Pancreatic Enzyme Testing for Acute Pancreatitis AHS – G2153

Description of Procedure or Service

Pancreatitis is an inflammation of pancreatic tissue and can be either acute or chronic. Pancreatic enzymes, including amylase, lipase, and trypsinogen can be used to monitor the relative health of the pancreatic tissue. Damage to the pancreatic tissue, including pancreatitis, can result in elevated pancreatic enzyme concentrations whereas depressed enzyme levels are associated with exocrine pancreatic insufficiency (P. A. Banks et al., 2013; Stevens & Conwell, 2016).

Background

Acute Pancreatitis

Acute pancreatitis (AP) is inflammation of the pancreatic tissue that can range considerably in clinical manifestations. Due to the lack of consensus in diagnosing, characterizing, and treating AP, an international group of researchers and practitioners convened in Atlanta in 1992 to write a clinically based classification system for AP, which is now commonly referred to as the Atlanta convention or Atlanta classification system (Bradley & III, 1993). The Atlanta classification system was then revised in 2012 (P. A. Banks et al., 2013). For the diagnosis of AP, two of the three following criteria must be present: “(1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography” (italics emphasized by the manuscript’s authors)(P. A. Banks et al., 2013). This two-of-three criterion is recommended for diagnostic use by several professional societies (P. Banks & Freeman, 2006; Guidelines, 2013; S. Tenner, Baillie, DeWitt, Vege, & American College of, 2013). AP can be characterized by two temporal phases, early or late, with degrees of severity ranging from mild (with no organ failure) to moderate (organ failure less than 48 hours) to severe (where persistent organ failure has occurred for more than 48 hours). The two subclasses of AP are edematous AP and necrotizing AP. Edematous AP is due to inflammatory edema with relative homogeneity whereas necrotizing AP displays necrosis of pancreatic and/or peripancreatic tissues (P. A. Banks et al., 2013). The figure below from Bollen and colleagues (Bollen, Hazewinkel, & Smithuis, 2015) outlines the revised Atlanta classification system of AP:
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Chronic Pancreatitis

Chronic pancreatitis (CP) is also an inflammation of the pancreatic tissue. The two hallmarks of CP are severe abdominal pain and pancreatic insufficiency (Freedman, 2017). Alcohol-induced chronic pancreatitis (or alcohol pancreatitis) accounts for 60-70% of all cases of CP. CP can be classified in one of nine types (Wilson & Smith, 2015):

- Alcoholic
- Autoimmune (idiopathic)
- Due to trauma
- Inherited factors
- Congenital
- Due to hyperparathyroidism
- Hyperlipidemic
- Due to cystic fibrosis
- Due to protein-energy malnutrition

CP affects both the endocrine and exocrine functions of the pancreas. Fibrogenesis occurs within the pancreatic tissue due to activation of pancreatic stellate cells by toxins (for example, those from chronic alcohol consumption) or cytokines from necroinflammation. Measuring the serum levels of amylase, lipase, and/or trypsinogen is not helpful in diagnosing CP since not every CP patient experiences acute episodes, the relative serum concentrations may be either decreased or unaffected, and the sensitivities of the tests are not enough to distinguish reduced enzyme levels (Witt, Apte, Keim, & Wilson, 2007). The best method to diagnose CP is to histologically analyze a pancreatic biopsy, but this invasive procedure is not always the most practical so “the next best diagnostic methods to demonstrate changes consistent with chronic pancreatitis are computed axial tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS)” (Wilson & Smith, 2015). Previously, ERCP was commonly used to diagnose CP, but the procedure can cause post-ERCP pancreatitis. Genetic factors are also implicated in CP, especially those related to trypsin activity, the serine protease inhibitor SPINK 1, and cystic fibrosis (Borowitz, Grant, & Durie, 1995; Wilson & Smith, 2015; Witt et al., 2007).

