Introduction

Pancreatic fluid collection (PFC) is a frequent complication of pancreatitis. It is estimated that 5-15% of pancreatitis episodes are complicated by development of pseudocysts[1]. Fifteen percent of pancreatitis episodes are complicated by pancreatic necrosis, and approximately 33% (range 16-47%) of those with necrosis are complicated by infected necrosis[2]. Management of these collections can pose a challenge. Traditionally, the management has primarily been surgical. However, with new understanding of the pathophysiology paired with new technological advancements, the pendulum has swung towards an emphasis on a minimally invasive approach with a progression to more invasive options as necessary.

Classification of pancreatic fluid collections

Correctly classifying PFCs is critical for optimizing treatment and management. The first widespread classification system was developed in 1993 by an international consensus meeting in Atlanta, Georgia and became referred to as the Atlanta Criteria [3]. This criteria classified pancreatic fluid collections as acute or chronic collections, with chronic collections being further divided into pancreatic necrosis, pseudocysts, and pancreatic abscesses.

However, with improving pathophysiologic understanding and improving diagnostic tools, it became clear that a more detailed organizational system was required. More specifically, distinguishing between collections containing fluid alone versus those arising from necrosis and/or containing solid components. As such, a new classification system was developed known as the revised Atlanta criteria[4]. Similar to the original Atlanta Criteria, PFCs are classified as acute (<4 weeks after the pancreatitis episode) or chronic (>4 weeks after the pancreatitis episode). However, in the revised criteria, both acute and chronic collections are further subdivided based on the presence of necrosis within the collection. Acute collections are divided into: acute peripancreatic fluid collections (APFC) and acute necrotic collections (ANC); chronic fluid collections are divided into; pseudocysts or walled-off pancreatic necrosis (WOPN). These new classifications are important because the treatment and management varies depending on the type of collection.
Indications for drainage of PFCs

In the initial Atlanta criteria, PFCs were recommended for drainage based on the presence of symptoms and/or complications such as abdominal pain, gastrointestinal obstruction, vascular compression, biliary obstruction, or infection, as well as on the size of the collection. However, in the revised criteria, size alone does not necessitate treatment; only symptomatic PFCs are recommended for drainage. Historically, drainage has been managed via surgical techniques. But with the advent of newer and more advanced endoscopic tools and expertise, and an associated reduction in health care costs, minimally invasive endoscopic drainage has become the preferable approach.

Management of walled off pancreatic necrosis (WOPN)

Walled off pancreatic necrosis (WOPN) is a PFC that contains solid necrotic debris surrounded by a clearly defined capsule with or without concurrent fluid[4]. Although a small percentage of WOPN will resolve spontaneously, the majority of collections will require drainage.

1. Surgical drainage

Open surgical debridement has historically been the therapy for WOPN[5,6]Surgical management consists of 4 principal approaches, all involving accessing the pancreatic bed but differing in the surgical approach. The standard approaches include access via the lesser sac, the gastrocolic-omentum, or trans-mesenterially through the transverse mesocolon [7]. Once the necrosectomy has been performed, the options are (1): necrosectomy alongside open packing [8]; (2) planed, staged re-laparotomies with repeat lavage [9]; (3) closed continuous lavage of the lesser sac and retro-peritoneum [6]; and (4) closed packing [10].

Open necrosectomy is associated with high morbidity (34% to 95%) and mortality (6% to 25%) rates[11-16], and a plethora of adverse events including organ failure, perforation, wound infections, hemorrhage, chronic pancreatico-cutaneous and entero-cutaneous fistulae, and abdominal wall hernias [5,7, 10, 12, 13].

