Opinion

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The etiology of acute pancreatitis: caution on causation

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As the morbidity of acute pancreatitis continues to rise, establishing the etiology in order to prevent recurrence is important. While the myriad of causes of acute pancreatitis are listed in numerous chapters and review articles, most of the diagnoses are speculative at best, often based on a few case reports. Even when considering the most common causes of acute pancreatitis, alcoholism and gallstones, most patients with either alcoholism or gallstones will never suffer from acute pancreatitis. Desiring to establish a diagnosis, clinicians often order many unnecessary tests, make false claims and cause confusion that lead both patients and providers into false truths as to what caused the acute pancreatitis. At times patients are injured in the search of the underlying cause as unnecessary interventions, such as ERCP are performed. It is important for clinicians to understand the limits to our knowledge on the etiology of acute pancreatitis. It is best to consider the cause of acute pancreatitis as more elusive, with many causes likely merely contributory, and many obscure causes as simply false.

While the diagnosis of acute pancreatitis is relatively easy to establish in most patients by identifying two of the following three criteria:

1. Pain consistent with the disease,
2. Serum amylase and or lipase greater than 3times the upper limit of normal, and or
3. Imaging consistent with the disease, the etiology of acute pancreatitis often is difficult to establish.[1] Even though the most common causes of acute pancreatitis, alcohol and gallstones, seem so simple to establish in patients presenting with acute pancreatitis, there is marked confusion as to why some patients develop the disease and others do not when the factors are present.

For example, most patients with alcoholism, drinking far excess of 50grams per day will never develop acute pancreatitis. It is estimated that only 5-10% of persons consuming large amounts of alcohol will develop the disease. Moreover, binge drinkers do not develop the disease. As a person must drink for many years large quantities of alcohol on a daily basis prior to the development of acute pancreatitis, it appears that acute alcoholic pancreatitis is not acute at all.[2] There must be chronic damage to the organ before acute pancreatitis develops. This misnomer explains why we do not see college students in Emergency Rooms getting admitted with acute pancreatitis after heavy drinking. Alcohol is not a cause of acute pancreatitis in the absence of a chronically damaged pancreas.

Alcohol Acute Pancreatitis is a chronic disease. While the presentation may appear to satisfy the definition of acute pancreatitis, the organ must first be chronically damaged. Yet, despite all of our advanced biochemistry and imaging techniques, most patients with acute pancreatitis do not have any evidence of chronic pancreatitis on admission. Few patients have the classic findings of neither calcifications nor ductal dilatations.[3–5] Therefore, while the pathophysiology is clearly chronic in nature, the presentation of the disease is acute leaving clinicians falsely labeling the etiology as acute alcohol acute pancreatitis.

To complicate the issue further, it is becoming clear that alcohol alone is not the trigger for the disease. It appears that a complex interplay with multiple other factors, including genetics and tobacco are the true culprit leading to acute alcoholic pancreatitis. In the absence of these other factors, few patients develop pancreatic disease despite the consumption of large amounts of alcohol. This better explains the epidemiology and the reason few alcoholics develop the disease. The discovery of cationic trypsinogen mutations, CFTR mutations, SPINK, and variants of CTRC have provided gastroenterologists a greater insight into the nature of pancreatitis.

Therefore, when considering one of the most common causes of acute pancreatitis, it has become clear that blaming alcohol as a cause is too simplistic. Alcohol is a "contributory cause" working with many other factors. Many of these factors have not been identified. However, as research progresses, clinicians should look forward to a better understanding of causation, susceptibility, leading to treatments that target molecular differences.

While large gallstones (greater than 0.5cm) as an etiology is surrounded by less controversy and more evidence from a mechanical point of view as a cause of acute pancreatitis, most of the dozens of other causes of acute pancreatitis listed are merely speculative, including viruses, venoms, hypercalcemia, drugs, sphincter of Oddi dysfunction, pancreas divisum, etc. Similar to alcoholism, few patients with any of these disorders will develop the disease.

Consider drug-induced acute pancreatitis. It is claimed that as many as 5-10 percent of patients have drug induced acute pancreatitis. Yet, despite thousands of case reports in the literature identifying drugs as causing acute pancreatitis, most of the drugs studied show no difference between the drug and placebo in causing acute pancreatitis in large randomized trials or large pharmacoepidemiologic controlled trials. While some drugs such as 6-mercaptopurine and azathioprine

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have randomized trials showing an incidence of acute pancreatitis higher than placebo, the vast majority of drugs have been blamed as causing acute pancreatitis by poorly written speculative case reports.[6]

In the absence of gallstones or a history of alcoholism, the vast majority of patients have idiopathic acute pancreatitis. It is important for clinicians to accept the term "idiopathic", unknown or rising spontaneously. The complex jargon allows a physician to appear wise while admitting to the patient that the true cause is unknown. Similar to a patient with appendicitis or diverticulitis, when a clinician is asked "what caused my acute pancreatitis", most patients should be told, in the absence of gallstones and alcoholism, simply "I do not know". While patients should all have an ultrasound to rule out gallstones, a triglyceride level, and imaging in an older patient to rule out a mass, subjecting the vast majority of patients to extensive testing to determine the etiology is inappropriate. This is especially important in the area of advanced endoscopy. Many patients are injured as a result of ERCP in the search of the underlying cause of acute pancreatitis [7]. Patients with idiopathic acute pancreatitis should only be evaluated at centers of excellence focusing on pancreatic disease, providing advanced endoscopy services and a combined multidisciplinary approach. Even at these Centers, caution should be applied when considering ERCP. While pancreatologists use basic science and epidemiology to elucidate the underlying molecular contributory causes of acute pancreatitis, clinicians need to respect the complex nature of the etiology of acute pancreatitis and remember *primum non nocere*.

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