The Role of Endotherapy in Recurrent Acute Pancreatitis

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KEYWORDS

• Recurrent acute pancreatitis • Idiopathic pancreatitis
• Sphincter of Oddi dysfunction • Pancreas divisum • Endoscopic therapy
• Endoscopic sphincterotomy • Endoscopic stent placement

KEY POINTS

- Recurrent acute pancreatitis (RAP) is a significant cause of morbidity and mortality as well as a risk factor for the development of chronic pancreatitis.
- Endoscopic interventions have variable efficacies depending on the type of procedure and cause of RAP. To date, few long-term, prospective, randomized controlled trials assessing response rates to endotherapy have been conducted.
- Although endotherapy plays an important role in the management of RAP, whether or not endoscopic intervention truly alters the natural history of this disease remains unclear.

INTRODUCTION

Acute pancreatitis (AP) and chronic pancreatitis (CP) were originally described according to the Marseille Classification as 2 separate, well-defined clinical entities.[1] Mounting evidence now suggests that they can be opposite ends of a disease continuum with recurrent AP (RAP) being an intermediate transition stage.[2] AP is an acute inflammatory condition of the pancreas typified by epigastric pain, increased serum amylase or lipase level, and imaging consistent with pancreatitis. RAP is defined as 2 or more distinct episodes of AP with complete resolution of symptoms between episodes and no evidence of CP. AP has an incidence of 40 to 50 per 100,000 per year in the United States[3] and, among gastrointestinal diseases, is the most common indication for hospitalization, accounting for more than 250,000 annual admissions.[4] Although most cases of AP are self-limited and resolve without complication, a 2015 meta-analysis showed that, after a sentinel AP event, 22% of patients develop at least 1 episode of recurrence and 10% develop CP. Among those with RAP, 36% develop CP.[5] Given the significant morbidity and mortality associated with CP,

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interventions designed to eliminate recurrent episodes and prevent progression in these high-risk patients with RAP are critical to reducing health care costs and patient suffering. However, management options are limited. Although endoscopic therapy has provided a means to address biliary, obstructive, congenital, and functional causes of RAP via sphincterotomy and pancreatic stent placement, there is variable evidence supporting the efficacy of these interventions and their ability to alter the natural history of disease. This article discusses the current literature on the role of endotherapy in managing RAP with a focus on high-quality prospective randomized controlled studies.

RECURRENT ACUTE PANCREATITIS AND ITS NATURAL HISTORY

RAP is an incompletely understood and controversial clinical syndrome that is often misdiagnosed. By definition, patients must have 2 or more true episodes of pancreatitis in order to receive this diagnosis, which requires at least 2 of the following criteria: typical pancreatic pain, increased serum amylase and/or lipase level 3 times normal, and cross-sectional imaging findings supportive of inflammation. Patients with pain not severe enough to require hospitalization, those with only mild hyperenzymemia and no imaging findings, or those with only mild imaging abnormalities and normal laboratory tests may instead be more accurately classified as having abdominal pain without pancreatitis or sphincter of Oddi dysfunction (SOD) type 2 or 3. Symptom overlap between RAP and CP makes definitive diagnosis challenging. Patients presenting with an acute attack may either be having a true episode of recurrence or an acute-on-chronic flare with minimal imaging findings of CP. Alternatively, it is also possible for acute post pancreatitis changes to be mistaken for evidence of chronicity.

In addition to variable diagnosis, determining the cause of RAP remains challenging. Risk factors for RAP are numerous and are best summarized under the TIGAR-O (toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, obstructive) classification.[6] Failure to address any one of these factors after an initial AP episode may result in recurrence. Moreover, RAP is likely multifactorial and addressing one cause may not remediate another contributing factor, such as an underlying genetic mutation.[7] Preliminary testing in RAP reveals a cause in 70% to 80% of cases and advanced testing with endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) identifies another 10% to 15%, but in nearly 10% of cases no cause is discovered and these are termed idiopathic.[7] Patients with idiopathic RAP (IRAP) thus have no definite cause to intervene on and are left with few treatment options (**Table 1**).

The natural history of RAP is also poorly defined. In general, patients with RAP may cease to have recurrent episodes, continue to have symptom recurrence with no pathologic changes characteristic of CP, or continue to have attacks with progression to CP. Thirty-six percent of patients with at least 1 recurrence develop CP,[5] but not all of these patients have the same risk of progression. Subgroups within this high-risk group of patients may be stratified according to cause. Gallstone disease, which accounts for 10% to 30% of RAP cases,[3] is readily addressed after standard evaluation for an initial AP episode. Cholecystectomy dramatically reduces the risk of recurrence with delayed time to operation resulting in increased risk reduction in severe cases.[8,9] Alcohol abuse is the most common cause of RAP, with continued drinking at the same level tied to a 58% risk of recurrence and a 41% risk of progression to CP. Abstinence reduces this risk to a 20% and 13% risk of recurrence and progression, respectively.[10] A randomized controlled trial assessing the efficacy of abstinence programming on