# ADVANCES IN PANCREATIC NECROSECTOMY

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Medicine by

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ANC** | Acute necrotic collection |
| **APA** | American Pancreatic Association |
| **APFC** | Acute pancreatic fluid collection |
| **BFMS** | Bi-flanged metal stent |
| **CCA** | Cost consequence analysis |
| **CNST** | Clinical Negligence Scheme for Trusts |
| **CRP** | C reactive protein |
| **CT** | Computed tomography |
| **CTSI** | CT severity index |
| **DPS** | Double pigtail stent |
| **EN** | Endoscopic necrosectomy |
| **EUS** | Endoscopic ultrasound |
| **FCSEMS** | Fully covered self-expanding metal stent |
| **HRG** | Healthcare resource group |
| **IAP** | International Association of Pancreatology |
| **IQR** | Interquartile range |
| **ITU** | Intensive therapy unit |
| **LAMS** | Lumen apposing metal stent |
| **MARPN** | Minimal access retroperitoneal pancreatic necrosectomy |
| **MDT** | Multi-disciplinary team |
| **MOF** | Multi-organ failure |
| **MRCP** | Magnetic resonance cholangiopancreatography |
| **NCEPOD** | National Confidential Enquiry into Patient Outcome & Death |
| **NICE** | National Institute for Health and Care Excellence |
| **OPN** | Open pancreatic necrosectomy |

| | |
|---|---|
| **PCD** | Percutaneous drain |
| **PFC** | Pancreatic fluid collection |
| **PLICS** | Patient level information and costing systems |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **QALY** | Quality Adjusted Life Year |
| **RCT** | Randomised controlled trial |
| **RR** | Risk ratio |
| **SILS** | Single incision laparoscopic surgery |
| **SIRS** | Systemic inflammatory response syndrome |
| **SMV** | Superior mesenteric vein |
| **SPRPN** | Single-port retroperitoneal pancreatic necrosectomy |
| **VARD** | Video-assisted Retroperitoneal Debridement |
| **WON** | Walled off necrosis |

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## ABSTRACT

**Advances in pancreatic necrosectomy**

**Rebecca Saunders**

Acute pancreatitis is a common inflammatory disorder of the pancreas that accounts for approximately 100 admissions per year per hospital within the UK. The majority of patients with acute pancreatitis can be managed by non-operative treatment, however some patients progress to severe acute pancreatitis and the complications associated with this. Local complications include the development of pancreatic fluid collections; acute pancreatic fluid collections, pseudocysts, acute necrotic collections or walled off necrosis, classified by the contents of the collection and the time post onset of acute pancreatitis. Approximately 20% of patients develop pancreatic necrosis, with infection occurring in 30-40% of these cases. The mortality associated with necrotising pancreatitis is significant at 15% and rising to 30% for infected pancreatic necrosis. Patients with infected pancreatic necrosis may require intervention for further treatment of their disease. Different interventions have been described and include surgical, endoscopic and radiological guided approaches but practice differs between centres.

The overall aim of this thesis is to review these different interventional approaches and to produce an algorithm that can be used to aid clinical decisions for the management of pancreatic necrosis. This will be achieved by reviewing published literature and analysis of results from our regional tertiary referral centre.

Systematic review and meta-analysis were performed to review the use of metal and plastic stents for the endoscopic drainage of pancreatic fluid collections. This found the current literature supported the use of metal stents with a more patients achieving clinical success (1.11 [95% CI, 0.98-1.24] p=0.089) and a reduced incidence of adverse events (0.42 [95% CI, 0.22 - 0.81]; p=0.010). The next chapter reports the data from our centre regarding the outcomes of metal and plastic stents for the endoscopic drainage of pseudocysts. Using metal stents increased the chance of successful drainage at 6 weeks (92% vs 75%, p=0.023) and reduced the risk of requiring further intervention for the treatment of the pseudocyst (8% vs 31%, p=0.017).

Endoscopic ultrasound guided necrosectomy was adopted in our centre in 2016. We prospectively evaluated the outcomes of the first fifty patients treated by the technique, finding it to be effective in treating pancreatic necrosis in 84% of patients. The mortality rate

was 8% with no deaths during the study period due to procedural complications. We then compared endoscopic necrosectomy to minimal access surgical necrosectomy, the gold standard for management. This analysis found the length of stay was significantly reduced in patients treated by endoscopic necrosectomy (51 days vs 95 days, $p<0.001$). We performed a cost-consequence analysis demonstrating that the total cost was reduced when performing endoscopic necrosectomy (£31,364 vs £52,770, $p=0.008$). Pancreatic necrosis may be extra-pancreatic, we report the outcomes for the first cohort of patients treated by a novel procedure, Single Port Retroperitoneal Pancreatic Necrosectomy.

These results are summated in to an evidence-based algorithm for the management of pancreatic necrosis, considering the site of the collection and response to treatment to inform clinical practice and decision making. Consolidating a literature review and our own data, we state endoscopic necrosectomy should be performed when possible, utilising a step up approach. The algorithm incorporates Minimal Access Retroperitoneal Pancreatic Necrosectomy when the endoscopic approach is not suitable and adjuncts including additional percutaneous drains, Single Port Retroperitoneal Pancreatic Necrosectomy and open pancreatic necrosectomy where required. Physiological parameters and laboratory tests are monitored and repeat imaging performed every seven to ten days, or earlier in the case of clinical deterioration.

## AIMS & OBJECTIVES

### Aim

The overall aim of this thesis is to evaluate the different interventions for the management of pancreatic necrosis in order to define an algorithm to aid clinical decision making.

### Objectives

1. Perform a literature review of the current available interventions for pancreatic necrosis
2. Undertake a systematic review and meta-analysis investigating plastic versus metal stents for endoscopic ultrasound guided drainage of pancreatic fluid collections
3. Assimilate and report local unit data for the management of pancreatic fluid collections
4. Evaluate the introduction and use of endoscopic necrosectomy, comparing clinical outcomes to minimal access retroperitoneal pancreatic necrosectomy
5. Perform a cost analysis of different interventions for pancreatic necrosectomy
6. Evaluate the efficacy and safety of a new technique for extra-pancreatic necrosis, single port retroperitoneal pancreatic necrosectomy
7. Develop a treatment algorithm for patients with pancreatic necrosis require it intervention

## CHAPTER ONE: General Introduction

### Overview

Acute pancreatitis is an inflammatory disorder of the pancreas leading to approximately 100 admissions per hospital per year in the United Kingdom [2]. The global incidence is thought to be 34 per 100,00 person-years[3]. There are many documented risk factors for developing acute pancreatitis, with gallstones (47%) and alcohol excess (22%) being the two most common in the UK. Other causes are shown below in Table 1[3].

*Table 1: Aetiology of acute pancreatitis*

| **Aetiology** | |
|---|---|
| *Gallstones* | |
| *Alcohol* | |
| *Trauma* | ERCP, EUS + fine needle aspiration, aortic surgery, pancreatic resection |
| *Malignant conditions* | Intraductal papillary mucinous neoplasm, ductal adenocarcinoma |
| *Metabolic* | Hypercalcaemia, hypertriglycerideaemia |
| *Genetic* | PRSS1, SPINK1, CFTR, CASR |
| *Autoimmune* | |
| *Drugs* | Mesalamine, furosemide, azothiaprine, losartan |
| *Infections* | Viral including COVID[4], bacterial, parasitic |
| *Idiopathic* | |

The pathogenesis of pancreatitis is still not fully understood. Pancreatitis occurs following the exposure of pancreatic acinar cells to toxic agents, for example ethanol, bile acids or nicotine. Cellular events including mitochondrial dysfunction, premature trypsinogen activation, endoplasmic reticulum stress and impaired autophagy mediated by pathological intracellular calcium signalling lead to acinar cell death. Pancreatic ductal obstruction secondary to gallstones results in increased pressure, luminal acidification and ductal cell exposure to bile acid which also indirectly lead to these cellular events. This leads to an inflammatory response and infiltration of neutrophils and macrophages, release of tumour necrosis factor α and interleukins 1,6 and 8 within the pancreatic parenchyma[3,5].

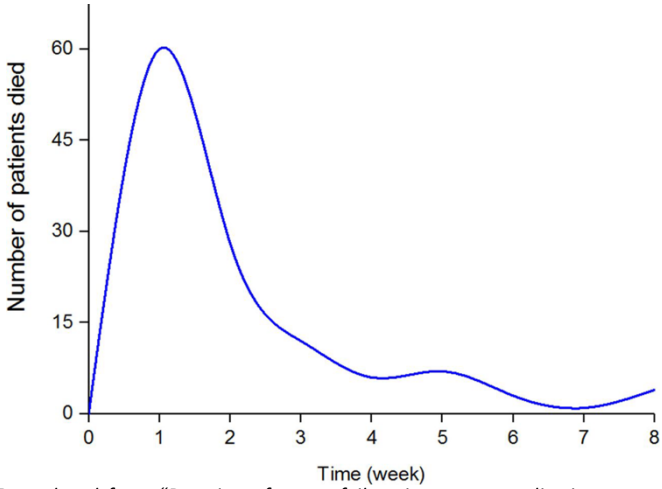
### Diagnosis and Definitions

The diagnosis of acute pancreatitis, as defined by the revised Atlanta criteria [6], is made when two of the following criteria are met; abdominal pain consistent with acute pancreatitis, serum lipase or amylase at least three times the upper limit of normal and characteristic

findings on abdominal imaging, most commonly contrast enhanced computerised tomography (CT). Acute pancreatitis can be divided in to interstitial oedematous pancreatitis and necrotising pancreatitis. Acute interstitial pancreatitis can be characterised by diffuse oedema and swelling of the pancreas, with homogenous enhancement and peripancreatic fat stranding on CT. Approximately 5-10% of patients with acute pancreatitis will develop necrotising pancreatitis with parenchymal or peripancreatic fat necrosis. Early (within 72–96 hours post-onset) CT imaging demonstrates patchy parenchymal perfusion and severity may be underestimated from these scans [6]. Pancreatic necrosis may liquefy or remain solid over time. The development of infected pancreatic necrosis is significant and is associated with a mortality rate of approximately 30% without intervention [7].

