Received: 23 January 2025 | Accepted: 14 May 2025

DOI: 10.1002/jpn3.70119

JPGN

ORIGINAL ARTICLE

Pancreatology

The first pediatric study investigating the utility of a noninvasive urine-based test for acute pancreatitis diagnosis

Tamar Orgad[1] | **Isra Abu-Rahma**[1] | **David Rekhtman**[2] | **Saar Hashavya**[2] | **Peri Milman**[1] | **Mordechai Slae**[1] | **Zev Davidovics**[1] | **Michael Wilschanski**[1] | **Liron Birimberg-Schwartz**[1]

[1]Department of Pediatric Gastroenterology, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

[2]Department of Pediatric Emergency Medicine, Hadassah Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel

Correspondence

Liron Birimberg-Schwartz.
Email: lbschwartz@hadassah.org.il

Funding information

None

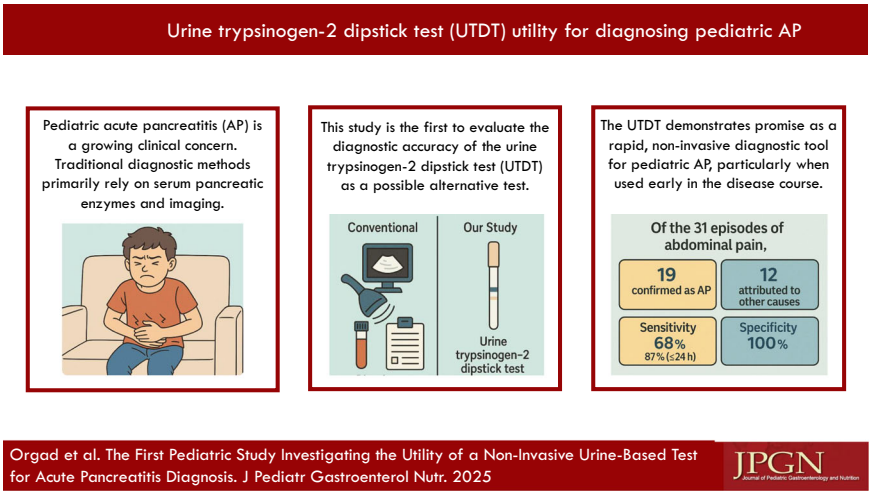
Abstract

Objectives: Pediatric acute pancreatitis (AP) is a growing clinical concern with a wide spectrum of severity, from mild episodes to life-threatening conditions. Traditional diagnostic methods primarily rely on serum amylase and lipase measurements, which are invasive and can be challenging in children. This study is the first to evaluate the diagnostic accuracy of the urine trypsinogen-2 dipstick test (UTDT) as a noninvasive test for diagnosing pediatric AP.

Methods: This prospective study included 28 pediatric patients (31 episodes) presenting with acute abdominal pain at a tertiary medical center from November 2022 to October 2024. AP was diagnosed based on the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) criteria. Urine samples were collected either within the first 24 hours (h) or later during hospitalization. UTDT sensitivity and specificity were calculated and compared to serum amylase and lipase levels.

Results: Of the 31 episodes, 19 (61%) were confirmed as AP, and 12 (39%) were attributed to other causes. The UTDT had an overall sensitivity of 68% and specificity of 100%. Sensitivity increased to 87% when urine samples were collected within 24 h of admission. In non-AP cases, UTDT consistently produced negative results, with the high specificity supporting its reliability in distinguishing AP from other conditions.

Conclusions: The UTDT demonstrates promise as a rapid, noninvasive diagnostic tool for pediatric AP, particularly when used early in the disease course. Its high specificity and ease of use suggest that it may serve as an alternative to invasive blood tests once validated through larger-scale studies. Further research is needed to confirm these findings and establish the role of UTDT in clinical practice.



