 8 and 14; Table 1).

Third, the UT tests actually were performed in a research laboratory rather than in the ED. Although the test is similar to urine pregnancy tests, it is possible that the results may have differed with testing at the POC in the ED. Several studies have shown that POC testing reduces length of stay in the ED,[18–20] but this was not assessed in this study, and it is unknown how UT would impact the length of stay for patients with pancreatitis.

Finally, although the urine samples were tested within 24 hours of collection, according to manufacturer guidelines, the manufacturer also recommends immediate testing for improved accuracy. It is unclear how this may have affected our results, however, because there were no false negatives in our sample.

CONCLUSIONS

The qualitative Actim Pancreatitis test to detect urinary trypsinogen-2 compares favorably to plasma amylase and lipase for the diagnosis of acute pancreatitis in an ED population of adults.

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