Acute pancreatitis broadly shows two peaks of mortality, early and late phases, see Figure 1. The early phase is typified by pancreatic cellular injury results in cytokines cascades and systemic disturbances leading to systemic inflammatory response syndrome (SIRS). This may cause transient (<48hrs) or more persistent organ dysfunction leading to Multiple Organ Failure Syndrome (MODS). The late phase consists of persistent systemic signs of inflammation and /or the development of infection, also leading to MODS. The associated local complications that lead to and precede this allow a window of opportunity for treatment.

*Figure 1: Pattern of mortality in patients with acute pancreatitis[1]*

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Local complications are defined as acute peripancreatic fluid collections, pseudocysts, acute necrotic collections and walled off-necrosis. The definition and classification of these

collections have evolved over time and are currently defined in the Revised Atlanta classification[6] (See Table 2). Acute peripancreatic fluid collections are associated with interstitial oedematous pancreatitis and occur within the first four weeks after onset of the disease. They are homogenous with no encapsulation and are found adjacent to the pancreas. Pancreatic pseudocysts occur at least four to six weeks after onset of interstitial pancreatitis and have a well circumscribed and defined wall of granulation tissue. Importantly they do not contain any free floating solid material but have markedly increased amylase activity. A pseudocyst may occur in acute necrotising pancreatitis secondary to a disrupted main pancreatic duct, whereby parenchymal necrosis of the neck or body isolates a viable distal remnant [8]. Acute necrotic collections are found in the early phase following acute necrotising pancreatitis and are heterogeneous on imaging with some non-liquid component. They can involve pancreatic parenchyma or peripancreatic tissues or both. Walled off necrosis (WON) is an encapsulated collection with both liquid and non-liquid components occurring over four weeks following necrotising pancreatitis. WON can be intrapancreatic or extrapancreatic and may be present in multiple sites. Infected pancreatic necrosis is suspected by the presence of gas within the collection or a deterioration in the patient's clinical condition and can be confirmed by fine needle aspiration and culture of the collection[6].

*Table 2: Classification of pancreatic fluid collections[6]*

| | ***Interstitial oedematous pancreatitis*** | ***Necrotising pancreatitis*** |
|---|---|---|
| ***<4 weeks post onset*** | **Acute peripancreatic fluid collection (APFC)**<br>• Homogenous<br>• No definable wall<br>• Confined to normal peripancreatic fascial plane<br>• Adjacent to pancreas | **Acute necrotic collection (ANC)**<br>• Heterogenous with different non-liquid densities in different locations<br>• No definable wall<br>• Intra and/or extrapancreatic |
| ***>4 weeks post onset*** | **Pancreatic pseudocyst**<br>• Well circumscribed<br>• Homogenous<br>• No non-liquid component<br>• Well defined wall | **Walled-off necrosis (WON)**<br>• Heterogeneous with liquid and non-liquid density<br>• Well defined wall<br>• Intra and/or extrapancreatic |

**Management**

The initial management of acute pancreatitis is largely supportive with aggressive fluid resuscitation to preserve organ function in the setting of a systematic inflammatory response syndrome (SIRS). Current guidelines recommend goal directed fluid therapy of 5-10mg/kg/h with the aim of normalising physiological targets of heart rate, urine output, mean arterial pressure and haematocrit[9,10]. Abdominal ultrasound can be performed to determine whether gallstones are present, the recent NCEPOD report recommends gallstones are excluded in all patients presenting with acute pancreatitis[11]. Initial CT is indicated if there is diagnostic uncertainty at presentation and then to assess severity and for the presence of local complications as the disease progresses. The use of prophylactic antibiotics in sterile pancreatic necrosis is not recommended[9]. Multiple trials have not shown a significant reduction in either morbidity or mortality with the administration of prophylactic antibiotics. However, it is acknowledged that is can sometimes be challenging to confirm the presence of infected necrosis with infection difficult to clinically differentiate from a systematic inflammatory response or infection of different sites[12]. Nutritional support with enteral feeding has been found to reduce infectious complications and improve outcomes including mortality compared to parental nutrition[10].

**Interventions for pancreatic necrosis**

The management of pancreatic necrosis has changed throughout the past decade, with new techniques and multi-modal strategies becoming available. With recent surgical and technological improvements, clinicians now potentially have options for the management of pancreatic fluid collections, depending on local expertise, with different minimally invasive procedures now available. Current National Institute for Health and Care Excellence (NICE) guideline for the management of pancreatitis was last published in 2018. It recommends offering an endoscopic approach where anatomically possible citing one randomised control trial as low grade evidence [13].

**Indication for intervention**

The majority of patients with acute pancreatitis will only require conservative supportive management. Current IAP/APA guidelines state the indications for intervention in necrotising pancreatitis are clinical suspicion or documented infected pancreatic necrosis with clinical deterioration and ongoing organ failure for several weeks after the onset of pancreatitis. Some patients who are not suspected to have infected necrosis may also

require intervention, including patients with ongoing gastric outlet or intestinal obstruction secondary to a mass effect of the collection, those with persistent symptoms with WON and patients with symptomatic disconnected duct syndrome[9]. It is important to accurately categorise pancreatic collections when considering the most appropriate management. Infected necrosis can be diagnosed from positive cultures from fine needle aspiration (FNA) or first drainage procedure, or by the presence of gas in the pancreatic or peri-pancreatic collection on CT scan [6,13].

Invasive intervention for necrotising pancreatitis should be delayed where possible for at least four weeks post onset of the disease to allow the collection to wall off [9]. Intervening prior to this is technically challenging with greater risk of bleeding or perforation of adjacent organs. However, much of the data supporting this approach is from studies where an open approach was the standard for the management of pancreatic necrosis which is no longer the case [14].

A large retrospective study has shown that 62% of patients with necrotising pancreatitis can be managed conservatively, without percutaneous, endoscopic or surgical intervention. Only 3% of the conservatively managed patients had infected necrosis and 16% had organ failure. The mortality of patients with organ failure that were managed conservatively was 37% [15].

**Percutaneous catheter drainage**

Percutaneous drainage (PCD) performed under CT or US guidance or endoscopic transmural drainage is recommended as the primary intervention for pancreatic necrosis [16]. The step-up approach mandates catheter drainage should be performed, followed by minimally access necrosectomy if clinically indicated[17]. PCD allows source control of sepsis by removal of infected fluid and definitive intervention to be delayed until the necrosis is walled off [18]. Patients undergoing PCD as initial management experience fewer complications than those who undergo primary necrosectomy[15] and necrosectomy is facilitated if a retroperitoneal approach is used for catheter insertion [19]. Preferred catheter size on initial placement is 6-24 French, with upsizing at subsequent procedures up to 40 French [20-23].

A systematic review found up to 52% of patients with necrosis can be managed by PCD alone, although not all patients included had infected pancreatic necrosis[21]. This has been replicated by the TENSION trial where 51% of the surgical treatment arm were successfully managed by percutaneous drainage alone[24]. Studies have been designed to investigate possible predictive factors for successful PCD drainage [22,23]. Male sex, multiple organ failure

(MOF), a heterogeneous collection and increasing pancreatic necrosis were all significantly associated with a reduced rate of successful drainage[22,23]. Female patients with <30% necrosis, no MOF and homogenous collections were predicted to have a 91% probability of successful catheter drainage [23]. The mortality following PCD is up to 17% and complications reported in 21%[21]. The most frequent complications are pancreaticocutaneous and pancreaticoenteric fistulae and bleeding [21,22].

Current evidence-based guidelines recommend delaying invasive intervention for at least 4 weeks to allow complete encapsulation and walled off necrosis [16]. Technically however, it is possible to drain collections safely before they are completely walled off[18] and this is frequently performed with collections of different aetiology, for example post pancreatic resection[25]. Earlier intervention with percutaneous catheter to drain infected fluid and attempt to control sepsis may improve outcomes but there is currently no evidence to support this and a lack of consensus between experts[26]. The optimum timing of percutaneous catheter drainage was recently investigated by a randomised control trial with treatment arms of immediate (within 24 hours after randomisation) or delayed (until walled off necrosis when feasible) catheter drainage. This study found that there was no superiority of early drainage in terms of complications but patients with early drainage received a greater number of invasive interventions[27,28].

**Minimal access pancreatic necrosectomy**

In 39-76% [22,24,29] of patients with infected pancreatic necrosis, catheter drainage alone will not be sufficient. Minimal access retroperitoneal necrosectomy is the next stage of the percutaneous step up approach. Techniques vary between centres but can be broadly categorised in to sinus tract endoscopy and video assisted retroperitoneal debridement (VARD)[30-33]. The aim of procedure is debridement, with care taken to only remove free and accessible necrosis rather than complete necrosectomy in one sitting [31,33].

VARD is preferred in many centres in the US and the Netherlands and was first described in 2001[31,34]. A 4-5cm incision is made close to the site of the percutaneous drain on the flank and the collection opened with finger dissection. Initial necrosectomy is performed with finger dissection and suction. A laparoscope is inserted in to the cavity to aid debridement, the necrotic tissue is then removed under direct vision with forceps. A review of VARD found on average patients require 3 (range 1-5) procedures with complications occurring in 35% of patients, however only 61% of patients were managed successfully by VARD alone [31].

Sinus tract endoscopy is an alternative and less invasive technique, commonly referred to as minimal access retroperitoneal pancreatic necrosectomy (MARPN). Under fluoroscopic guidance, the percutaneous catheter is exchanged for a guidewire and the tract is dilated up to 30 French. An operating nephroscope is introduced in to the tract allowing debridement under direct vision and simultaneous irrigation with warm saline. In both MARPN and VARD drains are secured in to the cavity to enable post-operative irrigation[20,33,30,35]. A median of 3 procedures (IQR 2-4) are required for adequate resolution and symptom control. Approximately 13% of patients are converted to open necrosectomy[20].

Minimal access surgical techniques were developed to reduce the unacceptably high morbidity and mortality of open necrosectomy in early studies. A minimal access approach reduces surgical stress and has been shown to reduce the pro-inflammatory response, leading to potential benefits in this critically ill cohort of patients[17,36,37]. It also reduces the potential morbidity from a large abdominal incision[38]. These benefits translating to a reduction in mortality has been shown in some but not all studies[39,40]. A multicentre randomised control trial of 88 patients reported mortality of 19% for a minimally invasive step-up approach compared to 16% for open necrosectomy ($p=0.70$)[24]. A retrospective review of 394 patients stated mortality of 15% for minimal access necrosectomy vs. 23% for open necrosectomy ($p=0.064$). Analysis of 1980 patients from 15 different cohorts of patients found minimally invasive surgical necrosectomy significantly reduced mortality only in very high risk patients, stratified by risk of death at baseline (38% vs 53%, RR 0.70 95% confidence interval 0.52-0.95, $p=0.02$)[38].