Amylase

Amylase is an enzyme produced predominantly in the salivary glands (s-isoform) and the pancreas (p-isoform or p-isomylase) and is responsible for the digestion of polysaccharides, cleaving at the
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internal 1→4 alpha linkage. Up to 60% of the total serum amylase can be of the s-isoform. The concentration of total serum amylase as well as the pancreatic isoenzyme increase following pancreatic insult or inflammation (Basnayake & Ratnam, 2015; Vege, 2018). Even though the serum concentration of the pancreatic diagnostic enzymes, including amylase, lipase, elastase, and immunoreactive trypsin all increase within 24 hours of onset of symptomology, amylase is the first pancreatic enzyme to return to normal levels so the timing of testing is of considerable importance for diagnostic value (Basnayake & Ratnam, 2015; Ventrucci et al., 1987; Yadav, Agarwal, & Pitchumoni, 2002). The half-life of amylase is 12 hours since it is excreted by the kidneys so its clinical value decreases considerably after initial onset of AP. The etiology of the condition can also affect the relative serum amylase concentration. In up to 50% of AP instances due to hypertriglyceridemia, the serum amylase concentration falls into the normal range, and normal concentrations of amylase has been reported in cases of alcohol-induced AP (Basnayake & Ratnam, 2015; Quinlan, 2014); in fact, one study shows that 58% of the cases of normoamylasemic AP was associated with alcohol use (Clavien et al., 1989). Elevated serum amylase concentrations also can occur in conditions other than AP, including hyperamylasemia due to drug exposure (Ceylan, Evrensel, & Önen Ünsalver, 2016; Liu et al., 2016), bulimia nervosa (Wolfe, Jimerson, Smith, & Keel, 2011), leptospirosis (Herrmann-Storck et al., 2010), and macroamylasemia (Vege, 2018).

Macroamylasemia is a condition where the amylase concentration increases due to the formation of macroamylases, complexes of amylase with immunoglobulins and/or polysaccharides. Macroamylasemia is associated with other disease pathologies, “including celiac disease, HIV infection, lymphoma, ulcerative colitis, rheumatoid arthritis, and monoclonal gammopathy”. Suspected macroamylasemia in instances of isolated amylase elevation can be confirmed by measuring the amylase-to-creatinine clearance ratio (ACCR) since macroamylase complexes are too large to be adequately filtered. Normal values range from 3-4% with values of less than 1% supporting the diagnosis of macroamylasemia. ACCR itself is not a good indicator of AP since low ACCR is also exhibited in diabetic ketoacidosis and severe burns (Vege, 2018a). Hyperamylasemia is also seen in other extrapancreatic conditions, such as appendicitis, salivary disease, gynecologic disease, extra-pancreatic tumors, and gastrointestinal disease (Terui et al., 2013; Vege, 2018a). Gullo’s Syndrome (or benign pancreatic hyperenzymemia) is a rare condition that also exhibits high serum concentrations of pancreatic enzymes without showing other signs of pancreatitis (Kumar, Ghosh, Tandon, & Sahoo, 2016). No correlation has been found between the concentration of serum amylase and the severity or prognosis of AP (Lippi, Valentino, & Cervellin, 2012).

Urinary amylase and peritoneal amylase concentrations can also be measured. Rompianesi and colleagues (2017) reviewed the use of urinary amylase and trypsinogen as compared to serum amylase and serum lipase testing. They note that “with regard to urinary amylase, there is no clear-cut level beyond which someone with abdominal pain is considered to have acute pancreatitis.” They reviewed three studies of urinary amylase—each with 134-218 participants—and used the hierarchical summary receiver operating characteristics curve (HSROC) analysis to compare the accuracy of the studies. They found that “the models did not converge” and concluded that “we were therefore unable to formally compare the diagnostic performance of the different tests” (Rompianesi et al., 2017).