KEYWORDS

diagnostic utility, pediatric acute pancreatitis, urine trypsinogen-2 dipstick test

1 | INTRODUCTION

Pediatric acute pancreatitis (AP) is a significant and increasingly recognized condition characterized by inflammation of the pancreas. The clinical spectrum of AP ranges from mild, self-limiting episodes to severe, life-threatening disease that can result in multiple organ dysfunction.[1,2] Although less common in children than in adults, the incidence of pediatric AP has risen steadily over the past two decades, making it an emerging concern in pediatric medicine.[3-6]

Classically, AP presents with severe upper abdominal pain radiating to the back, often accompanied by vomiting. However, its clinical presentation in children can sometimes be atypical, overlapping with other acute abdominal conditions, which can delay diagnosis. Timely assessment in the emergency setting, including measurement of serum amylase and lipase levels, is crucial for diagnosis.

According to the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE), the diagnosis of AP requires meeting at least two of three criteria: (i) abdominal pain consistent with AP, (ii) serum amylase or lipase levels at least three times the upper limit of normal, and (iii) imaging findings indicative of AP.[7] While this definition provides a practical framework for clinical diagnosis, it necessitates hospital-based evaluation and lacks a universally accepted biological marker as a "gold standard."

In recent years, efforts have been made to identify alternative diagnostic methods that eliminate the need for invasive blood tests. One such tool is the urine trypsinogen-2 dipstick test (UTDT), which has demonstrated good diagnostic accuracy for AP in adults.[8,9] However, its effectiveness and applicability in pediatric populations have yet to be evaluated.

This study aims to evaluate the diagnostic accuracy of the UTDT in pediatric AP by comparing its performance to standard serum amylase and lipase tests. By exploring the potential of UTDT as a rapid, noninvasive diagnostic tool, we seek to address an important gap in the diagnosis and management of pediatric AP.

What is Known?

- Pediatric acute pancreatitis (AP) incidence has increased significantly in recent decades.
- Diagnosis of pediatric AP is based on clinical presentation, elevated serum pancreatic enzymes, and imaging findings.
- The urinary trypsinogen-2 dipstick test (UTDT) has demonstrated high sensitivity and specificity for diagnosing AP in adults, but pediatric data are lacking.

What is New?

- UTDT is a sensitive and specific tool for diagnosing pediatric AP.
- Sensitivity improves significantly when performed early in the disease course.
- UTDT provides a noninvasive alternative to blood tests, reducing discomfort for children.
- The test enhances diagnostic accuracy by distinguishing AP from other causes of abdominal pain.

2 | METHODS

2.1 | Study design

This prospective study included 28 pediatric patients presenting with acute abdominal pain who were admitted to the pediatric emergency department (ED) at Hadassah University Medical Center between November 2022 and October 2024. Some patients presented to the ED on multiple occasions, resulting in a total of 31 reported cases.

2.2 | Ethics statement

Written informed consent was obtained from all participants or their legal guardians, and the study was approved by the institutional ethics committee (approval number HMO-0018-22).

2.3 | Inclusion criteria

Children aged 0–19 years admitted to the ED with complaints of pain in the upper or central abdomen or vomiting, without suspicion of acute gastroenteritis, were eligible for inclusion. The study also included children with a history of chronic pancreatitis or recurrent pancreatitis. Patients with a history of chronic abdominal pain or a primary complaint of diarrhea or constipation were excluded.

The diagnosis of AP was based on criteria defined by the INSPPIRE consortium, as outlined in the introduction.[7]

2.4 | Data collection

For each participant, data collected included demographic information, vital signs, and findings on physical exam. A detailed medical history was recorded, capturing information on underlying diseases, previous episodes of AP, and any history of chronic pancreatitis. Laboratory findings were documented, encompassing liver enzyme levels, kidney function tests, C-reactive protein (CRP), and pancreatic enzyme measurements, along with the results of imaging studies.

Serum amylase and lipase levels were obtained for all patients upon admission to the ED. For most patients, a second blood test was performed on the same day as urine collection. However, in some cases, urine samples were collected later during hospitalization due to technical limitations.

Imaging studies were performed as part of the diagnostic workup, with most patients undergoing abdominal ultrasound. Abdominal computed tomography (CT) scans were conducted when clinically necessary.

All collected data were anonymized and coded to ensure confidentiality.