Morbidity is reduced by minimal access surgical necrosectomy compared to open necrosectomy, total complications were reduced from 82% to 64% ($p<0.001$)[20]. New multiple organ failure or systemic complications were reduced from 42% to 12% ($p=0.001$) in the PANTER trial[24]. Other documented benefits are reduced ITU admission, pancreatic fistulae, incisional hernia, new onset diabetes and requirement of pancreatic enzyme replacement [20,24]. Despite these advantages, reduced length of stay is not frequently demonstrated in studies and in some cases it is increased, likely due to the number of repeat procedures required for minimal access retroperitoneal necrosectomy (MARPN) and VARD [20,24,35,41].

**Endoscopic necrosectomy**

An endoscopic step-up approach with endoscopic transluminal drainage and endoscopic necrosectomy performed if clinically indicated is a potentially less invasive alternative to a

minimal access surgical approach [29,31]. Direct endoscopic necrosectomy was first described in 1996 [42] and is now becoming the preferred management approach in many centres.

Endoscopic transluminal drainage is performed under endoscopic ultrasound (EUS) guidance under sedation or general anaesthetic. The optimum site for stent placement is located, then the cavity is punctured using needle aspiration, needle-knife cautery or a cystotome. Doppler may be used to avoid disrupting gastric vessels[43]. A plastic or metal stent is then inserted in to the cavity over a guidewire [44]. Minimal necrosectomy can be performed at this point[43] or the patient is brought back for further procedures if clinically indicated. Direct necrosectomy within the cavity of walled off necrosis may be performed mechanically with endoscopic forceps, basket, snares or with lavage [43,45]. Some centres advocate an indirect approach using lavage and suction within the stomach, stating a reduced risk of complications[46]. The is currently no consensus as to the optimum way of performing endoscopic necrosectomy among experts[47] and many centres continue to modify and adapt their technique and protocol, particularly with technology and equipment evolving. Patients require between 2-6[48,49,29,50,51] necrosectomy procedures for clinical resolution, the range in number demonstrating the heterogeneity of patient and collection characteristics reported within the literature.

The type of stent used for transluminal drainage has become an important debate topic and an area of significant development. The procedure was first described using double pigtail plastic stents (DPS)[42,52]. Practice progressed to using multiple plastic stents, the multiple gateway technique, which enables better drainage and irrigation of the collection[53]. The effectiveness of plastic stents for draining walled off necrosis is limited by a number of factors. They have a small diameter and the cystogastrostomy closes around the stent meaning more solid debris and necrosis does not drain easily[54]. Inserting multiple plastic stents is time consuming[55,56] and increases the risk of procedural bleeding[45] as multiple puncture sites requiring dilatation are made.

Biliary self-expanding metal stents (SEMS)[57,58] gained popularity for drainage of walled off necrosis and more recently, specifically designed lumen apposing metal stents (LAMS) and bi-flanged metal stents (BFMS) have become available[54]. These metal stents have large lumens, commonly 10-16mm diameter, and therefore allow spontaneous discharge of necrotic debris and pus in to the stomach, improving drainage. They also allow direct endoscopic access to the cavity for necrosectomy to be performed if required[51]. Several studies demonstrate the improved drainage over plastic stents, with successful drainage

occurring in 82-95% of patients with metal stents compared with 73-81% for plastic stents [45,54]. Additionally, patients are less likely to require further subsequent necrosectomy post insertion of metal compared to plastic stents[45,59]. A randomised trial confirmed placing FCSEMS was quicker than DPS[56] and many operators find inserting metal stents less technically challenging than plastic stents, particularly with the advent of single step insertion devices[54]. However, reservations remain about the increasing use of LAMS/BFMS with some studies reporting high rates of adverse events, specifically embedded stents, bleeding and stent migration [60 ,61].

Mortality following endoscopic drainage necrosectomy is 8-18%[17,29,38]. Morbidity is more difficult to evaluate due to many studies only reporting procedure or stent related complications[50,54]. The TENSION trial reported 25% of patients had major complications following an endoscopic step up approach. Bleeding that required intervention occurred in 22% of endoscopic patients and 21% of surgical step-up patients[29]. Currently there is minimal evidence that endoscopic necrosectomy reduces major complications or death compared to minimal access surgical approaches. A 20 patient RCT did find reduced new onset organ failure (0 vs 50%) with an endoscopic approach compared to minimal access surgery, however 4/10 patients underwent laparotomy in the surgical arm of the trial[17]. New trials are awaited that compare the use of endoscopic drainage and necrosectomy using specifically designed metal stents to other approaches as the only current RCT used DPS for the study protocol [29].

There are potential advantages of an endoscopic compared to a surgical step up approach. Minimally invasive surgery is not possible in up to 30% of patients due to anatomical difficulties with the retroperitoneal access route [20], however endoscopic drainage is possible in 96% of patients[29]. The rate of pancreatic fistulae is significantly less following an endoscopic step up approach compared to surgical (5 vs 32%)[29]. The patient does not have any external drains left in situ, potentially improving quality of life and enabling a faster discharge from hospital. Length of stay was a reduced by 16 days for the endoscopic group in the TENSION trial, but there was no significant difference in QALY gained or cost, although the trend was towards reduced costs in the endoscopic arm [29].

**Laparoscopic necrosectomy**

Laparoscopic trans-peritoneal necrosectomy was first described in 1996 [62]. It has not gained widespread popularity and only several small volume case series exist, therefore doubts

remain about its safety and effectiveness. These studies were published prior to the PANTER trial and the acceptance of minimal access retroperitoneal necrosectomy as the gold standard. The collection is located laparoscopically and debridement is performed with a hand assisted or laparoscopic port[63]. Transgastric necrosectomy is an alternative laparoscopic approach. Advocates for laparoscopic necrosectomy quote reduced length of stay compared to other minimal access techniques and simultaneous cholecystectomy as potential advantages [19,30]. Laparoscopic necrosectomy is only feasible once the necrosis has become walled off [64].

**Open necrosectomy**

Open necrosectomy had historically been the gold standard of operative management for pancreatic necrosis requiring intervention. Different techniques have been reported and approach differs depending on the clinical presentation of the patient and between institutions[65]. The consensus opinion is that post-operative continuous lavage and closed packing is better than open packing or planned re-laparotomy in the majority of patients [19]. Operative intervention should treat the local focus of ongoing inflammation and sepsis without removing viable pancreatic tissue. Formal resections have been performed but had an unacceptably high mortality rate [66].

Open necrosectomy is performed either with a subcostal or midline incision. The lesser sac is exposed and then entered though a transmesocoelic or transgastocoeilc approach and debridement is performed, usually by digital dissection. Care should be taken to avoid viable pancreatic tissue. The cavity is washed out with several litres of isotonic saline to help clear the pancreatic surface and any affected extra pancreatic spaces. A double lumen and a large-bore single bore drainage catheter are placed in to the cavity to allow continuous irrigation. The gastrocolic and duodenocolic ligaments can be closed to help restrict the lavage to the cavity [67].

If there is significant extension of the necrotic collection in to the paracolic or mesenteric spaces then it is unlikely complete necrosectomy can be performed in a single operation and the probability of further septic episodes is high. One approach in these patients is to perform open packing and staged laparotomy. Other indications for this approach include a large volume of necrosis and poor delineation between healthy and necrotic tissue[68]. After operative debridement, soft large calibre drains are placed and brought out laterally. The cavity is then packed with gauze. The stomach, bowel and vessels can be protected with a

non-adhesive material to prevent trauma on removal of the packing. The abdominal wall is temporarily closed. Repeat laparotomy is performed every 48-72 hours until necrosectomy is complete and there is granulation tissue present. A large drain is left in-situ and the abdomen is closed when possible[67].

An alternative technique is debridement and closed packing, in which following debridement and lavage, large calibre drains stuffed with gauze and closed suction drains are positioned in to the cavity. Drains are removed gradually beginning 7-10 days post operatively allowing the cavity to collapse. This technique is advocated by some groups as it allows the advantages of packing whilst enabling drainage of necrotic tissue[69].

Recent case series for open necrosectomy report morbidity of 33-86% and a 7-33% mortality rate. Bleeding occurred in 2-22% of patients and the incidence of persistent fistulae was 38-60% [40,38,24,70,71,72,73]. The use of open necrosectomy has declined after the PANTER trial found higher rates of major complications and death following open necrosectomy compared to a minimal access step up approach[24]. Open necrosectomy is now often used as a last resort, when the collection is inaccessible to minimal access or endoscopic routes, if these techniques are not available and to manage complications or a poor clinical response following them. A retrospective study found reduced length of stay compared to MARPN[20] however centres preferring VARD report an increased length of stay with open necrosectomy[24] .

This thesis is focused on the management options and strategies for intervention of pancreatic fluid collections. It will review the current approaches available and assess our current practice with respect of clinical outcomes and effectiveness and options for future advances. Despite international consensus guidelines there is not complete agreement over when or how to intervene in pancreatic collections. Over recent years, local practice has evolved and endoscopic interventions for pancreatic fluid collections have been introduced. This thesis will review these new approaches and evaluate their use locally in terms of clinical and economic outcomes.

In addition, it will review interventions for both pancreatic pseudocysts and walled off necrosis. The overarching hypothesis is that endoscopic necrosectomy is now the preferred approach for the intervention for infected pancreatic necrosis. A systematic review and meta-analysis of the use of plastic vs metal stents for the endoscopic drainage of pancreatic fluid collections has been undertaken. The results of local outcomes of a retrospective

analysis of the use of metal vs plastic stents for the drainage of pancreatic pseudocysts will be reported. Moving on from pseudocysts, a review current management of pancreatic walled off necrosis and evaluate the results of the first fifty patients treated by endoscopic necrosectomy in our institution is undertaken. Prior to the introduction of endoscopic necrosectomy minimal access retroperitoneal necrosectomy was preferred approach for intervention in infected pancreatic necrosis. A comparison of the outcomes of endoscopic and minimal access necrosectomy in out unit is performed, followed by a cost comparison analysis of the different approaches to intervention. Finally, a small case series of patients with extra-pancreatic necrosis treated by single incision laparoscopic surgery (SILS) flank necrosectomy is presented. The results will be consolidated with the literature with the aim of developing a treatment algorithm to be implemented for the interventional strategy for pancreatic necrosis.