Another study investigated the use of peritoneal amylase concentrations for diagnostic measures and discovered that patients with Intra-abdominal peritonitis had a mean peritoneal amylase concentration of 816 U/L (142-1746 U/L range), patients with pancreatitis had a mean concentration of 550 U/L (100-1140 U/L range), and patients with other “typical infectious peritonitis” had a mean concentration of 11.1 U/L (0-90 U/L range). They conclude “that peritoneal fluid amylase levels were helpful in the differential diagnosis of peritonitis in these patients” and that levels >100 U/L “differentiated those patients with other intra-abdominal causes of peritonitis from those with typical infectious peritonitis” (Burkart, Haigler, Caruana, & Hylander, 1991). They do not state if intraperitoneal amylase is specifically useful in diagnosing AP.
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**Lipase (Pancreatic Lipase or Pancreatic Triacylglycerol Lipase)**

Pancreatic Lipase or triacylglycerol lipase (herein referred to as “lipase”) is an enzyme responsible for hydrolyzing triglycerides to aid in the digestion of fats. Similar to amylase, lipase concentration increases shortly after pancreatic injury (within 3-6 hours). However, contrary to amylase, serum lipase concentrations remain elevated for 1-2 weeks after initial onset of AP since lipase can be reabsorbed by the kidney tubules (Lippi et al., 2012). Moreover, the pancreatic lipase concentration is 100-fold higher than the concentration of other forms of lipases found in other tissues such as the duodenum and stomach (Basnayake & Ratnam, 2015). Both, the sensitivity and the specificity of lipase in laboratory testing of AP are higher than that of amylase (Yadav et al., 2002). A study by Coffey and colleagues (Coffey, Nightingale, & Ooi, 2013) found “an odds ratio of 7.1 (95% confidence interval 2.5-20.5; P<0.001) for developing severe AP” in patients ages 18 or younger when the serum lipase concentration is at least 7-fold higher than upper limit of normal. However, in general, elevated serum lipase concentration is not used to determine the severity or prognosis of AP (Ismail & Bhayana, 2017). Hyperlipasemia can also occur in other conditions, such as Gullo’s Syndrome (Kumar et al., 2016). The use of lipase to determine etiology of AP is of debate. A study by Levy and colleagues (Levy et al., 2005) reports that lipase alone cannot be used to determine biliary cause of AP whereas other studies have indicated that a ratio of lipase-to-amylase concentrations ranging from 2:1 to more than 5:1 can be indicative of alcohol-induced AP (Gumaste, Dave, Weissman, & Messer, 1991; Ismail & Bhayana, 2017; Pacheco & Oliveira, 2007; S. M. Tenner & Steinberg, 1992).

The review by Ismail and Bhayana (Ismail & Bhayana, 2017) included a summary table (Table 1 below) comparing various studies concerning the use of amylase and lipase for diagnosis of AP as well as a table (Table 2 below) comparing the cost implication of the elimination of double-testing for AP.
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This table is a list of individual studies examining the specificity and sensitivity of serum lipase and serum amylase in diagnosing AP. In each of the listed studies except one, the authors concluded that serum lipase is better than serum amylase for AP. The only outlier used a lower threshold in considering enzyme elevation. They used two times the upper limit of reference interval (URL) whereas the Atlanta classification system recommends at least three times the URL to determine enzyme elevation (Ismail & Bhayana, 2017).

This table specifically outlines studies that compared the financial cost of the serum amylase and serum lipase tests for diagnosing AP. All three studies show cost savings if only lipase concentration is used. In fact, one study by researchers in Pennsylvania resulted in the removal of the amylase test “from common order sets in the electronic medical record” (Ismail & Bhayana, 2017).
Trypsin/Trypsinogen/TAP

Trypsin is a protease produced by the pancreatic acinar cells. It is first synthesized in its zymogen form, trypsinogen, which has its N-terminus cleaved to form the mature trypsin. Pancreatitis can result in blockage of the release of the proteases while their synthesis continues. This increase in both intracellular trypsinogen and cathepsin B, an enzyme that can cleave the trypsinogen activation peptide (TAP) from the zymogen to form mature trypsin, results in a premature intrapancreatic activation of trypsin. This triggers a release of both trypsin and TAP extracellularly into the serum and surrounding peripancreatic tissue. Due to the proteolytic nature of trypsin, this response can result in degradation of both the pancreatic and peripancreatic tissues (i.e. necrotizing AP) (Vege, 2019; Yadav et al., 2002).