2.5 | UTDT

Urine trypsinogen-2 levels were measured using the Actim® Pancreatitis urine test (Medix Biochemica). This immunochromatographic assay employs monoclonal anti-trypsinogen-2 antibodies, with a detection limit of 50 µg/L.

The test procedure involved immersing the strip in a urine sample for 20 seconds, removing it, and allowing it to rest at room temperature for 5 min. Results were interpreted based on the appearance of stripes: two blue stripes (a test stripe and a control stripe) indicated elevated trypsinogen-2 levels (> 50 µg/L), a single blue stripe (control stripe only) signified normal trypsinogen-2 levels, and the absence of both stripes rendered the test invalid, requiring repetition. The presence of the control stripe validated the reliability of the test. The test kits were provided as a gift to the research team by the manufacturer for the purposes of this study.

2.6 | Statistical analysis

The sensitivity and specificity of the diagnostic tests were calculated along with 95% confidence intervals using the MedCalc Software Ltd. Diagnostic Test Evaluation Calculator (Version 23.0.9; accessed December 1, 2024). The software is available online at https://www.medcalc.org/calc/diagnostic_test.php.

3 | RESULTS

3.1 | Patient demographics and study overview

A total of 28 patients, accounting for 31 episodes of acute abdominal pain, were included in this study. The median age of the participants was 12 years (range: 6 months to 19 years). Of the 31 episodes, 19 (61%) were diagnosed as AP, while 12 (39%) were attributed to non-AP-related abdominal pain.

Presenting symptoms and findings from physical examinations were collected and summarized for both AP and non-AP groups, as shown in Table 1. Notably, one case involved a 6-month-old infant with significant developmental delay, making it challenging to evaluate abdominal pain clinically.

TABLE 1 Patient clinical characteristics.

Variable	Acute pancreatitis patients ($n = 19$)	Non- Acute pancreatitis ($n = 12$)
Age (years), median	12	12.5
Sex, male, *n* (%)	6 (30%)	4 (33%)
Complaints, *n* (%)		
Abdominal pain	18 (95%)	12 (100%)
Nausea	11 (57%)	7 (58%)
Vomiting	12 (63%)	6 (50%)
Diarrhea	4 (21%)	4 (33%)
Pain radiating to the back	5 (26%)	5 (42%)
Physical examination findings, *n* (%)		
Diffuse abdominal tenderness	7 (37%)	7 (58%)
Epigastric tenderness	8 (42%)	8 (67%)
Signs of dehydration	2 (10%)	0 (0%)

3.2 | Non-AP diagnoses

Among the non-AP cases, 6 (19.3%) were classified as unexplained abdominal pain, 2 (6.4%) were due to gastroenteritis, and there was one case each (3.2%) of mesenteric lymphadenitis, cholangitis, *Clostridium difficile* infection, and parotitis.

3.3 | Etiologies of AP

The study also aimed to identify the underlying etiologies of the 16 patients (19 AP episodes) presenting to the ED during the study period. The distribution of etiologies for AP in this study is shown in Figure 1. Hereditary pancreatitis accounted for 25% of patients, with two patients identified as carrying mutations in the *Protease serine 1* (*PRSS1*) gene and 2 with mutations in the *Cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene. Biliary disease was observed in 12% of cases, including one patient with gallstones and another with a choledochal cyst. Congenital pancreatic malformations were identified in 6% of cases, represented by one patient with pancreatic divisum. Other etiologies included a patient with infection (6%) and two patients (13%) with complications from percutaneous endoscopic gastrostomy (PEG), leading to obstruction of the Ampulla of Vater. Similarly, recurrent pancreatitis episodes represented 13% of cases. In 25% of the cases, the underlying cause remained unknown.