As this thesis addresses several different topics, it is structured with separate chapters addressing each issue in a paper format with introduction, methods, results and discussion for each topic. The final chapter provides general conclusions and the development of a treatment algorithm for the management of pancreatic necrosis.

## CHAPTER TWO: Systematic review of plastic vs metal stents for drainage of pancreatic fluid collections

Saunders R, Ramesh J, Cicconi S, Evans J, Yip VS, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP & Halloran C. A systematic review and meta-analysis of metal versus plastic stents for drainage of pancreatic fluid collections: metal stents are advantageous. Surgical Endoscopy, 2019; 33(5):1412-1425.

(see Supporting Papers, page 97)

### INTRODUCTION

It is established that pancreatic and peri-pancreatic fluid collections (PFC) are common following an insult to the pancreas [74,75]. Infected or persistently symptomatic collections will require treatment [6,16]. A recent randomised trial has shown equal efficacy between surgery and endoscopic drainage of pseudocysts but found reduced length of hospital stay and reduced costs for endoscopic intervention[76]. Thus, endoscopic management is now often regarded as first line management of PFCs with multiple studies demonstrating its safety and high success rates [17,77].

Endoscopic drainage of PFCs has progressed from plastic stents to the use of fully covered self-expanding metal stents (FCSEMS), initially designed for biliary stenting and latterly specifically designed FCSEMS as well as lumen apposing metal stents (LAMS)[42,77]. Metal stents have the advantage of large diameter lumens, which facilitate better drainage, particularly when there is debris or necrotic tissue present. They also allow easy and safe access to the cavity for direct endoscopic necrosectomy if required [78]. However, metal stents are significantly more expensive than plastic stents and some early reports raised safety concerns regarding their use, notably delayed bleeding and embedded stents [61]. With high success rates using plastic stents published, some centres do not see the benefit of metal stents, particularly for pseudocyst drainage [77].

A systematic review published in 2015 concluded there was no evidence to support the routine use of metal stents for drainage of pancreatic fluid collections [79]. Since then however, several studies comparing plastic double pigtail stents and FCSEMS/LAMS have been published in the literature.

The aim of this systematic review and meta-analysis is to review these recently published studies to assess clinical success rates, adverse events and requirement of further intervention, when treating PFC of any description.

## MATERIALS AND METHODS

### Eligibility criteria

The inclusion criteria for qualitative and quantitative analysis were comparative studies between plastic double pigtail stents and metal stents for drainage of both walled off necrosis (WON) and pseudocysts. Randomised controlled trials, prospective and retrospective studies were all eligible for inclusion as preliminary searches demonstrated few randomised controlled trials. Studies that used lumen apposing metal stents (LAMS), fully covered self-expanding metal stents (FCSEMS) and biliary self-expanding metal stents were all included. Only English language adult studies were included. No date criteria were set. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[80] and the protocol was registered on PROSPERO (www.crd.york.ac.uk/PROSPERO, CRD42017071101).

### Information sources

MEDLINE, Pubmed and SCOPUS databases were searched, with the final search conducted on 20/10/17. References of included studies were also screened.

### Search

The search terms were “pseudocyst” OR “pancreatic fluid collection” OR “walled off necrosis” AND “endoscopy” OR “endoscopic ultrasound” OR “EUS” AND “stent”.

### Study selection

Search results were combined on the Covidence software platform. Duplicate records were removed. Two reviewers (RSa, JR) independently scanned the title and abstract of all records identified during the search. Full text articles were retrieved and reviewed if it was not clear from the abstract if inclusion criteria were met. We included studies irrespective of whether they reported all outcome measures. Studies not meeting the inclusion criteria were excluded with the reason for exclusion recorded.

### Data collection process

Data was extracted independently in a standardised table by two reviewers (RSa, SC). Agreement was reached by consensus.

**Data items**

The following characteristics were extracted from the studies: Study design, number of centres, location of centres, date of studies, total number of participants, mean age, sex, type of PFC, type of metal stent, type and number of plastic stent, follow up period and size of PFC.

The primary outcome measure recorded was clinical success, defined as resolution of pancreatic fluid collection. Secondary outcome measures were adverse events and rate of reintervention. Other outcomes recorded were technical success, recurrence, length of stay and stent migration.

**Statistics**

Random effects modelling was undertaken for each of the outcomes of interest. The effect size between metal and plastic stents was described in terms of individual and pooled risk ratios with 95% confidence intervals and weighting estimated using the Mantel-Haenszel method. Forest plots were generated and study heterogeneity was investigated using the $I^2$ statistic. An $I^2$ exceeding 50% was considered to indicate significant heterogeneity. Sensitivity analyses were performed on the outcomes when heterogeneity or outlier studies were found. The effect size between metal and plastic stents was also explored for pseudocyst and WON separately. Funnel plots were used to explore the presence of publication bias and Egger's regression test for assessing their asymmetry. We considered P values <0.05 to be statistically significant. All the analyses were performed in Stata 14 (StataCorp, College Station, Texas, USA), using the command *Metan* for fitting random effects models and producing forest plots.

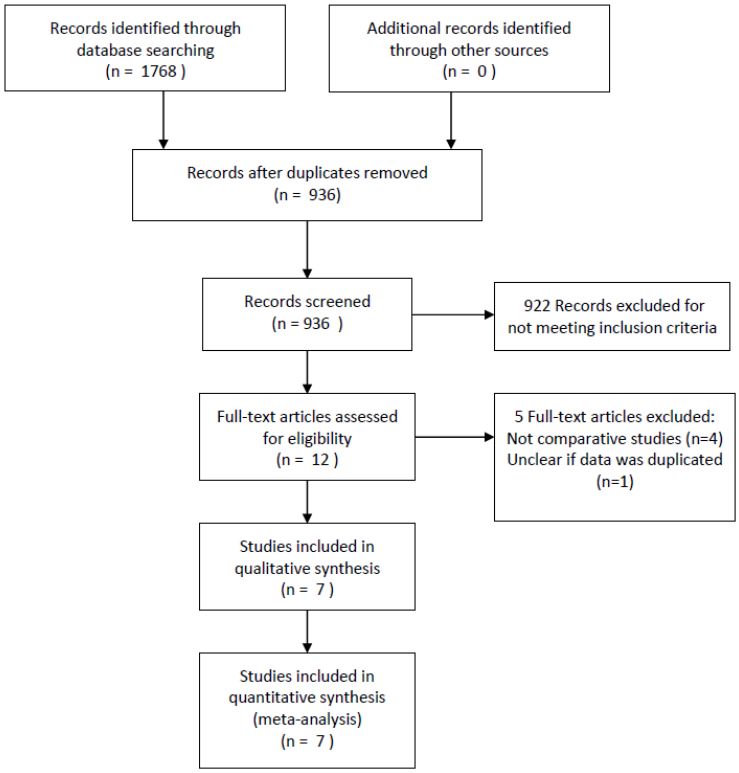
**RESULTS**

**Study selection**

The database search returned 1768 articles, 936 remained after duplicates were removed (see Figure 2). 12 full text articles were reviewed and five were excluded; four were not comparative studies and another was from the same centre as an included study [54,57] and it was unclear if the data was duplicated. Seven studies were included in the analysis [45,50,55-

[57,81,82]. It is important to state that patient allocation to study group was by stent, rather than by type of pancreatic fluid collection.

*Figure 2: PRISMA flow chart of search[80]*




**Study characteristics**

The characteristics of included studies are shown in Table 1. Patient demographic information and characteristics are summarised in Table 2. The outcome measures of individual studies are summarised in Table 3.

*Table 1: Characteristics of included studies*

| AUTHOR YEAR | STUDY TYPE | NUMBER OF PATIENTS (%) | | PFC TYPE (%) | | METAL STENT TYPE (diameter mm) | PLASTIC STENT SIZE (number of stents) |
|---|---|---|---|---|---|---|---|
| | | Plastic stent | Metal Stent | Pseudocyst | WON | | |
| **Ang et al 2016** [82] | Retrospective 2 centre | 37 (76) | 12 (24) | 31 (63) | 18 (37) | Nagi (16mm) | (1-2) |
| **Bang et al 2016** [55] | Retrospective case control | 40 (67) | 20 (33) | 21 (35) | 39 (65) | Hot AXIOS (15mm) | 7f 4cm (2) |
| **Bapaye et al 2016** [50] | Retrospective | 61 (46) | 72 (54) | - | 133 (100) | Nagi (16mm) | 7f (2-4) |
| **Dayyeh et al 2017** [45] | Retrospective | 36 (38) | 58 (62) | - | 94 (100) | Axios (15mm), Niti-s (18 or 20mm) | 7f or 10f (2 or more) |
| **Lee et al 2014** [56] | *RCT | 25 (50) | 25 (50) | 14 (28) | 36 (72) | BONA-Soo (8mm) | 7f (2-3) |
| **Mukai et al 2014** [81] | Retrospective | 27 (39) | 43 (61) | - | 70 (100) | Axios (10 or 15mm) Niti-s (16mm) Hanaro (12mm) | 7f (1-2) |
| **Shariaha et al 2015** [82] | Retrospective 2 centre cohort | 118 (51) | 112 (49) | 230 (100) | - | Wallflex Gore Viabl (10mm) | 10f (2) |

**In Lee et al, 5 patients were lost to follow-up (3 and 2 in plastic and metal stent respectively). Therefore, the number of patients used for calculating clinical success, reintervention and recurrence was 45 (22/23).*

