Using the literature to evaluate diagnostic tests: amylase or lipase for diagnosing acute pancreatitis?

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INTRODUCTION

In the previous installments of this case study column, librarians addressed complex questions that related to the care of specific patients [1, 2]. This issue’s case study addresses a clinical question with a much broader scope, exploring evidence that will guide best practices for a hospital department and provide an important tool for educating health care professionals.

THE CASE

Your hospital’s Emergency Department (ED) holds weekly teaching conferences for its residents. These sessions are composed of didactic lectures and oral case reports in which one resident presents a challenging patient case and another resident works through the process of evaluating and managing the situation. These sessions are a key part of the residents’ training and present opportunities to evaluate current medical practices and determine the best methods of care based on the evidence.

During a particular case conference, a resident is managing a practice case that is clinically suspicious for pancreatitis. The two most common tests for diagnosing acute pancreatitis are serum amylase and serum lipase levels, and the resident requests both tests as part of the laboratory work-up of the case. The attending physician interrupts and queries the resident regarding his rationale for ordering both tests and whether one of the tests may be sufficient. An animated discussion ensues, with opinions voiced by several attending physicians and residents, about whether it is necessary to order both tests in this kind of case and, if not, which one should be used. During this debate, the lead attending turns to you as the group’s consulting librarian and asks you to search and report on the literature surrounding the issue.

THE QUESTION

Which diagnostic test, serum amylase or serum lipase, is the best for making an accurate diagnosis of acute pancreatitis in the adult ED setting?

Figure 1 provides commentary from the attending physician on the importance of this question.

UNDERSTANDING THE CONCEPTS

Medical concepts

Your first step is to develop an understanding of the question’s key concepts, namely, pancreatitis, amylase, and lipase (Table 1). Consumer sites developed by the American Association for Clinical Chemistry [3] and the National Institutes of Health [4] provide thorough and convenient overviews of this case’s medical concepts. In addition, consulting the Medical Subject Headings (MeSH) database [5] is useful for obtaining a quick definition, as well as determining a term’s place in the MeSH tree structure for more effective searching.

Statistical concepts

It is also necessary to have some understanding of the statistics used to evaluate diagnostic studies prior to examining the articles for inclusion or exclusion in your summary of the literature for this question. The accuracy of a diagnostic test is usually represented by its sensitivity and specificity, test characteristics that are defined by comparison of a potential diagnostic testing strategy (e.g., amylase) to an existing gold standard test for diagnosing the disease or condition (e.g., computed tomography) [11]. “Sensitivity” represents the probability of a positive result for the novel diagnostic test in people who definitely have the disease in question, as defined by the gold standard test. “Specificity” is the probability of a negative test result for the novel diagnostic test in people who definitely do not have the disease, as defined by the gold standard (Figure 2).

Another set of values commonly calculated based on sensitivity and specificity are a test’s positive and negative predictive values. The “positive predictive value” represents the probability of a positive test result indicating the true presence of disease. The “negative predictive value” represents the probability of a negative test result indicating that the disease is truly absent (Figure 2).

Additional statistical values that may be provided in studies include the likelihood and odds ratios and receiver operating characteristic (ROC) curves. ROC curves plot the true positives of a diagnostic test result on the Y-axis versus the false positives of the test on the X-axis. ROC curves are used to evaluate diagnostic tests and are well described elsewhere [11, 12].

This examination of sensitivity, specificity, and other test characteristics highlights one of the most important problems with evaluating any diagnostic test: the choice of the “gold standard” diagnostic standard to which other diagnostic strategies are compared. How does the study identify which patients truly have the disease in question? All of the test evaluation measures (sensitivity, specificity, etc.) are based on the ability to correctly divide patients into disease and non-disease categories. Therefore, the most accurate studies will utilize diagnostic criteria that are objective and definitive, as well as separate from any alternative diagnostic tests under study.
CONSTRUCTING A LITERATURE SEARCH

As with the previous cases, PubMed serves as a major starting point for identifying evidence related to this question. Your query of the MeSH Browser in PubMed identifies several MeSH terms that may be useful for this question: “Pancreatitis,” “Amylases,” “Lipase,” and “Sensitivity and Specificity.” Additionally, the subheading “Diagnosis” (attached to the “Pancreatitis” term mentioned above) and the MeSH term “Diagnosis” may be useful components of the search strategy. Using these concepts to search PubMed, your search strategies may look something like the following:

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"Pancreatitis/diagnosis"[MeSH] AND Amylases[MeSH] AND Lipase[MeSH]