With the development of laparoscopic surgery, minimally invasive procedures supplanted open debridement as the surgical option of choice. Laparoscopic debridement can be performed using 2 approaches: trans-peritoneal (anterior) or retroperitoneal (posterior) [6]. The trans-peritoneal approach involves an anterior access through the stomach or the bowel to drain the collection. The retroperitoneal approach uses a mini-lumbotomy, usually left-sided, through which a laparoscope is introduced to remove the necrotic debris under direct visualization. Currently, the trans-peritoneal approach is rarely used due to increased technical difficulty and the risk of contamination of the peritoneal cavity [17]. Additionally, a retroperitoneal approach can be performed with minimal or no gas insufflation and avoids the complications associated with severing the peritoneum [13,14].
Table 1. Fully-Covered Self-Expanding Metal Stents for WOPN

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Type of Stent</th>
<th>Cyst Resolution Rate</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabbri et al</td>
<td>2012</td>
<td>2</td>
<td>Wallflex</td>
<td>50% (n=1)</td>
<td>50% (n=1)</td>
</tr>
<tr>
<td>Berzosa et al</td>
<td>2012</td>
<td>2</td>
<td>Viabil</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Antillon et al</td>
<td>2009</td>
<td></td>
<td>Esophageal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarkaria et al</td>
<td>2014</td>
<td>17</td>
<td>Esophageal</td>
<td>88%</td>
<td>17-Feb</td>
</tr>
<tr>
<td>Attam et al</td>
<td>2014</td>
<td>10</td>
<td>Esophageal</td>
<td>90%</td>
<td>10-Mar</td>
</tr>
<tr>
<td>Shah et al</td>
<td>2014</td>
<td>11</td>
<td>Axios</td>
<td>11-Oct</td>
<td></td>
</tr>
<tr>
<td>Walter et al</td>
<td>2015</td>
<td>46</td>
<td>Axios</td>
<td>81%</td>
<td>9%</td>
</tr>
</tbody>
</table>

2. Percutaneous drainage

Percutaneous drainage for WOPN involves placement of a catheter into the collection under US guidance with fluoroscopy or CT guidance. Ideally, a retroperitoneal approach is taken. After placement and aspiration of as much fluid as possible, 12French drains are left in place and irrigated with 10–20 mL of sterile saline 3 times daily. The catheters can be upsized to a maximum of 28French as the patient’s follow-up requires [15].

Traditionally, the success rate of percutaneous drainage alone (defined as survival without the need for additional surgical necrosectomy) ranged from 35% - 84%, with mortality rates ranging from 5.6% - 34% and morbidity ranges of 11% - 42%, most commonly due to pancreatico-cutaneous fistulas and pancreatico-enteric fistulas which occur in as many as 20% of cases [16–20]. Consequently, percutaneous drainage is more often used as an adjunct therapy, often serving as the first step of a step-up approach to endoscopic or surgical drainage [5,16,21–25]. The Dutch PANTER trial illustrated this concept by comparing open necrosectomy with a less-invasive step-up approach in 88 patients [26]. In the step-up approach, patients first underwent percutaneous drainage of the collection followed by minimally invasive retroperitoneal necrosectomy if clinical improvement was not achieved. Results showed that the minimally invasive approach was associated with an overall decreased mortality rate, fewer major and long-term complications, and reduced overall healthcare costs. Of note, percutaneous drainage alone without subsequent necrosectomy was achieved only in 30% of patients.

3. Endoscopic necrosectomy

The endoscopic technique for drainage of WOPN is called direct endoscopic necrosectomy (DEN). As in pseudocyst drainage, EUS is used to identify and access the collection, a wire is coiled within the cavity lumen, and the fistulous tract is created. However, unlike pseudocyst drainage, the tract is then dilated enough to allow for passage of an endoscope into the collection. Mechanical cleaning with removal of necrotic debris is then performed.

Nasocystic drainage is typically performed to facilitate liquefaction of the debris and improve drainage.

The first experiences with endoscopic necrosectomy were done through the deployment of plastic stents and placement of a nasocystic drain without direct mechanical debridement. This was first described by Baron et al in 1996[27], in which 11 patients underwent WOPN drainage with an overall success rate of 81% and a complication rate of 36% (bleeding and infection). Papachristou et al reported similar findings in 2007 in a study of 53 patients, with an overall success rate of 81% and a complication rate of 21%[28]. Subsequent studies reported similar findings, with success rates ranging from 75% - 95%, and complication rates ranging from 0 to 35% .