Since trypsinogen is readily excreted, a urine trypsinogen-2 dipstick test has been developed (Actim Pancreatitis test strip from Medix Biochemica), which has a reported specificity of 85% for severe AP within 24 hours of hospital admission (Lempinen et al., 2001). Another study reported that the trypsinogen-2 dipstick test has a specificity of 95% and a sensitivity of 94% for AP, which is higher than a comparable urine test for amylase (Kemppainen et al., 1997). As of 2019, the FDA has not approved the use of the trypsinogen-2 dipstick test for the detection or diagnosis of AP. Clinical trials are underway in the United States (Eastler, 2017). The use of TAP for either a diagnostic or prognostic tool is of debate (Lippi et al., 2012).

The study by Neoptolemos and colleagues (Neoptolemos et al., 2000) reported that a urinary TAP assay had a 73% specificity for AP. However, another study using a serum TAP methodology reported a 23.5% sensitivity and 91.7% specificity for AP and concluded that “TAP is of limited value in assessing the diagnosis and the severity of acute pancreatic damage” (Pezzilli et al., 2004).

Other Biochemical Markers (CRP, Procalcitonin, IL-6, IL-8)

AP results in the activation of the immune system. Specific markers including C-reactive protein (CRP), procalcitonin, interleukin-6 (IL-6), and interleukin-8 (IL-8) have been linked to AP (Toouli et al., 2002; Vege, 2018b; Yadav et al., 2002). CRP is a nonspecific marker for inflammation that takes 48-72 hours to reach maximal concentration after initial onset of AP but is reported to have a specificity of 93% in detecting pancreatic necrosis. CRP can be used in monitoring the severity of AP; however, imaging techniques, including CT, and evaluative tools, such as the APACHE-II (acute physiology and chronic health evaluation) test, are preferred methods (Guidelines, 2013; Quinlan, 2014).

Procalcitonin is the inactive precursor of the hormone calcitonin. Like CRP, procalcitonin has been linked to inflammatory responses, especially in response to infections and sepsis. Procalcitonin levels are elevated in AP and are significantly elevated (≥3.5 ng/mL for at least two consecutive days) in cases of AP associated with multiorgan dysfunction syndrome (MODS) (Rau et al., 2007). Moreover, the elevated procalcitonin levels decrease upon treatment for AP; “however, further research is needed in order to understand how these biomarkers can help to monitor inflammatory responses in AP” (Simsek et al., 2018).

The concentration of inflammatory cytokines IL-6 and IL-8 become elevated in AP with a maximal peak within the first 24 hours after initial onset of AP (Yadav et al., 2002). One study (Jakkampudi et al., 2017) shows that IL-6 and IL-8 are released in a time-dependent manner after injury to the pancreatic acinar cells. This, in turn, activated the peripheral blood mononuclear cells (PBMCs), which propagate acinar cell apoptosis that results in further release of cytokines to increase the likelihood of additional cellular damage.

A study conducted by Khanna and colleagues (Khanna et al., 2013) compares the use of biochemical markers, such as CRP, IL-6, and procalcitonin, in predicting the severity of AP and necrosis to that of the clinically used evaluative tools, including the Glasgow score and APACHE-
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II test. Their results indicate that CRP has a sensitivity and specificity of 86.2% and 100%, respectively, for severe AP and a sensitivity and specificity of 100% and 81.4%, respectively, for pancreatic necrosis. These scores are better than those reported for the clinical evaluative tools (see table below). IL-6 also show an increase in both sensitivity and specificity; however, the values for procalcitonin are considerably lower than either CRP or IL-6 in all parameters (Khanna et al., 2013).

