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Exocrine Pancreatic Insufficiency Following Acute Pancreatitis: True Association or EPIphenomenon?

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Exocrine pancreatic insufficiency (EPI) is caused by inadequate delivery of pancreatic digestive enzymes to the intestinal lumen, leading to maldigestion. While longstanding chronic pancreatitis (CP) is the most well known cause, EPI is also very common in patients with pancreatic malignancy, and in those who have undergone pancreatic resection for benign or malignant disease. Less commonly known are a number of additional conditions, which may also have EPI as a consequence (Table). One such condition is acute pancreatitis. While clinicians might recognize that EPI could develop after an episode of severe acute pancreatitis (AP) associated with significant pancreatic necrosis, it is becoming more apparent that EPI may occur even in those with less severe episodes of AP. The systematic review and meta-analysis published in this issue of *Digestive Disease and Sciences* (1) provides an estimate of the prevalence and predictors of EPI after AP.

Estimating the true prevalence of EPI following acute pancreatitis is difficult due to significant heterogeneity among relevant studies. Moreover, methods used to detect and measure EPI are extremely varied amongst studies, making it difficult to draw conclusions on the true prevalence of EPI. In this current systematic review and meta-analysis, Huang et al (1) were able to determine the pooled prevalence of EPI during the index hospitalization for AP and during follow-up, in contrast to the only other large-scale meta-analysis that was focused on EPI after AP, reported by Holleman et al, (2), that measured the prevalence of EPI following AP only during up to 36 months of follow up. Huang et al found the cumulative prevalence of EPI in all studies with AP was a rather shocking 62%, when including those with EPI at any point during the index hospitalization, much greater than the 27% prevalence reported in previous meta-analysis (2). Nevertheless, when comparing the prevalence of EPI in AP patients only after long term follow up, both analyses had very similar EPI prevalence rates (33% and 27% respectively), suggesting approximately a third of patients with acute pancreatitis will develop persistent EPI after discharge, still a startlingly high prevalence. Importantly, Huang demonstrated that the prevalence of EPI during the index attack of AP was approximately 2/3, implying a significant majority of

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patients with acute pancreatitis will have at least some degree of maldigestion during their initial hospitalization for acute pancreatitis. Interestingly, the pooled analysis demonstrated roughly half of the patients who developed EPI during the index AP attack will recover at least some exocrine function, implying either recovery of function of injured acinar cells or their regeneration (3). The analysis from Huang et al and the second meta-analysis suggests a paradigm shift towards understanding AP as a clinical condition that can have long-lasting consequences even without the development of obvious radiologic evidence of chronic pancreatitis such as pancreatic calcifications. The study also heightens the value of identifying EPI earlier in the course of an AP attack in order to ensure that adequate long-term monitoring of maldigestion can be established.

This then begs the question: is it possible to identify those patients most at risk for EPI after an attack of AP? The literature has already reached consensus on the pancreatic diseases most at risk for EPI: chronic pancreatitis (4), pancreatic cancer (5), and pancreatic resection. Cystic fibrosis, autoimmune pancreatitis, and diabetes can also result in EPI through several mechanisms (Table). Less is known regarding which patients need to be screened for EPI after an episode of AP. Both Huang and Holleman's studies, however, were able to conclude that alcohol-induced acute pancreatitis, severe pancreatitis (based on Atlanta Classification), and necrotizing pancreatitis were the highest predictors of EPI during long-term follow up (2), which conceptually seems logical since alcohol abuse and necrotizing pancreatitis both are followed by actual and functional loss of enzyme-releasing acinar cells and can impair the release of adequate amounts of pancreatic digestive enzymes (6). Surprisingly however, both analyses corroborate that even in patients with mild pancreatitis, a significant minority (25%) will go on to develop EPI.

The principal limitation in performing large meta-analyses such as these is significant heterogeneity among study designs and in the methods used to diagnose EPI. This is not unexpected, as there is no consensus regarding the most effective method of diagnosing patients with EPI, since a single accurate, reproducible, noninvasive, and simple diagnostic test has not yet been developed. Although many of the studies analyzed by the authors used traditional tests of pancreatic function that involved duodenal intubation, hormone injection, consumption of high fat diets, and prolonged stool collection, these tests are no longer readily available outside of research centers. Currently, the diagnosis of EPI is often achieved when identifying at-risk individuals through assessing symptoms of maldigestion (steatorrhea, weight loss, or inability to gain weight), and attempts at confirmation with clinical tests such as fecal elastase-1. Although attractive to use since stool concentrations are not affected by pancreatic enzyme replacement therapy (PERT) (7), fecal elastase-1 is relatively inaccurate. It is sensitive and specific for detecting patients with severe EPI, but not for milder forms of EPI (8), and can be confounded by dilution from stool liquid, although its negative predictive value is high. Thus, it is no surprise that Huang et al found a lower pooled prevalence of EPI in AP when fecal elastase-1 was used as the diagnostic test of choice (11%). In actuality, the incidence of EPI may be even higher than is suggested by Huang's analysis, highlighting the point that a number of patients may be underdiagnosed, and may have subclinical maldigestion.