3.4 | UTDT diagnostic performance

Among the 19 confirmed cases of AP, 13 (68%) tested positive using the Actim® Pancreatitis urine test. Urine samples were collected within the first 24 hours (h) of hospital presentation for eight of these patients, of whom seven (87%) had positive results. In contrast, for the remaining 11 children whose urine tests were collected after the first 24 h, only six (55%) tested positive. Conversely, all non-AP cases yielded negative results on the urine test. A detailed breakdown of true positives, false positives, true negatives, and false negatives is provided in Supplementary Information (Supporting Information S2: Tables S1–S3). Notably, for all non-AP cases, the urine test was conducted within the first 24 h of admission. The overall sensitivity and specificity of the urine test were 0.68 and 1.0, respectively. Sensitivity increased significantly to 0.87 when the test was performed within the first 24 h of admission (Table 2).

4 | DISCUSSION

This study is the first to evaluate the diagnostic utility of the UTDT for pediatric AP. Our findings demonstrate that the UTDT has both high sensitivity and specificity, particularly when performed early in the disease course, suggesting that it could be a valuable diagnostic tool for pediatric AP.

Trypsinogen, a proenzyme produced in the pancreas, is converted to its active form, trypsin, in the duodenum by intestinal enterokinase.[10] During pancreatic inflammation, both trypsinogen-1 (cationic) and trypsinogen-2 (anionic) are released into the bloodstream, with trypsinogen-2 typically reaching higher concentrations. These enzymes are subsequently filtered into the urine, making trypsinogen-2 a specific marker for pancreatic injury.[11,12] Unlike serum amylase or lipase, both of which can be elevated in non-pancreatic conditions (e.g., renal failure, gastrointestinal disorders), trypsinogen-2 is more specific to pancreatic injury.

The UTDT is an immunochromatographic rapid urine test that detects trypsinogen-2 in urine samples. Previous studies in adults have shown a strong correlation between quantitative measurements of urinary trypsinogen-2 and UTDT results, validating the accuracy of the test strip for detecting elevated trypsinogen-2 levels.[8,9] Studies in adults have demonstrated the high sensitivity and specificity of the UTDT for diagnosing AP.[9,11,13-18] Our study extends these findings to children, underscoring its potential role in pediatric practice.

Urine sampling offers significant advantages over blood tests in pediatric populations due to its non-invasive, painless, and convenient nature. Obtaining venous access in young children, particularly those