"Sensitivity and Specificity"[MeSH] AND “Amylases” [MeSH] AND “Lipase”[MeSH]

“Pancreatitis”[MeSH] AND acute[tw] AND “Diagnosis” [MeSH] AND “Sensitivity and Specificity”[MeSH]
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Table 1

| Medical concept | Brief definition |
|-----------------|------------------|
| Pancreatitis    | Inflammation or swelling of the pancreas, which can be classified as acute or chronic. Acute pancreatitis is most commonly caused by gallstones or excessive alcohol use. Serious complications are associated with acute pancreatitis that require immediate care and hospitalization. These complications include breathing problems, excessive vomiting, and/or inability to eat. Acute pancreatitis commonly presents as abdominal pain, nausea, vomiting, fever, or rapid pulse. Chronic pancreatitis occurs over a long period of time and results when digestive enzymes destroy the pancreas and nearby tissues, causing scarring. Excessive alcohol use, blocked or narrowed pancreatic duct, trauma, and heredity (i.e., a genetic disorder that usually manifests in childhood) are common causes of chronic pancreatitis. Individuals with chronic pancreatitis may experience chronic or episodic abdominal pain, while others do not have any pain or the pain eventually goes away. To diagnose pancreatic, physicians will often order blood tests to determine if the levels of pancreatic enzymes (i.e., amylase and lipase) have markedly increased [6]. |
| Amylase         | An enzyme made primarily in the pancreas and released into the digestive tract to aid in the digestion of starch and glycogen, the stored form of glucose in the body’s cells [7]. Amylase levels rise at the beginning of a pancreatic attack and taper off after 2 days. The normal or reference range for serum amylase varies due to patient factors (e.g., age, gender) and the specific assay used and is typically 20–300 units/L for automated methods [8]. Amylase levels can be 5–10 times higher than normal during pancreatitis, and its rise in levels usually mirror those of the enzyme lipase [7]. |
| Lipase          | An enzyme made primarily in the pancreas and released into the digestive tract to aid in the digestion of fats. This enzyme also maintains cell permeability, which allows for the flow of nutrients into the cell and the flow of wastes out of the cell [9]. Like amylase, the reference range for serum lipase varies due to patient and test factors and is typically < 200 units/L [10]. In acute pancreatitis, lipase levels can be 2–5 times higher than normal and remain elevated for 4–7 days. Amylase and lipase levels often rise in parallel and are often ordered together to diagnose acute pancreatitis, as well as monitor chronic pancreatitis [9]. |
You also find that limiting a search to English language articles and only to those referring to adult patients can tighten a strategy. Applying these limits to the following search reduces the number of results from approximately 450 to 120 citations. These same limits can be applied to any of the above searches to focus the retrieval.

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"Pancreatitis/diagnosis"[MeSH] AND "amylases"[MeSH] AND "lipase"[MeSH] AND English[lang] AND ("adult"[MeSH] OR "middle aged"[MeSH] OR "aged"[MeSH])
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Your background reading indicates that patients with acute pancreatitis often present to the ED with abdominal pain as their primary complaint. Therefore, the MeSH heading for "Abdominal Pain" may also be useful, as amylase and lipase are often measured to distinguish acute pancreatitis from other causes of acute abdominal pain in the ED. Additionally, the text-word "acute" or the MeSH heading "Acute Disease" may be helpful in eliminating some of the articles that focus only on chronic pancreatitis or chronic abdominal pain, disease entities less relevant to the acute disease portion of the current question. The following strategy returns about forty-five results:

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("Acute Disease"[MeSH] OR acute[tw]) AND "Pancreatitis"[MeSH] AND "Amylases"[MeSH] AND "Lipase"[MeSH] AND "Sensitivity and Specificity"[MeSH]
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The text-words for "amylase," "lipase," "pancreatitis," and "abdominal pain" may also be helpful, particularly in identifying the most current literature that has yet to be indexed. The following text-word search retrieves approximately ninety results:

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sensitivity AND specificity AND amylase* AND lipase AND ("acute pancreatitis" OR "abdominal pain") AND English[lang]
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Searching additional databases is also likely to be essential to ensure that you have retrieved a comprehensive representation of the literature on this topic. Other resources such as Science Citation Index Expanded and CINAHL may be useful. The keywords noted above will provide useful entry points for examining retrieval from these databases.