The clinical impact of EPI is substantial due to impaired digestion mostly of fats and inadequate absorption of macro- and micronutrients (9), ultimately culminating in substantial weight loss, malnutrition, metabolic bone disease, and fat- soluble vitamin (A, D, E, K) deficiency (10). Since the risk of osteoporosis as a consequence of fat-soluble vitamin deficiency increases three-fold in patients with EPI secondary to chronic pancreatitis, periodic bone mineral density testing is recommended in this patient population (11). Moreover, one large cohort study found EPI to be a strong independent risk factor of mortality in patients with CP (12). Concurrently, the use of PERT in patients with EPI secondary to unresectable pancreatic cancer or pancreatic cancer surgery was associated with longer survival when compared with patients not receiving PERT (13–14). Unfortunately, the current literature suggests that many of these patients are underdiagnosed and undertreated, as demonstrated by a recent US-based study that reported that in patients with pancreatic cancer, only 2% had been tested for EPI, and 22% had received PERT, with only 5.5% receiving an effective dose) (15). The data clearly support the clinical burden associated with EPI, yet as a medical community we have not been able to adequately identify and treat patients with EPI even in known high-risk populations.

Huang's analysis enables the identification of another high-risk group, providing an opportunity to educate the medical community about the many clinical circumstances in which EPI may exist and require treatment, including but not limited to patients with CP, pancreatic ductal cancer, and most recently patients with AP due to alcohol use, smoking, autoimmune disease, and other causes. With these data, assessment of the relative risk of developing EPI is possible in many patient populations, and is particularly timely in an era where the internet and social media have encouraged patients to seek PERT for a wide variety of symptoms, some unrelated to EPI.

In conclusion, this analysis illuminates an underrecognized consequence of a clinical disease which is often thought of as "one and done". The systemic review and meta-analysis demonstrate the high prevalence of EPI in AP patients both during their initial hospitalization and in long term follow up. Although severe AP, alcohol-induced pancreatitis, and pancreatic necrosis were found to be the strongest predictors of developing EPI, even patients with milder AP developed a relatively high prevalence of EPI. The findings of both Huang and Holleman suggest that most patients with AP should be tested for EPI during the index hospitalization or shortly thereafter, a strategy that would facilitate the enrollment of at risk individuals into a surveillance program aimed at assessing the long-term effects of EPI with close monitoring. While the clinical benefit of treatment of AP-associated EPI with PERT is not known, evidence from other diseases associated with EPI strongly suggest it will be valuable

Future prospective studies are needed to assess the cost-effective ness of increasing testing for EPI, particularly since the morbidity and mortality associated with EPI is high. Randomized controls trials should be carried out to assess the benefit of PERT on AP, and if treatment can decrease the risk of developing long term EPI. Finally, developing simple diagnostic tests that can predict even mild EPI are needed and may allow for easier implementation of EPI screening in high-risk populations.

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Table:

Some of the causes of exocrine pancreatic insufficiency

Etiology	Frequency of EPI	Comments
Chronic pancreatitis	Dependent on etiology and duration of disease. Occurs in 30–50%	Usually requires loss of 90% of exocrine enzyme secretion. Most common in chronic pancreatitis due to genetic causes, alcohol, autoimmune, or smoking.
Cystic fibrosis	Nearly universal, from birth	
Pancreatic cancer	50–90%, depending on location	Most frequent with cancer of head of pancreas, with pancreatic ductal obstruction.
Pancreatic resection	Variable depending on operation	Most common with larger resections, most common after Whipple resection
Asynchrony after GI surgery	Roux-en-Y surgeries most common, including gastric bypass	While pancreatic enzyme secretion may be normal, inadequate mixing with food can cause maldigestion
Shwachman-Diamond and Johanson-Blizzard	EPI very common, but diseases are rare	Genetic syndromes usually detected in childhood
Acute pancreatitis	More common with more extensive necrosis and those	Can occur even in absence of necrosis, and may persist
	with alcohol or smoking as etiologies	
Diabetes	Reduced fecal elastase common, but EPI rare	Longstanding diabetes may produce pancreatic damage similar to chronic pancreatitis, termed “diabetic pancreatopathy”
Zollinger-lollinger-Ellison syndrome	EPI common, but condition quite rare	Acid denaturation of pancreatic enzymes