Seewald et al introduced the concept of dilation of the fistulous tract to allow for advancement of an endo-
Table 2. Endoscopic Therapy for Pancreatic Necrosis

<table>
<thead>
<tr>
<th>Primary Author</th>
<th>Patients (n)</th>
<th>Infected (%)</th>
<th>Mortality (%)</th>
<th>Success, n (%)</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron</td>
<td>11</td>
<td>27</td>
<td>0</td>
<td>9 (81%)</td>
<td>Bleeding (9%), Infection (36%)</td>
</tr>
<tr>
<td>Seewald</td>
<td>13</td>
<td>100</td>
<td>7.7</td>
<td>11 (85%)</td>
<td>Bleeding (31%)</td>
</tr>
<tr>
<td>Charnley</td>
<td>13</td>
<td>85</td>
<td>0</td>
<td>12 (92%)</td>
<td>None</td>
</tr>
<tr>
<td>Papachristou</td>
<td>53</td>
<td>49</td>
<td>0</td>
<td>43 (81%)</td>
<td>11 (21%), Bleeding, n = 9</td>
</tr>
<tr>
<td>Voermans</td>
<td>25</td>
<td>100</td>
<td>0</td>
<td>23 (93%)</td>
<td>Major bleeding (4%), minor bleeding (30%)</td>
</tr>
<tr>
<td>Escourrou</td>
<td>13</td>
<td>100</td>
<td>0</td>
<td>11 (85%)</td>
<td>Bleeding (n=3), sepsis aggravation (n=3)</td>
</tr>
<tr>
<td>Navaneethan</td>
<td>8</td>
<td>50</td>
<td>12.5</td>
<td>7 (87.5%)</td>
<td>Perforation of cyst wall (12.5%)</td>
</tr>
<tr>
<td>Schrover</td>
<td>8</td>
<td>100</td>
<td>12.5</td>
<td>6 (75%)</td>
<td>Bleeding (n=1), Perforation (n=1)</td>
</tr>
<tr>
<td>Matthew</td>
<td>6</td>
<td>100</td>
<td>0</td>
<td>5 (83.3%)</td>
<td>None</td>
</tr>
<tr>
<td>Hocke</td>
<td>19</td>
<td>100</td>
<td>10.5</td>
<td>17 (89%)</td>
<td>10%, bleeding, perforation, fistulation</td>
</tr>
<tr>
<td>Coelho</td>
<td>36</td>
<td>69</td>
<td>5.5</td>
<td>30 (83%)</td>
<td>Bleeding (n=2)</td>
</tr>
<tr>
<td>Gardner</td>
<td>25</td>
<td>24</td>
<td>0</td>
<td>22 (88%)</td>
<td>Bleeding (32%)</td>
</tr>
<tr>
<td>Seifert</td>
<td>93</td>
<td>100</td>
<td>7.5</td>
<td>75 (80%) initial 63 (85%) long term</td>
<td>24 (26%); bleeding (n=13), perforation (n=5), fistulae (n=2), air emboli (n=2), 2 other organs</td>
</tr>
<tr>
<td>Varadarajulu</td>
<td>12</td>
<td>NS</td>
<td>0</td>
<td>11 (92%)</td>
<td>None</td>
</tr>
<tr>
<td>Gardner</td>
<td>104</td>
<td>NS</td>
<td>2</td>
<td>95 (91%)</td>
<td>14%; retrogastric perf/pneumoperitoneum (n=5), infection (n=4), bleeding (n=3)</td>
</tr>
<tr>
<td>Will</td>
<td>18</td>
<td>100</td>
<td>0</td>
<td>17 (94%)</td>
<td>Bleeding (n=2), Cardiac arrhythmia (n=1)</td>
</tr>
<tr>
<td>Bakker</td>
<td>10</td>
<td>100</td>
<td>10</td>
<td>9 (90%)</td>
<td>Pancreatic fistula (n=1)</td>
</tr>
<tr>
<td>Jurgensen</td>
<td>35</td>
<td>54</td>
<td>15</td>
<td>33 (94%)</td>
<td>Bleeding (n=3), pulmonary aspiration (n=1)</td>
</tr>
</tbody>
</table>