*Table 2: Patient demographics and characteristics in included studies*

| AUTHOR YEAR | MEAN AGE, years | | MALE, % | | MEAN PFC SIZE, mm | | PFC INFECTION, % | | NASOCYSTIC DRAINAGE, % | | MEDIAN FOLLOW UP DURATION, months | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal |
| **Ang et al 2016** [82] | *Cross-over of stent summary presented | | *Cross-over of stent summary presented | | *Cross-over of stent summary presented | | - | - | Not routine | | - | |
| **Bang et al 2016** [55] | 52.9 | 50.7 | 62.5 | 55.0 | 109.3 | 120.0 | - | - | 20.0 | 5.0 | 26.5 | 5.3 |
| **Bapaye et al 2016** [50] | 40.7 | 43.9 | 88.5 | 86.1 | 117.1 | 100.9 | - | - | Yes | | Until stent removal | |
| **Dayyeh et al 2017** [45] | 59.7 | 52.7 | 77.7 | 77.6 | 128.0 | 134.0 | 44.4 | 39.7 | No | | - | |
| **Lee et al 2014** [56] | 51.6 | 53.7 | 76.0 | 88.0 | 89.0 | 84.0 | 32.0 | 44.0 | If debris/pus | | - | |
| **Mukai et al 2014** [81] | 55.9 | 54.4 | 77.8 | 86.0 | 77.1 | 105.6 | 59.3 | 53.4 | 92.6 | 25.6 | - | |
| **Sharaiha et al 2015** [57] | 52.2 | 53.2 | 69.5 | 55.4 | 97.8 | 98.6 | - | - | No | | 16 | |

*****Ang et al reports a cross-over summary of patient characteristics. Initial stent placement was plastic in 37 patients and metal in 12, 4 patients with plastic stents went on to have metal stents inserted at a further procedure.*

*Table 3: Summary table of outcome measures*

| AUTHOR YEAR | TECHNICAL SUCCESS, % | | CLINICAL SUCCESS, % | | ADVERSE EVENTS, % | | PFC RECURRENCE, % | | REINTERVENTION, % | | MEAN LENGTH OF STAY, days | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal |
| **Ang et al 2016** [82] | 100.0 | 100.0 | 94.6 | 100.0 | 13.5 | 0.0 | - | | 35.1 | 8.3 | - | |
| **Bang et al 2016** [55] | 100.0 | 100.0 | 92.5 | 95.0 | 15.0 | 20.0 | 0.0 | 0.0 | 30.0 | 25.0 | 9.2 | 9.3 |
| **Bapaye et al 2016** [50] | 100.0 | 100.0 | 73.8 | 94.4 | 36.1 | 5.6 | 0.0 | 0.0 | 26.2 | 2.8 | 8.0 | 4.1 |
| **Dayyeh et al 2017** [83] | - | | 75.0 | 82.8 | Summaries of specific AE presented | | - | | - | | *8.0 | *4.0 |
| **Lee et al 2014** [56] | 100.0 | 100.0 | 90.9 | 87.0 | 8.0 | 0.0 | 0.0 | 4.5 | 9.1 | 13.0 | - | |
| **Mukai et al 2014** [81] | 100.0 | 100.0 | 92.6 | 97.7 | 18.5 | 7.0 | - | | 25.9 | 23.3 | 28.7 | 22.5 |
| **Sharaiha et al 2015** [57] | 92.0 | 98.0 | 89.0 | 98.2 | 31.4 | 16.1 | 3.4 | 0.9 | - | | - | |

**Dayyeh et al summarised median length of stay*

## Synthesis of results

### *Clinical success*

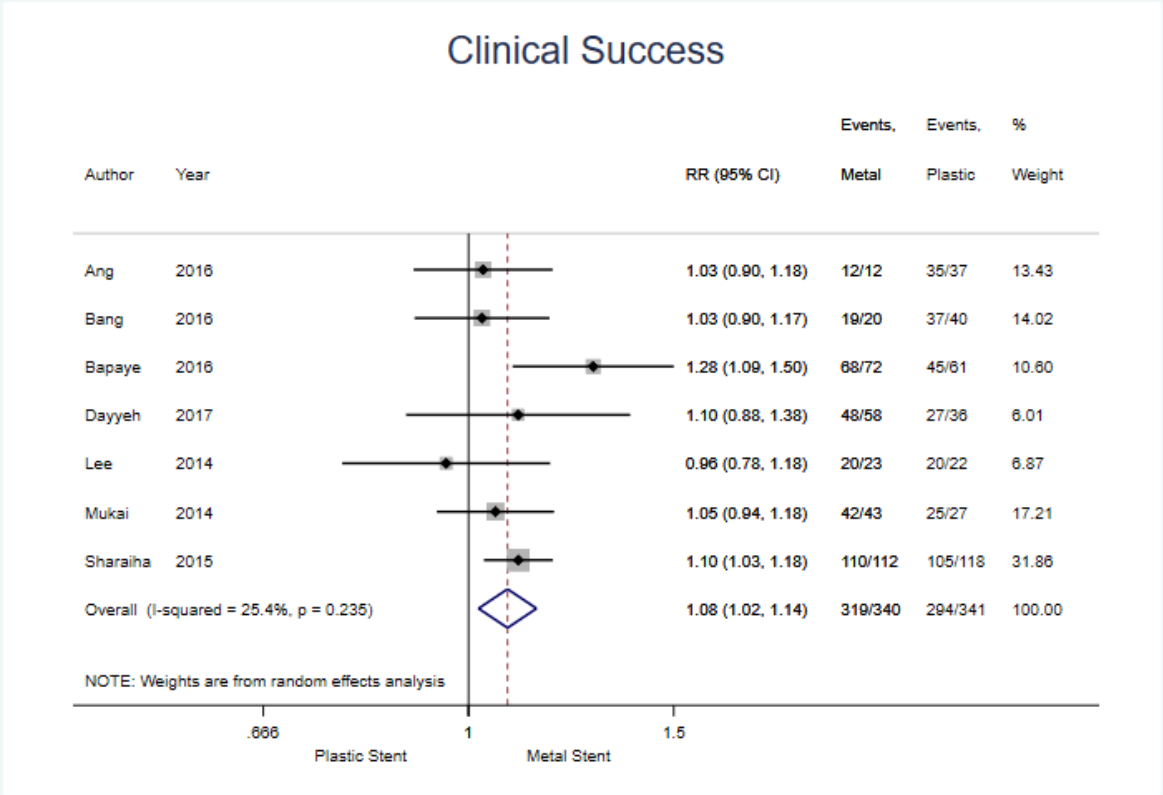
The results for the primary outcome measure of clinical success are shown in Figure 2. The seven papers included in this analysis contained a total of 681 patients, 340 and 341 had metal and plastic stents respectively. Overall, 93.8% of patients in the metal stent group and 86.2% in the plastic stent group achieved clinical success. The pooled Risk Ratio (RR) suggests an increase in clinical success when metal stents are used compared to plastic stents (1.08 [95% CI, 1.02 - 1.14]; p=0.009), $I^2$ = 25.4%.

There was heterogeneity of definition of clinical success between studies, summarised in Table 4. Five studies defined success using both radiological and clinical criteria. One study assessed clinical improvement only and one study reported radiological resolution. For the Ang et al, we included final clinical success for the quantitative analysis, for Dayyeh et al, we included the results that regarded concomitant percutaneous drainage as a failure of endoscopic drainage for better consistency across studies.

*Table 4: Definitions of clinical success*

| AUTHOR YEAR | DEFINITION CLINICAL SUCCESS |
|---|---|
| **Ang et al 2016** [82] | Size <2cm on imaging and resolution of symptoms |
| **Bang et al 2016** [55] | Size <2cm on imaging with resolution of symptoms at 8 weeks |
| **Bapaye et al 2016** [50] | Symptom resolution and complete resolution on imaging at end of treatment period |
| **Dayyeh et al 2017** [45] | Complete clinical amelioration of acute index symptoms and resolution on imaging |
| **Lee et al 2014** [56] | Size <2cm on CT performed every 4 weeks with resolution of symptoms |
| **Mukai et al 2014** [81] | Resolution of symptoms |
| **Sharaiha et al 2015** [57] | Resolution at 12 months on imaging |

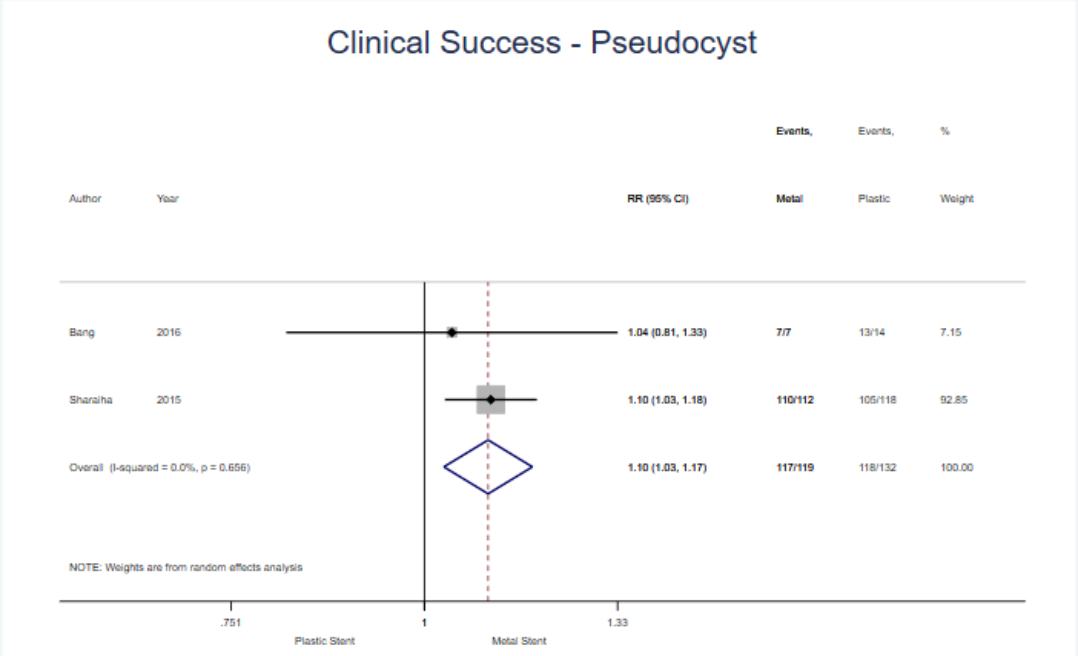
*Figure 2: Forest plot for individual and pooled risk ratio of clinical success*