**EXPLORING THE LITERATURE**

Your search retrieval contains several studies including primary data. The vast majority are either prospective [13–22] or retrospective cohort studies [23–27]. A prospective study follows patients into the future and collects data in real time, whereas a retrospective study analyzes patient data collected in the past. Prospective and retrospective designs are a common feature of diagnostic studies because the use of diagnostic tests alone is evaluated less frequently with a randomized controlled clinical trial. In fact, guidelines from the American College of Emergency Physicians consider a prospective cohort study with a well-chosen criterion standard (a standard for diagnosis that is separate from the tests under study and is generally accepted to be definitive) to be the top class of evidence for a diagnostic study [28]. However, many published studies are conducted retrospectively [23–27], which is not surprising as it is easier to evaluate existing medical records than to develop and conduct a prospective study.

You scrutinize your retrieved articles for several key characteristics:

- direct comparison of the use of serum amylase and serum lipase for the diagnosis of acute pancreatitis
- choice of diagnostic criteria for determining which patients have or do not have acute pancreatitis, including criteria that is objective and does not include the two tests being evaluated
- design (prospective vs. retrospective)
- population size, with preference given to larger studies, as larger sample sizes tend to provide greater statistical power; statistical power refers to the study’s ability to avoid missing a significant effect, which would disprove the null hypothesis (that there is no effect) [12]
- publication date, with priority given to more recent articles (if possible)

Many of the studies have confusing or unspecified diagnostic criteria for acute pancreatitis, including a few studies that confirm a diagnosis of acute pancreatitis on the vague notion of “presentation and clinical course” [24] or only state that there was a “clinical diagnosis” of acute pancreatitis [17]. This type of ambiguity is particularly troubling for retrospective studies in which patients were selected by a search of medical records for a diagnosis of acute pancreatitis without clarification or details regarding how the original clinical diagnosis of acute pancreatitis was established. A clear concern about these studies is the potentially significant lack of consistency in how this disease has been diagnosed. As discussed above, a clearly defined standard for accurately identifying which patients do and do not have the disease is question is essential for high-quality evaluations of diagnostic test accuracy.

In the case of pancreatitis, the best diagnostic standard is the use of an imaging modality (e.g., computed tomography or abdominal ultrasound) [29] or direct histological examination of the affected tissue (i.e., needle biopsy of the pancreas). Histological examination is the most definitive diagnostic standard for this disease; however, its invasive nature makes it more difficult and potentially risky to apply. Nonetheless, only studies that included patients whose final diagnosis is based on criteria that did not include amylase and lipase measurements should be selected for inclusion. You also note that these studies primarily used imaging techniques such as ultrasound and computed tomography to confirm the presence of acute pancreatitis in their patient populations [16, 17, 23, 27].

You consider one practice guideline from Japan [30]. However, on closer inspection, you realize that this guideline references literature from the 1980s, omits several more recently published studies, and references a much older review article as a source for data. The older nature of the literature on this topic is not sur-
prising and mirrors your own findings, likely due to the fact that the main diagnostic tests for pancreatitis have been in use for several decades and some of the original studies were done many years ago. Due to these weaknesses, you decide not to include this guideline in your final pool of evidence. Another potential issue limiting this guideline’s generalizability is that it is written for physicians in Japan, not in the United States, and clinical practice can sometimes vary significantly among different countries.

You further refine your pool of studies to represent the key data on this topic, selecting the four that come closest to meeting the diagnostic gold standard. You consider the population sizes and study designs (retrospective and prospective) as well, but, in the end, the requirement to choose studies with quality diagnostic criteria dictates which articles to include in your report to the team. All four selected studies utilize a diagnostic criterion separate from amylase or lipase for at least a subgroup of patients, and all four provide sensitivity and specificity for serum amylase and lipase compared to that standard. These studies include two retrospective studies [23, 27] and two prospective studies [16, 17]. Of these four selected articles, three were published in the 1990s and one was published in 2005 (Table 2).