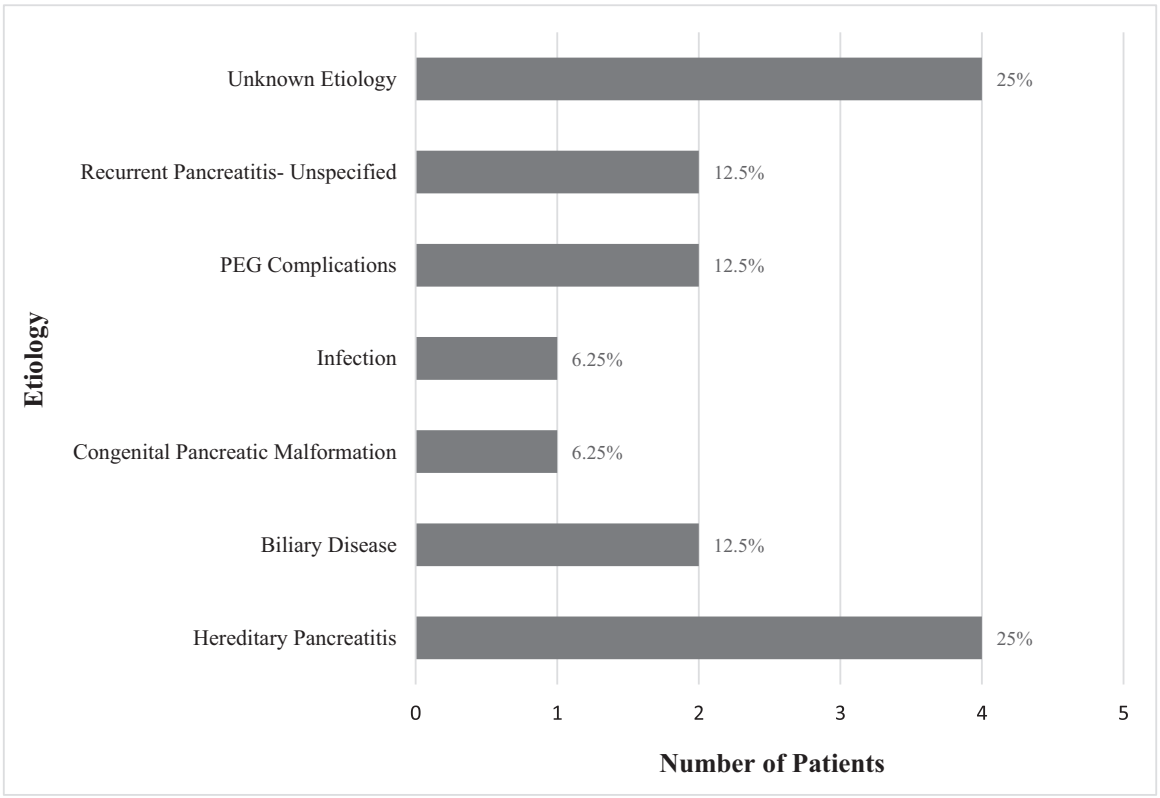


FIGURE 1 Etiology of AP episodes. Distribution of AP episodes (total of 16 patients with AP episodes) based on etiology, represented as the number and percentage of patients. AP, acute pancreatitis; PEG, percutaneous endoscopic gastrostomy.

TABLE 2 Diagnostic performance of the urine test for acute pancreatitis.

Metric	Value (%)	95% confidence interval
Sensitivity	68.42	43.45–87.42
Specificity	100.00	73.54–100.00
Positive predictive value	100.00	75.29–100.00
Negative predictive value	66.67	50.78–79.49
Sensitivity[a]	87.50	47.35–99.68
Sensitivity[b]	54.55	23.38–83.25

[a]Urine test taken during the first 24 h of admission.
[b]Urine test taken after more than 24 h of admission.

with recurrent illnesses, is often challenging, especially in emergency settings where rapid intervention is critical. The advantages of noninvasive testing are particularly valuable for children with acute recurrent pancreatitis, who frequently present to the ED with abdominal pain. There patients often require imaging and blood tests to confirm AP or rule out other serious conditions, such as pyelonephritis or appendicitis. A reliable, noninvasive diagnostic tool like the UTDT could significantly reduce the need for invasive procedures, expedite diagnosis, and potentially reduce unnecessary hospitalizations and healthcare costs. Moreover, families could perform the test at home, avoiding unnecessary ED visits for negative results while ensuring prompt medical intervention for patients with persistent symptoms.

In comparison to other existing diagnostic tools for pediatric AP, the UTDT offers unique advantages. While serum lipase and amylase are routinely used, their diagnostic accuracy is imperfect, and they may be elevated in nonpancreatic conditions such as renal failure or gastrointestinal disorders. Imaging, particularly abdominal ultrasound, is limited in sensitivity—detecting AP in only 30%–50% of pediatric cases[19] and, in our cohort, only 5 of 15 ultrasounds showed findings consistent with pancreatitis. CT imaging, though more sensitive, is associated with significant radiation exposure and was reserved for select cases in our study. Other urine-based tests, such as urinary amylase, have been evaluated in small pediatric case series,[20] and urine proteomic profiling shows promise in children,[21] but neither has sufficient evidence nor clinical feasibility for routine use. Given these limitations, the UTDT emerges as a particularly promising candidate for integration into current pediatric AP diagnostic pathways.

Our findings also indicate that the UTDT is most accurate when performed early in the course of the disease, particularly when urine samples are collected within the first 24 h of presentation. This is consistent with prior studies in adults that demonstrated higher sensitivity when the test was performed early.[22] Intravenous fluids may dilute urinary substrates,[23] potentially lowering trypsinogen concentrations and increasing false-negative results. Further research is needed to assess the impact of fluid administration specifically on urinary trypsinogen levels. Notably, in our study, all cases of non-AP cases yielded negative UTDT results, even when urine samples were collected within 24 h of admission. These findings highlight the test's specificity and the critical role of early sampling in optimizing its sensitivity.