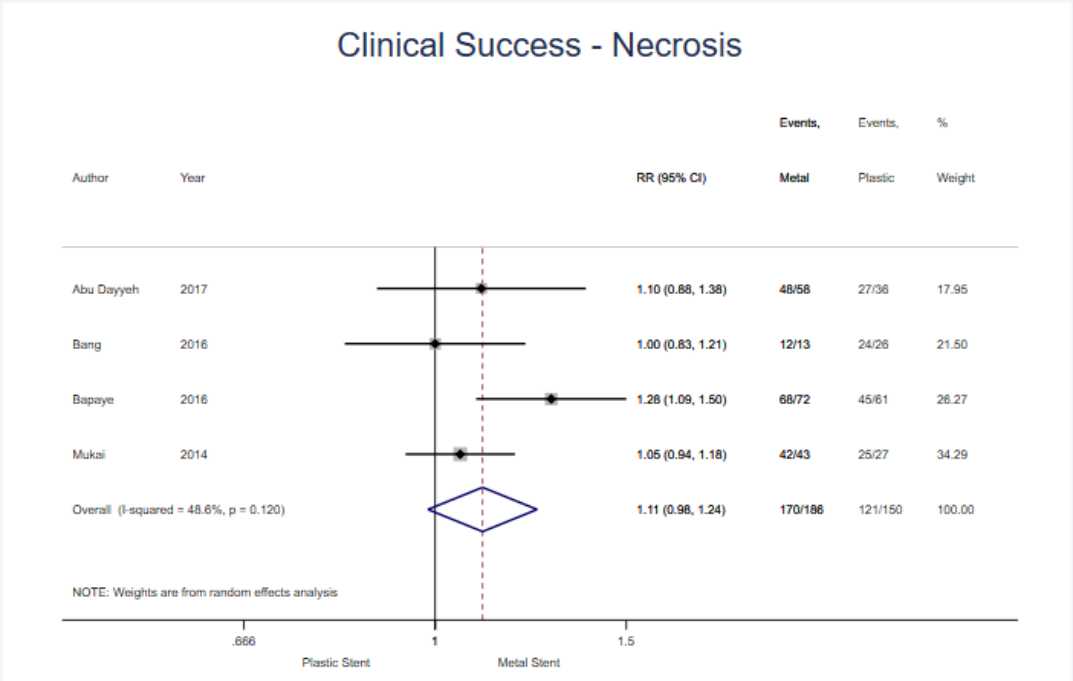



Sub group analysis was undertaken and found four studies specific for WON, comprising of 186 and 150 for metal and plastic stent groups respectively (see Figure 3). Only two studies were suitable for analysis for pseudocysts, including 119 patients with metal and 132 with plastic stents. For WON, clinical success was achieved in 91.4% of the metal stent group and 80.7% of patients with plastic stents. The pooled Risk Ratio suggests superiority of metal stents but does not reach significance (1.11 [95% CI, 0.98-1.24] p=0.089), $I^2$= 48.6%. Similarly, clinical success in the pseudocyst group occurred in 98.3% of those patients with metal stents

and 89.4% of those with plastic stents. The pooled Risk Ratio (1.10 [95%CI 1.03-1.17] p=0.005), $I^2$=0.0%, suggests placing metal stents increases clinical success in patients with a pseudocyst, however interpretation is limited due to the small number of studies included.

*Figure 3: Forest plot showing individual and pooled risk rations of clinical success for pseudocysts and walled off necrosis.*

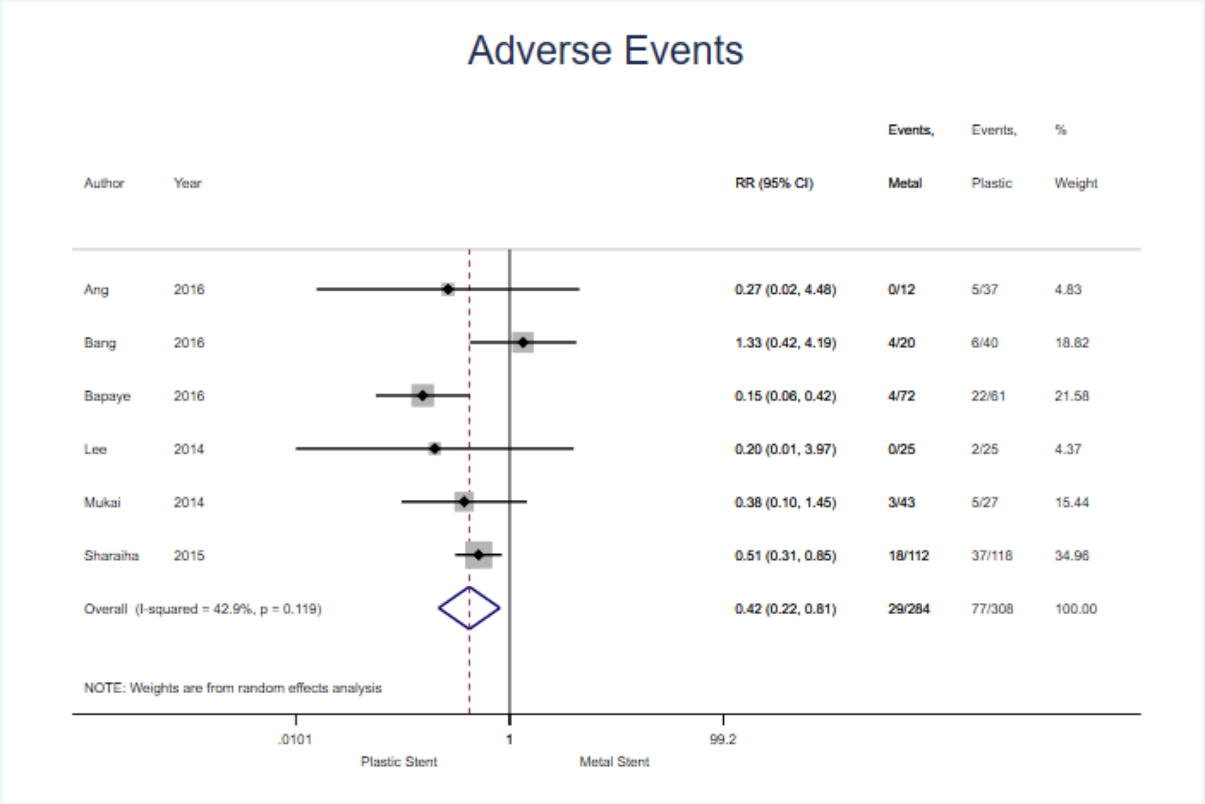


***Adverse events***

The adverse events reported in individual studies are summarised in Table 5. A total of 592 patients from six studies were considered for this analysis; 284 in the metal and 308 in the plastic stent group (see Figure 3). Adverse events were noted in 10.2% of the metal and 25.0% in plastic stent group. The pooled Risk Ratio demonstrated a 58% reduced risk of experiencing adverse events when a metal stent was used compared to plastic (0.42 [95% CI, 0.22 - 0.81]; p=0.010), $I^2$ = 42.9%. Results from Dayyeh et al were not included as the summaries were reported for each adverse event separately. Random effects models for stent migration and perforation were fitted, however no significant effect size between the two types of stents was identified.

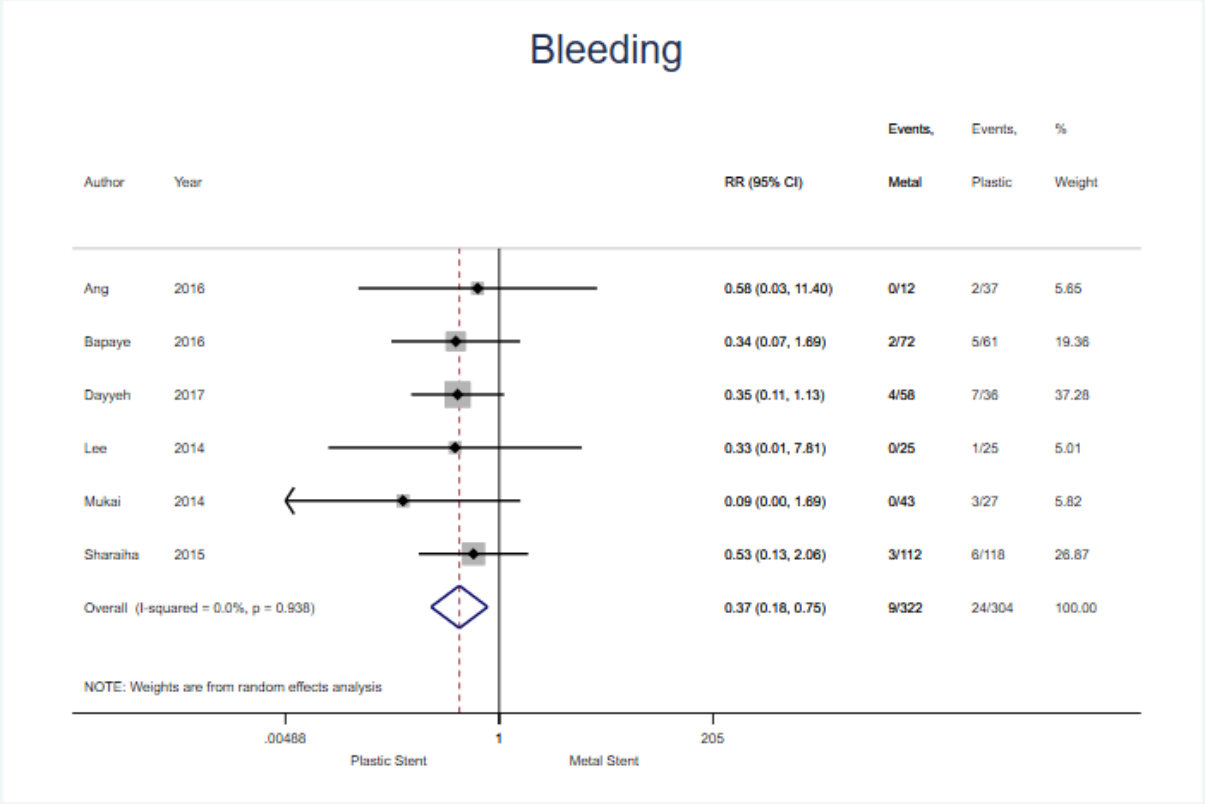
*Figure 4: Forest plot for individual and pooled risk ratio of adverse events*




