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Strategies for the Treatment of Pancreatic Pseudocysts and Walled-Off Necrosis After Acute Pancreatitis: Interventional Endoscopic Approaches

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Introduction

A series of trials following improvements in intensive care medicine and endoscopic techniques has led to a paradigm shift in the management of fluid collections developing after an attack of acute pancreatitis: if undertaken at all, interventions should be delayed as much as possible and the least-invasive method should be considered first, before escalating treatment (step-up approach) [1–3]. Intervening a post-acute pancreatic fluid collection (PFC) endoscopically is considered safe once a well-defined wall, then called WOPN (walled-off pancreatic necrosis) has developed, roughly 4 weeks into the disease course [4]. Immediate drainage of infected fluid collections is not superior to a delayed approach and with adequate antibiotic treatment, invasive procedures can often be avoided, as demonstrated by a Dutch multicenter trial (POINTER) [5]. Post-acute pancreatic pseudocysts are considered a rare complication arising from a disruption of the main pancreatic duct or major duct branches without considerable necrosis and by definition contain only fluid rich in pancreatic enzymes. In contrast, collections with a fibrous wall originating from pancreatic and/or peripancreatic necrosis are called walled-off pancreatic necrosis (WOPN), which will contain variable amounts of solid debris and may reach into areas distant from the gland [6].

Indications for Endoscopic Treatment

In general, only collections that cause symptoms or are at a high risk for severe complications require intervention. Indications for endoscopic intervention are features of infection on imaging or a high suspicion for infection with persistent signs of sepsis that do not improve under

adequate antimicrobial treatment. Less common indications are pain, persistent unwellness, and failure to thrive, jaundice caused by the collection compressing the bile duct, bleeding and arterial pseudoaneurysms, disconnected duct syndrome, gastric outlet obstruction, or pancreatic fistulas.

Endoscopic Drainage vs. Necrosectomy: Choosing the Right Patient

It is currently unclear which collections will improve spontaneously or with conservative management, which require drainage, which need irrigation, and for which collections should a patient undergo advanced endoscopic necrosectomy, as reflected by discordant results of a recent international expert survey [4]. In many cases, patients will initially improve after a drainage procedure and optional nasocystic lavage with few plastic pigtail stents in place to ensure the patency of the tract. A systematic review and meta-analysis comparing 324 patients who underwent conservative management of infected pancreatic necrosis with 157 who underwent necrosectomy concluded that conservative management was successful in 64% and that mortality was lower than in patients who underwent percutaneous treatment [7] although this result is fraught by significant selection bias. Multiple early case series that included pancreatic necrosis and pancreatic abscesses even reported full resolution of these collections without further necrosectomy in over 80% of cases [8–10]. Unfortunately, a nonuniform nomenclature impairs the comparability of these observations. These findings are supported by a recently published Dutch multicentre trial [5]. Between 2015 and 2019, 104 patients with infected pancreatic necrosis occurring within 35 days from onset of symptoms were

randomized to either receive immediate percutaneous or endoscopic drainage with optional necrosectomy or a delayed approach with antibiotic treatment first and escalation to drainage and necrosectomy only if clinical deterioration occurred. The median time difference to first invasive procedure between the treatment arms was 10 days and there was no difference with regard to complications, organ failure, or death. Patients in the delayed treatment arm had considerably fewer invasive procedures and were less often taken to necrosectomy. Notably, 39 % of patients in the delayed treatment arm did not require any invasive procedures at all, suggesting that immediate drainage, especially before encapsulation of a necrotic collection, is not generally beneficial.

However, in patients who do not improve on conservative treatment alone or whose recovery stalls at a certain level, the question remains, how soon should one move from drainage to necrosectomy. A Swedish trial comparing drainage of pseudocysts to pancreatic abscesses with variable amounts of debris showed that the rate of successful drainage was lower in abscesses (94% vs. 80%; $P=0.04$) and the risk for complications five times higher ($P=0.02$). Of note, all abscesses underwent necrosectomy and lavage later [11]. This suggests that in patients with a higher burden of necrotic material and/or infected collections a more invasive approach may be warranted. The amount of solid debris is best assessed by EUS or MRI.