A few cases in our study are unique and hence worth discussing. In one case, a female patient was admitted following trauma, presenting with abdominal pain and jaw pain. Physical examination revealed tenderness in the abdomen and at the angle of the jaw. Blood tests showed elevated amylase levels with normal lipase levels. Given the history of trauma and the elevated amylase, an abdominal computed tomography scan was performed, which revealed no evidence of pancreatic injury. The patient was ultimately diagnosed with a parotid gland injury. The UTDT was negative in this case, further supporting its specificity for pancreatic inflammation.

In two other cases from the non-AP group, patients presented with elevated amylase levels that did not meet the diagnostic threshold for AP (three times the upper limit of normal) and no significant lipase elevation. Imaging in these cases was negative for AP, and the UTDT also yielded negative results. This consistency highlights the test's correlation with diagnostic criteria for AP and its reliability in ruling out pancreatitis when those criteria are not met.

This study has several limitations. Despite being designed prospectively, a selection bias was evident, with a disproportionately high number of AP cases recruited compared to non-AP cases. This imbalance may reflect the heightened awareness of the study among ED medical teams when AP was suspected or confirmed. In contrast, more common causes of abdominal pain, which might not have raised the same level of diagnostic interest, were less likely to prompt study enrollment.

Additionally, obtaining informed consent for pediatric patients presented a significant challenge, particularly in the ED setting, where time-sensitive decisions and the stress of the situation may hinder parents or guardians from fully engaging in the consent process. As a result, we successfully collected data on 19 pediatric AP cases over a span of less than 2 years, which is a robust sample size for this condition. However, we lack the expected number of control patients. Practically, the sample size was limited by the availability of eligible patients. Consequently, the statistical power of the study may be limited, and the confidence intervals for sensitivity and specificity are relatively wide. Future research with a larger sample size is required for validating our results.

Another limitation of the study was the variability in the timing of urine test collection relative to the onset of symptoms. While this inconsistency posed a challenge in standardizing the data, it provided an opportunity to evaluate the effect of timing on the test's diagnostic performance.

5 | CONCLUSIONS

This prospective study provides preliminary evidence that the UTDT is a promising noninvasive diagnostic tool for early detection and exclusion of pediatric AP. Its practical advantages, including ease of use, high specificity, and improved sensitivity particularly when performed early, make it a valuable addition to current diagnostic strategies. However, further large-scale studies are required to validate these findings and explore the broader clinical applications of the UTDT in pediatric AP management. Upon validation, the use of the UTDT may be expanded, potentially enhancing diagnostic accuracy and streamlining clinical decision-making in pediatric AP.

ACKNOWLEDGMENTS

The authors acknowledge the use of the Artificial Intelligence Generated Content (AIGC) tool ChatGPT to assist in creating the images used in the visual highlights. The urine trypsinogen-2 dipstick test kits were generously supplied by Medix Biochemica (Kauniainen, Finland).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Liron Birimberg-Schwartz https://orcid.org/0000-0001-9014-3686

REFERENCES

1. Szatmary P, Grammatikopoulos T, Cai W, et al. Acute pancreatitis: diagnosis and treatment. *Drugs*. 2022;82(12):1251-1276.
2. Abu-El-Haija M, Kumar S, Szabo F, et al. Classification of acute pancreatitis in the pediatric population: clinical report from the NASPGHAN Pancreas Committee. *J Pediatr Gastroenterol Nutr*. 2017;64(6):984-990.
3. Uc A, Husain SZ. Pancreatitis in children. *Gastroenterology*. 2019;156(7):1969-1978.
4. Abu-El-Haija M, Kumar S, Quiros JA, et al. Management of acute pancreatitis in the pediatric population: a clinical report from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Pancreas Committee. *J Pediatr Gastroenterol Nutr*. 2018;66(1):159-176.