The outcome of bleeding was analysed separately (see Figure 4). The six papers included in the analysis contained a total of 626 patients, 322 of which treated with metal stents and 304 with plastic stents. Bleeding was reported for 2.8 % and 7.9% of patients treated with metal and plastic stents respectively. The pooled Risk Ratio indicates that the use of metal stents reduced the risk of bleeding by 63% compared to plastic stents (0.37; [95% CI, 0.18 - 0.75]; p=0.006), $I^2$ = 0.0%. The results do not show heterogeneity, suggesting bleeding risk

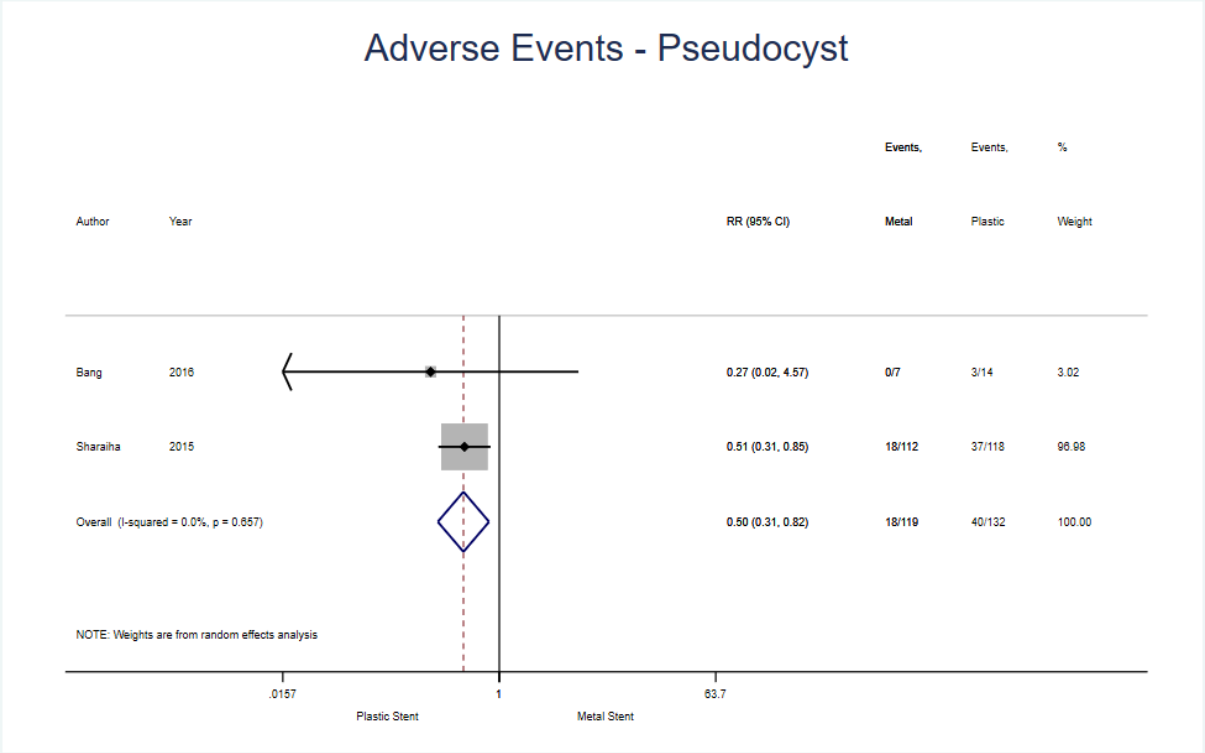
was consistent across the publications. Results from Bang et al were not included as it does not specifically report bleeding adverse events.

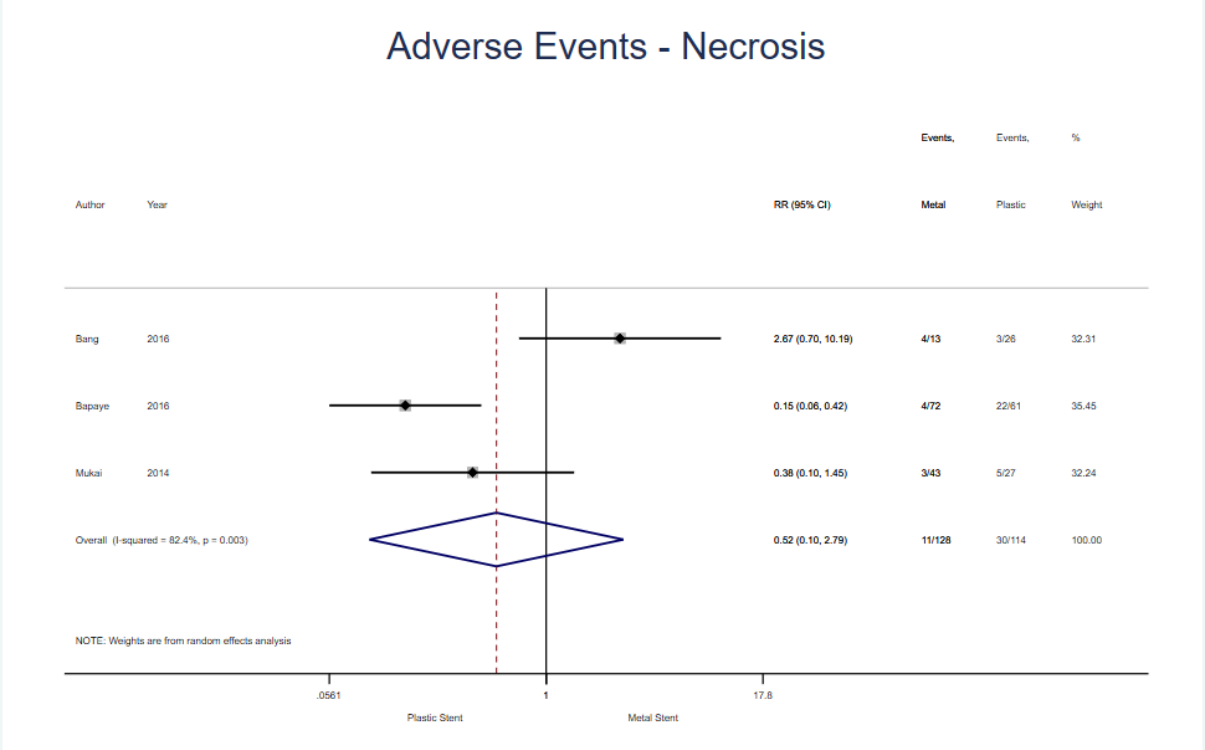
*Figure 5: Forest plot for individual and pooled risk ratio of bleeding*




Sub group analysis was undertaken and found three studies reporting adverse events for WON separately and were included in the analysis, 128 patients had metal stents included and 114 for plastic (see Figure 6). Adverse events occurred in 8.6% of patients with metal stents and 26.3% of the plastic stent group. The pooled Risk Ratio (0.52 [95%CI 0.10-2.79] p=0.442), $I^2$=82.4%, does not suggest a significant reduction in adverse events for either plastic or metal stents for patients with WON. Two studies with 119 and 132 patients with metal and plastic stents respectively were likewise reported for pseudocysts. Adverse events occurred in 15.1% of patients with metal stents and 30.3% of those with plastic stents. The pooled Risk Ratio (0.50 [0.31-0.82] p=0.006), $I^2$=0.0%, suggests that inserting a metal stent reduced the risk of experiencing an adverse event in patients with pseudocysts.

*Figure 6: Forest plot showing individual and pooled risk ratios for adverse events for pseudocysts and walled off necrosis*




The infection rate post stent insertion for metal stents was 5.4% and 13.2% for plastic stents. The pooled Risk Ratio (0.53 [95% CI 0.23-1.20] p=0.127), $I^2$=41.9%, does not suggest a difference between the groups. The severity of post procedural infection was not well

defined within the studies [57,82]. One study reported a single mortality from uncontrolled sepsis [81], another reported 2/58 (3%) of metal 2/36 and (6%) of plastic stent patients required transfer to intensive care for sepsis management [45]. In three studies either surgical or endoscopic intervention was required for control of infection [50,55,56]. Bang et al stated 3/20 (15%) and 5/40 (12.5%) patients in the metal and plastic groups respectively developed post procedural infection, 4 patients were managed with further endoscopic procedures and 3 by surgical techniques but this is not specified by stent type [55]. Bapaye et al reported 2/72 (2.8%) patients with metal and 16/61 (26.2%) with plastic stents developed infection that were all managed surgically [50]. In the study by Lee, 2/25 (8%) of metal and 3/25 (12%) of the plastic group were found to have post procedural infection and were all managed with further endoscopic drainage [56].