<table>
<thead>
<tr>
<th>Data from (Khanna et al., 2013)</th>
<th>Severe AP</th>
<th>Pancreatic necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Glasgow</td>
<td>71.0</td>
<td>78.0</td>
</tr>
<tr>
<td>APACHE-II</td>
<td>80.6</td>
<td>82.9</td>
</tr>
<tr>
<td>CRP</td>
<td>86.2</td>
<td>100</td>
</tr>
<tr>
<td>IL-6</td>
<td>93.1</td>
<td>96.8</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>86.4</td>
<td>75.0</td>
</tr>
</tbody>
</table>

Another study (Hagjer & Kumar, 2018) comparing the efficacy of the bedside index for severity in acute pancreatitis (BISAP) scoring system to CRP and procalcitonin shows that CRP is not as good for prognostication as BISAP. BISAP has AUCs for predicting severe AP and death of 0.875 and 0.740, respectively, as compared to the scores of CRP (0.755 and 0.693, respectively). Procalcitonin, on the other hand, had values of 0.940 and 0.769 for predicting severe AP and death, respectively. The authors concluded that it “is a promising inflammatory marker with prediction rates similar to BISAP” (Hagjer & Kumar, 2018).

**Applicable Federal Regulations**

**Amylase**

The FDA has approved multiple tests for human serum total amylase as well as for pancreatic amylase. FDA Device database accessed on 2/27/2019 yielded 141 records for amylase test.

**Lipase**

The FDA has approved multiple tests for human serum lipase. FDA Device database accessed on 2/27/2019 yielded 51 records for lipase test.

**Trypsinogen/Trypsin/TAP**

Trypsin immunostaining, trypsinogen-2 dipstick, and TAP serum tests are considered laboratory developed tests (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**CRP**
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The FDA has approved multiple tests for human CRP, including assays for conventional CRP, high sensitivity CRP (hsCRP), and cardiac CRP (cCRP). On September 22, 2005, the FDA issued guidelines concerning the assessment of CRP (FDA, 2005).

Procalcitonin

On April 18, 2017, the FDA approved the Diazyme Procalcitonin PCT Assay, Diazyme Procalcitonin Calibrator Set, and Diazyme Procalcitonin Control Set as substantially equivalent and has received FDA 510K clearance for marketing.

IL-6/IL-8

IL-6 and IL-8 are ELISA-based tests and are considered laboratory developed tests (LDT); developed, validated and performed by individual laboratories. IL-6 and IL-8 can also be components of a cytokine panel test, which is also an LDT.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for pancreatic enzyme testing for acute pancreatitis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Pancreatic Enzyme Testing for Acute Pancreatitis is covered

1. Reimbursement is allowed for measurement of either serum lipase OR amylase concentration for the initial diagnosis of acute pancreatitis in all patients presenting with signs and symptoms of acute pancreatitis* (please see Note 1).

When Pancreatic Enzyme Testing for Acute Pancreatitis is not covered

1. Reimbursement is allowed for measurement of either serum lipase OR amylase concentration in the following situations:
   i. As part of an ongoing assessment of therapy for acute pancreatitis; OR
   ii. In determining the prognosis of pancreatitis; OR
   iii. In determining the severity or progression of pancreatitis; OR
   iv. More than once per visit; OR
   v. For the diagnosis, prognosis or severity of chronic pancreatitis; OR
   vi. As part of ongoing assessment or therapy of chronic pancreatitis
2. Reimbursement is not allowed for measurement of the following biomarkers for the diagnosis or assessment of acute pancreatitis, prognosis, and/or determination of severity of acute pancreatitis:
   a. measurement of both amylase AND serum lipase; OR
   b. serum trypsin/trypsinogen/TAP (trypsinogen activation peptide)