Transmural endoscopic necrosectomy has been shown to be a safe and efficient way to deal with necrotic collections accessible to endoscopy. It is equally safe and effective when compared to minimally invasive surgical approaches, but appears to be more cost-effective and leads less often to pancreatic fistulas [3,12]. It remains burdened, however, with serious complications even in the hands of experienced investigators [13–16]. In a retrospective comparison of conventional transmural drainage versus necrosectomy in patients with evidence of WOPN on contrast-enhanced computed tomography (CT), Gardner et al. showed superiority of direct necrosectomy in terms of treatment success, need for surgery or additional percutaneous drainage, and recurrence [17]. Another registry-based, matched cohort study comparing direct necrosectomy to initial percutaneous access as suggested by the original “step-up approach” in 12 patients showed favorable outcomes for the direct endoscopic approach [18]. Taken together, the current data suggest that mere endoscopic drainage is reasonable and often sufficient in defined collections with minimal amounts of solid material, whereas patients with WOPN and more extensive necrotic material will most likely profit from sometimes repeated sessions of endoscopic removal of necrotic tissue [19]. In unstable patients who develop sepsis due to infected WOPN requiring

ventilator support and vasopressors, an initial endoscopic or even percutaneous drainage to achieve sepsis control and delayed more advanced endoscopic necrosectomy may be more appropriate. Endoscopic drainage is generally preferred over percutaneous drainage for infected fluid collections, but if drainage is required before a fibrous wall has formed (generally 4 weeks) percutaneous drainage is still a valid and frequently used alternative.

The introduction of through the scope, electrocautery-enhanced deployment devices for fully covered self-expandable lumen-apposing metal stents (LAMS), which allow efficient endoscopic drainage as well as necrosectomy through the same access route, have replaced the use of conventional double-pigtail stents for treatment of WOPN in many centers. Placement of LAMS is faster and comes at lower risk for stent dislocation and rupture of the wall of the collection. However, they bear a considerable risk for stent migration and delayed bleeding if left in place for more than 3 weeks (32.3% vs. 6.9%, $P=0.01$) [20] and despite the larger diameter, they are not more effective with regard to resolution of WOPN when compared to conventional pigtails [21].

Due to shorter procedure duration for the initial placement and the option of through-the-stent necrosectomy, many centers now use a dual approach: LAMS are used initially to allow for effective large-bore drainage and if needed endoscopic necrosectomy, but will be replaced by multiple pigtail stents later, when collections can be managed in an outpatient setting.

Preventing Recurrence by Treating Disconnected Duct Syndrome

A disconnected pancreatic duct with pancreatic juice leaking into the connected PFC is a major complication of acute pancreatitis and a well-known risk factor for persistence or recurrence of PFC. This includes pseudocysts and WOPN, even after initially successful endoscopic treatment [22,23]. The integrity of the pancreatic duct should therefore be confirmed whenever pancreatic necrosis requiring an intervention is present and preferably by noninvasive methods such as magnetic resonance cholangiopancreatography (MRCP). Although found in up to 50% of patients with acute necrotizing pancreatitis, studies on the optimal management of PFC associated with disconnected pancreatic duct syndrome are scarce. A small randomized controlled trial ($n=28$) recruiting patients with and without disconnected pancreatic duct showed a significant reduction of recurrence (0 vs. 5, $P=0.013$) when transmural stents were not removed [24]. The approach of long-term indwelling plastic stents has been adopted for the treatment of WOPN with disconnected pancreatic duct syndrome as reported in two

retrospective series including 26 and 33 patients, respectively, in which it appears to have led to a satisfactory outcome with regard to resolution of the collection [25,26]. Another approach involves stenting the pancreatic duct after transmural access and cavity stenting is established. This allows transpapillary drainage of both the content of the connected collection and, more importantly, pancreatic juice away from vital pancreatic tissue distal to the duct disruption [27]. ERCP should be performed with caution in these patients as it is associated with considerable rates of adverse events [28]. A small preliminary study by a group from Mumbai, India described a promising strategy in 42 patients with symptomatic post-acute pancreatic pseudocysts. Three weeks after initially successful drainage using an expandable covered nitinol stent, the patients underwent MRCP. A pancreatic duct leak was detected in three patients and treated successfully by stenting the pancreatic duct with consecutive

retrieval of the transmural stent [29]. A larger retrospective study including 375 patients from the USA with different types of PFC compared the treatment success after transmural treatment alone with combined transmural and transpapillary access with no difference in long-term resolution (69% vs. 62%; $P=0.61$). The presence of duct disruption was not routinely investigated [30]. It is due to these shortcomings in study design and the lack of prospective data that the optimal treatment of disconnected duct syndrome is still unknown, as highlighted by two recent meta-analyses [31,32]. Subject to the significant heterogeneity of the studies included, transpapillary drainage has so far not been shown to be superior to transmural approaches, but combination strategies or step-up management as suggested by Dhir et al. have not been studied. Of note, also surgical treatment such as cystgastrostomy or distal pancreatectomy are a viable option in selected cases.

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