### Table 2
Summary table of references

| First author/date       | Study design         | Patient population                                      | Diagnostic criteria for pancreatitis                                                                 | Results                                                                 | Conclusion                                      |
|-------------------------|----------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------|
| Clave, 1995 [17]        | Prospective case series | 384 patients, 60 with acute pancreatitis, remaining patients with other abdominal diseases | Clinical presentation and hospital course and the elimination of any other cause of abdominal pain; some patients also received confirmation by sonogram, CT, laparotomy, or necropsy | Diagnostic thresholds were serum amylase > 180 U/L or urine amylase > 900 U/L | No diagnostic advantage seen for amylase, lipase, isoamylase, or urine amylase compared to each other; PLA not recommended. |
| Gumaste, 1992 [16]     | Prospective study    | 29 patients with imaging-proven acute alcoholic etiology pancreatitis; 13 with chronic pancreatitis; remaining patients with other abdominal diseases; of the 320 patients with acute pancreatitis, values for both serum amylase and serum lipase were available for 207 (64.7%) | In the pancreatitis group, imaging studies (CT scanning) confirmed the diagnosis of acute pancreatitis | Sensitivity and specificity was calculated based on serum levels of 3 times the normal level. | Lipase was superior for diagnosing acute alcoholic pancreatitis. |
| Smith, 2005 [27]       | Retrospective chart review | 8,937 patients (320 with acute pancreatitis; 13 with chronic pancreatitis; remaining patients with other abdominal diseases); of the 320 patients with acute pancreatitis, values for both serum amylase and serum lipase were available for 207 (64.7%) | CT or ultrasound confirmation | Diagnostic thresholds were > 114 U/L for serum amylase and > 208 U/L for serum lipase. | Serum lipase and serum amylase were similar, with serum lipase being slightly more accurate in terms of both sensitivity and specificity. |
| Chase, 1996 [23]       | Retrospective chart review | 306 patients (123 male, 183 female) admitted with acute abdominal pain | Clinical history and evidence from roentgenograms, ultrasound, CT, endoscopy, and/or surgical exploration | For admission levels > upper limit of normal for serum amylase = 110 U/L and serum lipase = 208 U/L. | Both tests were accurate in diagnosing acute pancreatitis. |
SUMMARIZING THE INDIVIDUAL REFERENCES

To effectively display and summarize the information, the nature of both the clinical question and the literature need to be carefully considered. Given that the question is broad (in that it does not pertain to a specific patient, but rather is intended to guide general practice), paired with the fact that several studies are necessary to represent the evidence related to this question, highlighting the most relevant points for each study in a tabular format will allow for quick and easy processing of the information presented. A table will also allow for quick comparison of the methodology, results, and characteristics (sensitivity, specificity, etc) for each of the studies. The order in which to display the articles is also important. Given that prospective studies are the most appropriate study design for evaluating diagnostic tests [28], you decide to list these first, followed by the retrospective chart reviews.

To organize and represent the key features for each of the studies, you may wish to consider table columns (Table 2) such as:

- study design: type of study employed (e.g., retrospective or prospective)
- patient population: details characterizing the patients included in study, including the number of patients evaluated, as well as amylase or lipase levels, gender ratio, or type of pancreatitis, if applicable
- diagnostic criteria: the standards on which the authors base their diagnosis of pancreatitis
- results: specificity and sensitivity of each test and other findings regarding their efficacy
- conclusion: summarizing the authors’ key findings and/or clinical recommendations

OVERALL STATE OF THE LITERATURE

As discussed in the previous cases [1, 2], the team would likely benefit from your creation of an overall summary of the key findings in the literature for this question. Based on your examination of the breadth of citations in the literature via PubMed and other resources, key points you consider for inclusion in this overall summary include:

- overall state of the literature (i.e., comprising prospective, retrospective, and review articles)
- any conclusions that can be drawn; in this case, that the tests are relatively similar in sensitivity and specificity, with a slight advantage toward lipase
- comments on the potential limitations of retrospective chart reviews
- other impacting issues; in this case, these include the issues regarding the diagnostic standard for confirming acute pancreatitis
- summary points of the chosen articles as related to the question

Figure 3 includes one example of an overall summary that pulls together these points.

CONCLUDING REMARKS

Your systematic identification and evaluation of diagnostic studies has provided you with a challenging and rewarding task that makes you an essential part of the ED team, informing clinical practices and education for this key hospital constituency. By participating in these sessions, you provide supporting evidence from the literature that contributes to the atmosphere emphasizing learning and professional growth.

Also, it is interesting to observe how the clinician interprets and uses the evidence that you have provided. In this case, the supervising physician utilizes the results in two separate but related ways. First, he combines the evidence you provided with his concerns about providing cost-effective medical care, judging that it was best to recommend to the residents that one test was sufficient rather than two. Thus, he incorporates the evidence you provide with his expert clinical judgment, the essence of evidence-based medicine [33]. Second, he exploits the teaching moment by developing a short quiz for the residents that emphasizes the points he wishes to make (Figure 4).

As the residents consider their answers in the oral discussion of the quiz questions, the attending physician is able to expand their clinical knowledge and encourage them to think more carefully about their test ordering practices, both for pancreatitis and other diseases. By participating in this discussion based on your literature search, you demonstrate your knowledge and skills and receive, in turn, feedback on the clinical implications of your findings. This case serves
as a good example of the impact that a librarian can have on clinical practice.

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