3. Reimbursement is not allowed for measurement of the following biomarkers for the diagnosis or assessment of acute pancreatitis, prognosis, and/or determination of severity of acute pancreatitis:
   a. C-Reactive Protein (CRP)
   b. Interleukin-6 (IL-6)
   c. Interleukin-8 (IL-8)
   d. Procalcitonin

*Note 1: Acute Pancreatitis Signs and Symptoms (Vege, 2017b):

- Persistent, severe epigastric pain (that may be in the right upper quadrant for some patients)
- Nausea
- Vomiting
- “Approximately 5 to 10 percent of patients with acute severe pancreatitis may have painless disease and have unexplained hypotension.”
- Tender to palpitation of epigastrium
- Abdominal distention
- Hypoactive bowel sounds
- Fever
- Rapid pulse
- Tachypnea
- Hypoxemia
- Hypotension

Policy Guidelines

Guidelines and Recommendations

a. Recommendations of relevant professional societies

1. 2012 IAP/APA (Guidelines, 2013)

In 2012, a joint conference between the International Association of Pancreatolog (IAP) and the American Pancreatic Association (APA) convened to address the guidelines for the management of acute pancreatitis. This conference made their recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The guidelines are very detailed with 38 recommendations covering 12 different topics, ranging from diagnosis to predicting severity of disease to timing of treatments. As concerning the diagnosis and etiology of AP, the associations conclude with “GRADE 1B, strong agreement” that the definition of AP follow the Atlanta classification system where at least two of the following three criteria are evident—the clinical manifestation of upper abdominal pain, the laboratory testing of serum amylase or serum lipase where levels are >3 times the upper limit of normal values, and/or the affirmation of pancreatitis using imaging methods. They specifically did not include the trypsinogen-2 dipstick test in their recommendations “because of its presumed limited availability”. One question addressed by the committee was the continuation of oral feeding being withheld for patients until the
lab serum tests returned within normal values. With a GRADE 2B, strong agreement finding, they conclude that “it is not necessary to wait until pain or laboratory abnormalities completely resolve before restarting oral feeding”. No specific discussion on the preference of either serum amylase or lipase is included within the guidelines as well as no discussion of the use of either serum test beyond initial diagnosis of AP (i.e. no continual testing for disease monitoring is included). Furthermore, no discussion concerning the use of urinary or peritoneal amylase concentrations for AP.

With regards to CRP and/or procalcitonin, the IAP/APA does not address the topic in any detail. As part of their recommendation (GRADE 2B) concerning the best score or marker to predict the severity of AP, they state “that there are many different predictive scoring systems for acute pancreatitis..., including single serum markers (C-reactive protein, hematocrit, procalcitonin, blood urea nitrogen), but none of these are clearly superior or inferior to (persistent) SIRS”, which is Systemic inflammatory response syndrome. Moreover, in response to their recommendation for admission to an intensive care unit in AP (GRADE 1C), they state that “the routine use of single markers, such as CRP, hematocrit, BUN or procalcitonin alone to triage patients to an intensive care setting is not recommended.

2. 2007 AGA (Baillie, 2007)