scope into the necrotic cavity and mechanical removal of debris[29]. They described a 91% WOPN resolution rate in 13 patients, with 2 patients having recurrence on 4 month follow-up necessitating surgical resection. Voermans et al documented a 93% success rate in 25 patients, with only 2 patients requiring surgical intervention for bleeding and perforation[30]. Smaller studies by Escourrou et al [31] and Charnley et al [32] found similar results.

The first multicenter study evaluating endoscopic necrosectomy was performed by Seifert et al [33]. In this study of 93 patients, an 80% clinical success rate was achieved with a 23% complication rate and 7.5% mortality rate. A second multicenter study was published by Gardner et al in 2011[34] looking at 104 patients with WOPN. Successful resolution was achieved in 91% of patients, with a complication rate of 14% including 3 patients requiring surgical intervention either for bleeding or failed resolution, 5 patients dying of other causes prior to WOPN resolution, and 1 peri-procedural death due to hypotension.

4. Fully-covered self-expanding metal stents

Biliary FCSEMS provide a larger stent lumen for drainage of WOPN, but are limited in that they do not permit passage of an endoscope. Fabbri et al published results of 2 patients with WOPN drained with biliary FCSEMS (Wallflex, Boston Scientific)[35]. In 1 patient, the WOPN completely resolved; in the second patient, the stent migrated leading to widespread sepsis and need for surgical intervention.

Esophageal FCSEMS have a larger lumen diameter and allow for passage of the endoscope through the lumen
of the stent after deployment. The first reported case of WOPN drainage using an esophageal FCSEMS was published by Antillon et al [36]. Sarkaria et al published results of 17 patients who underwent WOPN drainage with placement of an esophageal stent, 88% of whom demonstrated complete resolution with an average of 5 endoscopic sessions and 2 of whom ultimately required surgical intervention[37]. No major complications were reported. Attam et al found similar results in 10 patients using a through-the-scope esophageal FCSEMS in which resolution was achieved in 90% of patients after an average of 3 endoscopic sessions[38]. 2 patients required stent revision due to persistent infection in long-term follow-up, and 1 patient died of gastrointestinal bleeding from a pseudoaneurysm. Esophageal FCSEMS are a promising concept in the endoscopic management of WOPN. However, the development of lumen apposing metal stent will probably surplant the utilization of esophageal FCSEMS.

5. A novel lumen-apposing metal stent (LAMS)

The previously mentioned LAMS (Axios, Xlumena) also allows for passage of an endoscope through the lumen of the stent into the cavity for mechanical necrosectomy. Only a small number of studies have been published specifically evaluating the use of LAMS for drainage of WOPN. Shah et al achieved WOPN resolution in 10 of 11 patients using a LAMS for drainage[39]. The largest clinical experience comes from Walter et al in which they looked at 46 patients with WOPN[40]. They reported a clinical success rate of 81%, with an overall major complication rate of 9%, due to infection from stent occlusion, all managed endoscopically with only 3 patients ultimately requiring surgical intervention for persistent infection. Additional multi-center studies are needed, but LAMS represent a promising advance in the endoscopic management of WOPN.

Cumulatively, these studies illustrate that while endoscopic necrosectomy is efficacious, it is a complicated procedure requiring a high-level of skill in endoscopy with complications occurring even in the most experienced of hands and requiring the presence of a strong multi-disciplinary team to be successful. The incorporation of metal stents that allow for a large drainage lumen and the advancement of an endoscope through the stent lumen for DEN is a major advance, which may ultimately improve efficacy and decrease complications associated with these procedures.