5. Lopez MJ. The changing incidence of acute pancreatitis in children: a single-institution perspective. *J Pediatr*. 2002;140(5):622-624.
6. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas*. 2010;39(1):5-8.
7. Morinville VD, Husain SZ, Bai H, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. *J Pediatr Gastroenterol Nutr*. 2012;55(3):261-265.
8. Kylänpää-Bäck ML, Kemppainen E, Puolakkainen P. Trypsin-based laboratory methods and carboxypeptidase activation peptide in acute pancreatitis. *J Pancreas*. 2002;3(2):34-48.
9. Hedstöm, J, Stenman UH, Korvuo A, et al. Urinary trypsinogen-2 test strip for acute pancreatitis. *Lancet*. 1996;347(9003):729-731.
10. Kassell B, Kay J. Zymogens of proteolytic enzymes. *Science*. 1973;180(4090):1022-1027.
11. Hedström J, Sainio V, Kemppainen E, et al. Urine trypsinogen-2 as marker of acute pancreatitis. *Clin Chem*. 1996;42(5):685-690.
12. Itkonen O, Koivunen E, Hurme M, Alfthan H, Schröder T, Stenman UH. Time-resolved immunofluorometric assays for trypsinogen-1 and 2 in serum reveal preferential elevation of trypsinogen-2 in pancreatitis. *J Lab Clin Med*. 1990;115(6):712-718.
13. Kamer E, Unalp HR, Derici H, Tansug T, Onal MA. Early diagnosis and prediction of severity in acute pancreatitis using the urine trypsinogen-2 dipstick test: a prospective study. *World J Gastroenterol*. 2007;13(46):6208-6212.
14. Kylänpää-Bäck ML, Kemppainen E, Puolakkainen P, et al. Reliable screening for acute pancreatitis with rapid urine trypsinogen-2 test strip. *J Br Surg*. 2000;87(1):49-52.
15. Yasuda H, Kataoka K, Takeyama Y, et al. Usefulness of urinary trypsinogen-2 and trypsinogen activation peptide in acute pancreatitis: a multicenter study in Japan. *World J Gastroenterol*. 2019;25(1):107-117.
16. Jin T, Huang W, Jiang K, et al. Urinary trypsinogen-2 for diagnosing acute pancreatitis: a meta-analysis. *Hepatobiliary Pancreatic Dis Int*. 2013;12(4):355-362.
17. Chang K, Lu W, Zhang K, et al. Rapid urinary trypsinogen-2 test in the early diagnosis of acute pancreatitis: a meta-analysis. *Clin Biochem*. 2012;45(13-14):1051-1056.
18. Kylänpää-Bäck ML, Kemppainen E, Puolakkainen P, et al. Comparison of urine trypsinogen-2 test strip with serum lipase in the diagnosis of acute pancreatitis. *Hepato Gastroenterol*. 2002;49(46):1130-1134.
19. Orkin SH, Trout AT, Fei L, et al. Sensitivity of biochemical and imaging findings for the diagnosis of acute pancreatitis in children. *J Pediatr*. 2019;213:143-148.
20. Zhang Q, Guo Q, Gui M, et al. Henoch-Schönlein purpura with acute pancreatitis: analysis of 13 cases. *BMC Pediatr*. 2018;18(1):159.
21. Akshintala VS, Moore MG, Cruz-Monserrate Z, Nathan JD, Searle BC, Abu-El-Haija M. Urine proteomics profiling identifies novel acute pancreatitis diagnostic biomarkers in a pediatric population. *Gastroenterology*. 2024;167(5):1019-1021.e2.
22. Chen YT, Chen CC, Wang SS, Chang FY, Lee SD. Rapid urinary trypsinogen-2 test strip in the diagnosis of acute pancreatitis. *Pancreas*. 2005;30(3):243-247.
23. Cone EJ, Caplan YH, Moser F, Robert T, Shelby MK, Black DL. Normalization of urinary drug concentrations with specific gravity and creatinine. *J Anal Toxicol*. 2009;33(1):1-7.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Orgad T, Abu-Rahma I, Rekhtman D, et al. The first pediatric study investigating the utility of a noninvasive urine-based test for acute pancreatitis diagnosis. *J Pediatr Gastroenterol Nutr*. 2025;1-7. doi:10.1002/jpn3.70119