The Clinical Practice and Economics Committee (CPEC) of the American Gastroenterological Association (AGA) Institute released the AGA Institute Medical Position Statement on Acute Pancreatitis as approved by the AGA Institute Governing Board in 2007 to address differences in the recommendations of various national and international societies concerning AP. Within their recommendations, they address the necessity of timeliness in the applicability of serum amylase and/or serum lipase testing. Per their recommendations, either serum amylase or serum lipase should be tested within 48 hours of admission. AP is consistent with amylase or lipase levels greater than 3 times the upper limit of the normal value. They specifically state that the “elevation of lipase levels is somewhat more specific and is thus preferred”. The AGA guidelines do not address the use of either urinary or peritoneal concentrations of amylase in AP. Also, any patient presenting symptoms of unexplained multiorgan failure or systemic inflammatory response syndrome should be tested for a possible AP diagnosis. Concerning possible etiology of the phenotype, they suggest that upon admission, “all patients should have serum obtained for measurement of amylase or lipase level, triglyceride level, calcium level, and liver chemistries”. Invasive evaluation, such as endoscopic retrograde cholangiopancreatography (ERCP), should be avoided for patients with a single occurrence of AP. The only mention of CRP in their guidelines is in the section concerning the severity (and not the diagnosis of) AP. “Laboratory tests may be used as an adjunct to clinical judgment, multiple factor scoring systems, and CT to guide clinical triage decisions. A serum C-reactive protein level >150 mg/L at 48 hours after disease onset is preferred.”

3. 2006 & 2013 ACG (P. Banks & Freeman, 2006; S. Tenner et al., 2013)

The American College of Gastroenterology (ACG) released guidelines concerning AP in both 2006 and 2013. Both sets of guidelines recommend the use of the Atlanta classification system regarding the threshold of either serum amylase or serum lipase levels in the diagnosis of AP (i.e. greater than three times the upper limit of normal range). Both sets of guidelines state that the standard diagnosis is meeting at least two of the three criteria as stated in the revised Atlanta classification system.

The 2006 guidelines discuss the differences between serum amylase and lipase in greater detail. First, although both enzymes can be elevated in AP, the sensitivity and half-life of lipase are more amenable for diagnosis since the levels of lipase remain elevated longer than
those of amylase. These guidelines also make note that “it is usually not necessary to
measure both serum amylase and lipase” and that “the daily measurement of serum amylase
or lipase after the diagnosis of acute pancreatitis has limited value in assessing the clinical
progress of the illness”. These guidelines discuss the possibility of elevated amylase levels
due to causes other than AP, including but not limited to macroamylasemia, whereas the
serum levels of lipase are unaffected by these conditions.

The 2013 guidelines do not explicitly state a preference of the serum lipase over serum
amylase test in the diagnosis of AP. They also state that lipase levels can be elevated in
macrolipasemia as well as certain nonpancreatic conditions, “such as renal disease,
appendicitis, cholecystitis, and so on”. Neither set of guidelines address the use of either
urinary or peritoneal amylase in AP. The 2006 guidelines list other diagnostic tests,
including the trypsin/trypsinogen tests as well as serum amyloid A and calcitonin but do not
address them further given their limited availability at that time whereas the 2013 guidelines
state that, even though other enzymes can be used for diagnostics, “none seems to offer
better diagnostic value than those of serum amylase and lipase”. They even state that “even
the acute-phase reactant C-reactive protein (CRP) the most widely studied inflammatory
marker in AP, is not practical as it takes 72h to become accurate.”

The UK Working Party on Acute Pancreatitis consists of a consortium of the British Society
of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic
Society of Great Britain and Ireland, and the Association of Upper GI Surgeons of Great
Britain and Ireland. The recommendation by the UK Working Party is that “although
amylase is widely available and provides acceptable accuracy of diagnosis, where lipase
estimation is available it is preferred for the diagnosis of acute pancreatitis (recommendation
grade A)”. One contrast of the guidelines of the UK Working Party as compared to other
professional societies is the relative threshold of the serum concentrations of pancreatic
enzymes. Rather than use the >3 times the upper limit of the normal concentrations of either
amylase or lipase as stated in the Atlanta classification system, the UK Working Party’s
guidelines state that AP diagnosis “should not rely on arbitrary limits of values 3 or 4 times
greater than normal, but values should be interpreted in light of the time since the onset of
abdominal pain”. These elevated serum levels as well as the clinical abdominal symptoms
are the “cornerstones of diagnosis”. They do not address the frequency of serum enzyme
testing or the use of trypsin/trypsinogen-based tests, urinary amylase, or peritoneal amylase.