6. Endoscopy versus percutaneous or surgery drainage

A recent randomized multicenter trial from 2012 directly compared endoscopic necrosectomy and surgical necrosectomy (video-assisted retroperitoneal debridement with open laparoscopic necrosectomy for rescue) in 22 patients [41]. Their results showed that endoscopic therapy was associated with a lower post-procedure inflammatory response (as demonstrated by interleukin levels), a lower complication rate, fewer pancreatic fistulæ developments, and less pancreatic enzyme use on 6 month follow-up. A more recent from 2014 directly compared a step-up approach starting with percutaneous drainage and escalating to more invasive therapy as needed to DEN in 24 patients[42]. Their results demonstrated a resolution rate of 92% versus 25% in the necrosectomy versus percutaneous drainage group, with 9 of 12 patients requiring surgery after percutaneous drainage alone. Additionally, less antibiotic use, pancreatic insufficiency, and hospitalization was seen in the endoscopic necrosectomy group.
**Take Home Points**

- Infected WOPN should be debrided endoscopically whenever feasible using newly approved FCSEMSs that allow for direct endoscopic necrosectomy and debridement through the stent lumen.
- When not accessible endoscopically, WOPN should be managed in a step-up approach using percutaneous approach followed by surgical or endoscopic debridement as necessary.

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**Ercp for pancreatic duct exploration**

An important component in the management of PFCs is ensuring the integrity of the pancreatic duct (PD) via ERCP. Disruptions in the PD are associated with an increased severity of pancreatitis, an increased risk of recurrent attacks of pancreatitis and long-term complications, and a decreased rate of PFC resolution after drainage [43-47].

1. **PD disruption and severity of pancreatitis**

   A PD disruption has been shown to be associated with a more severe course of pancreatitis. A retrospective review of 105 patients with acute pancreatitis found that nearly half of patients with severe pancreatitis had concurrent PD disruption, while a normal PD was noted in 100% of patients with mild pancreatitis [43]. Similarly, in a retrospective review of 144 patients with severe pancreatitis, Lau et al found that patients with a PD leak were 3.4 times more likely to have pancreatic necrosis [47]. Thus, assessing for a PD disruption in patients with pancreatitis is an important prognosticating step.

2. **PD disruption and recurrent pancreatitis / long-term complications**

   In addition to predicting the severity of pancreatitis, a PD disruption can also predict the likelihood of long-term complications and recurrent episodes of pancreatitis. Howard et al looked at 14 patients with WOPN who developed recurrent pancreatitis after initially-successful debridement, and found that all 14 patients had a pancreatic duct abnormality on either ERCP or MRCP [44]. No other predictive factor of recurrence was identified. Nealon et al demonstrated that in 174 patients with severe pancreatitis, long-term complications such as sepsis and recurrent pancreatitis occurred in 36-38% versus 0% and 62-89% versus 7% of patients with an abnormal PD compared to those with a normal PD [45].

3. **PD disruption and pfc resolution**

   Assessing for PD disruptions can also predict treatment success. In the same study as above mentioned, Nealon et al demonstrated that altered PD anatomy is directly correlated with a decreased rate of pseudocyst resolution [45]. In 563 patients with pseudocysts, they found that spontaneous resolution occurred only in 0-5% of patients with a ductal disruption compared to 87% of patients with a normal pancreatic duct. Similarly, Trevino et al demonstrated improved PFC resolution in both pseudocysts and WOPN in patients who underwent PFC drainage with transpapillary PD stenting compared with PFC drainage alone (97.5% vs 80%) [46]. Of note, undergoing ERCP was not associated with any increase in mortality, the need for necrose-
Pancreatitis can frequently result in the development of fluid collections, ranging from simple pseudocysts to WOPN. Endoscopic drainage can be successfully accomplished with improved safety and efficacy as compared to surgical or radiologic approaches. Patients with WOPN can safely undergo endoscopic necrosectomy, obviating the need for surgical exploration. Lastly, ERCP with PD exploration should be concurrently performed to evaluate for evidence of PD disruption in all patients with PFCs. In summary, all forms of PFC can be safely and effectively managed by a variety of endoscopic procedures.

References