5. 2016 ASCP/Choosing Wisely/ABIM (Pathology, 2016)
The American Board of Internal Medicine (ABIM) Foundation oversees the Choosing
Wisely initiative where various professional societies can publish recommendations. The
American Society for Clinical Pathology (ASCP) released a series of recommendations via
Choosing Wisely beginning in 2013. In 2016, the ASCP released a recommendation clearly
stating, “Do not test for amylase in cases of suspected acute pancreatitis. Instead, test for
lipase…. Current guidelines and recommendations indicate that lipase should be preferred
over total and pancreatic amylase for the initial diagnosis of acute pancreatitis and that the
assessment should not be repeated over time to monitor disease prognosis.” The ASCP
also states that performing both lipase and amylase tests are not cost-effective given “marginally
improving diagnostic efficiency compared to either marker alone”. The ASCP
recommendation does not mention any trypsin- or trypsinogen-based methodologies.

Please note that all societies reviewed prefer the use of serum lipase over serum amylase in the
diagnosis of AP based on the higher sensitivity and selectivity of lipase. No consensus concerning
the diagnostic threshold is reached between all of the societies where some use a threshold based
on the Atlanta classification system, some do not specify a threshold, and one consortium
recommends a time-based value system. A table from the review by Lippi et al. (Lippi et al., 2012)
summarizing the recommendations from various societies is below:
Table 2. Synthesis of available guidelines and recommendations for laboratory testing in the diagnosis of acute pancreatitis

<table>
<thead>
<tr>
<th>Organization/s</th>
<th>Preferred biomarker</th>
<th>Diagnostic threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Société Nationale Française de Gastro-Entérologie</td>
<td>Lipase</td>
<td>≥ 3 times the URL</td>
</tr>
<tr>
<td>Japanese Society of Emergency Abdominal Medicine</td>
<td>Lipase</td>
<td>Not set</td>
</tr>
<tr>
<td>British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland</td>
<td>Lipase</td>
<td>Value interpreted according to time since the onset of symptoms</td>
</tr>
<tr>
<td>American Gastroenterological Association</td>
<td>Lipase</td>
<td>≥ 2 to ≥ 4 times the URL</td>
</tr>
<tr>
<td>American Academy of Family Physicians</td>
<td>Lipase</td>
<td>Not set</td>
</tr>
<tr>
<td>Japanese Ministry of Health, Labour, and Welfare</td>
<td>Lipase</td>
<td>Not set</td>
</tr>
<tr>
<td>Working Group of the Italian Association for the Study of the Pancreas</td>
<td>Lipase</td>
<td>Not set</td>
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<td>URL, upper limit of the reference interval.</td>
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Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes:* 82150, 83519, 83520, 83690, 84145, 86140

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Pancreatic Enzyme Testing for Acute Pancreatitis AHS – G2153


Pancreatic Enzyme Testing for Acute Pancreatitis AHS – G2153


Specialty Matched Consultant Advisory Panel review 5/2020

Medical Director review 5/2020.

Policy Implementation/Update Information

1/1/2019  New policy developed. BCBSNC will provide coverage for pancreatic enzyme testing for acute pancreatitis when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

8/27/2019  Reviewed by Avalon 2nd Quarter 2019 CAB. Added “Related Policies” section, minor revisions to policy guidelines and coding table removed from the Billing/Coding section of the policy. No change to policy intent. References updated. Medical Director reviewed 8/2019. (jd)

10/1/2019  Policy statement revised to read: BCBSNC will provide coverage for pancreatic enzyme testing for acute pancreatitis when it is determined the medical criteria or reimbursement guidelines below are met. Wording revised in When Covered section. “Medically Necessary”
changed to “Reimbursement is allowed…” Wording revised in the Not Covered section.
“Not Medically Necessary” changed to read “Reimbursement is not allowed…” Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.