*Table 5: Frequency of specific adverse events*

| AUTHOR YEAR | BLEEDING, % | | STENT MIGRATION, % | | INFECTION, % | | PERFORATION, % | | TRACT DILATATION, mm | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | metal |
| **Ang et al 2016 [82]** | 5.4 | 0.0 | Cross-over of stent summary presented* | | 2.7 | 0.0 | 2.7 | 0.0 | 8.0 | 8.0 |
| **Bang et al 2016 [55]** | - | | 2.5 | 10.0 | 12.5 | 15.0 | - | | 12.0-15.0 | - |
| **Bapaye et al 2016 [50]** | 8.2 | 2.8 | 3.3 | 2.8 | 26.2 | 2.8 | - | | 18.0 | 6.0 |
| **Dayyeh et al 2017 [83]** | 19.4 | 6.9 | 19.4 | 20.7 | 5.6 | 3.4 | 8.3 | 1.7 | 15.0-18.0 | 15.0-18.0 |
| **Lee et al 2014 [56]** | 4.0 | 0.0 | 4.0 | 0.0 | 8.0 | 12.0 | - | | 8.0 | When resistance encountered |
| **Mukai et al 2014 [81]** | 11.1 | 0.0 | 3.7 | 4.7 | - | | 0.0 | 2.3 | 15.0-20.0 | - |
| **Sharaiha et al 2015 [57]** | 5.1 | 2.7 | 0.8 | 0.9 | 13.6 | 5.4 | 4.2 | 1.8 | 10.0 | 10.0 |

**Ang et al reports stent migration for stent cross-over.*

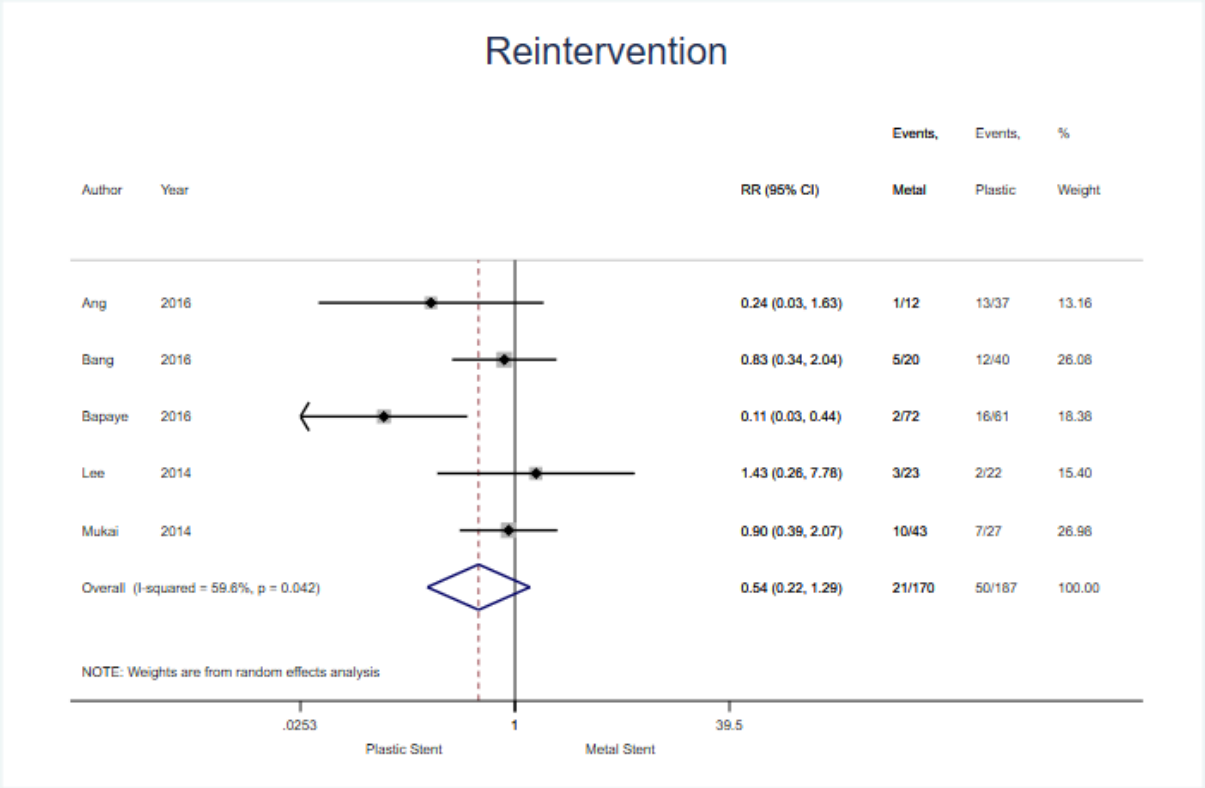
### *Reintervention*

Reintervention data were available from five studies (see Figure 5), therefore the analysis contains 357 patients, 170 and 187 in metal and plastic stent groups respectively. The percentage of patients requiring reintervention was 12.4% among those treated with metal stent and 26.7% in the plastic stent group. The pooled Risk Ratio suggests a higher risk of reintervention when plastic stents were used, however treatment effect failed to reach statistical significance (0.54; [95% CI, 0.22 – 1.29]; p=0.165), $I^2 = 59.6\%$.

The stated definitions for reintervention were a need for repeat endoscopy or surgery due to persistent symptoms associated with residual PFC that hadn't reduced by >50% in size[82], if symptoms or inflammation continued despite drainage and additional sessions of direct endoscopic necrosectomy[81], additional transmural drainage and/or endoscopic necrosectomy[55] and salvage surgical intervention[50].

Sharaiha et al and Dayyeh et al were not included as reintervention rates were not reported fully. Sharaiha et al stated that 52 (22%) patients required further interventions for pseudocysts within first month. Furthermore, it reported a significant difference in short term intervention (p=0.008) but does not include actual numbers or clarify which stent was superior[57].

*Figure 7: Forest plot for individual and pooled risk ratio for reintervention*




Sub group analysis was undertaken and found three studies specified reintervention in WON (see Figure 8). 128 and 114 patients had metal and plastic stents inserted respectively. 21.1% of those in the metal group and 22.9% in the plastic group required reintervention. The pooled Risk Ratio (0.65 [95% CI 0.16-2.60] p=0.543), $I^2$=84.8%) does not suggest a superiority for either stent. Only one study was suitable for inclusion in the pseudocyst analysis so meta-analysis was unable to be performed.

**Publication bias, sub group and sensitivity analyses**

The Bapaye study was a consistent outlier in the quantitative analysis. Sensitivity analyses performed without this study, confirmed the same findings of the main analyses and showed a considerable drop in heterogeneity. There was no significant difference in methodology or reporting to explain this and no reason to exclude it from the analysis.

Funnel plots to assess publication bias for outcomes were performed. The graphs do not reflect any publication bias and Egger's regression tests for asymmetry yielded statistically non-significant p-values.

**DISCUSSION**

This meta-analysis demonstrates superior clinical success and reduced adverse events for use of metal stents when compared to plastic for endoscopic transluminal drainage of pancreatic fluid collections. Previous meta-analysis by Bang et al showed no difference in the efficacy and adverse events between plastic and metal stents for drainage of PFCs [79]. The majority of these data were derived from the use of specifically designed, large calibre, covered metal stents with lumen apposing flanges, unlike the previous review. It is likely that the improved outcomes of metal stents in this review are as a result of these stents as they are tailored for PFC drainage.

The fistula created by balloon dilatation enables plastic stent placement and drainage of fluid, however this may be insufficient due to spontaneous closure of the fistula around the stent. Plastic stents have substantially smaller lumens than metal stents leaving them more susceptible to blockage or occlusion, even in pseudocysts or WON with minimal debris. Although the use of plastic or metal stents was not found to reduce infection post drainage, metal stents can facilitate drainage of both liquid and the viscous necrotic debris, leading to the higher rates of successful drainage. Patients are not always routinely investigated by EUS prior to intervention; this is reflected in these studies where PFC's were frequently diagnosed by CT or MR imaging. CT imaging has a low sensitivity for assessing necrosis so there is diagnostic uncertainty when judging a collection to be a pseudocyst or WON. Recent guidance suggests MRI or ultrasound assessment may be required to accurately characterise the collection [6].

There are several limitations of this systematic review and meta-analysis. All but one included studies are retrospective studies with the inherent bias associated with this methodology [45,50,55-57,81]. There was a discrepancy in type and quality of included studies

leading to the synthesis of results of variable reliability [84,85]. There were also differences between definitions for the outcomes reported. Different types of metal stent were used both in individual and across studies; it is not currently clear in published literature if there is any demonstrable clinical advantage of a particular stent. In 2 studies there is a discrete time point where practice changed and metal stents were used routinely, however in 4 studies plastic stents continued to be used for PFCs with certain characteristics leading to conceivable selection bias [81]. Furthermore, the sample sizes of some studies are relatively small and correspond to extended periods of time. The number of studies included in the meta-analyses is also quite limited and therefore meta-regression was not performed for exploring further the cause of heterogeneity.

All these studies were designed to investigate a difference in outcomes between stents not between types of PFC. There are huge limitations in combining pseudocysts and WON for data analysis and potential limitations in the classification of PFC within individual studies. The revised Atlanta criteria was introduced in 2012, therefore it is likely that patients were classified differently over the period the studies were ongoing. However, in the studies included except for Mukai et al [81], patients have short or no length of stay recorded and no clinical details suggesting these are not acutely unwell patients with infected pancreatic necrosis but rather patients being treated on a semi-elective basis. The subgroup analyses for drainage of pseudocysts in terms of clinical success and adverse events suggest that metal stents remain advantageous over that of plastic stents. Similar subgroup analyses for drainage of WON with metal stents are less convincing, with clinical success almost reaching significance, while adverse events or reintervention show no difference between metal or plastic stents. However, these subgroup analyses are limited by the very small numbers of studies which state these indications separately and therefore it is difficult to draw conclusions based on these data. Finally, the cost incurred was not evaluated in this analysis.

Our analysis showed patients were 58% less likely to experience an adverse event with metal compared to plastic stents. Inserting plastic stents, particularly multiple plastic stents can be technically demanding and time consuming which may in part explain the increased risk [56]. Bleeding was significantly more common in patients with a plastic stent (2.8 vs 7.9%, p=0.006), this may be due to the greater dilatation required for plastic stent insertion. Dilatation of the tract prior to stent insertion for plastic stents ranged from 8-20mm and 0-18mm for metal stents in studies included in this review. The majority of studies used

multiple plastic stents inserted, which has previously been shown to improve treatment success compared to using a single stent [53].

Delayed bleeding in patients with metal stents was reported in one study [50]. An interim analysis for a randomised control trial by Bang et al also reported significant delayed bleeding in 3 of 12 patients with LAMS [61]. This required a change in the trial protocol to remove stents earlier than initially planned. Investigators described buried stent syndrome in 2/12 patients and 1/12 patient with a biliary stricture secondary to a stent [61]. However, high rates of adverse events have not been seen in other cohorts of patients with LAMS [86]. The experience with LAMS is still early and more multicentre, prospective randomised data are required to accurately quantity the risk; elucidate causes for the risk and suggest potential solutions. It is likely that the delayed bleeding and buried stent problems seen with LAMS is due to its design rather than procedural steps in stent insertion.

There was no significant difference in the rate of reintervention between plastic and metal stents. This could be due to type 2 error as two of the largest studies were not included in the analysis and it was a relatively rare event for the sample size. Reported reintervention rates ranged from 2.8-35.1% between studies. The type of reintervention required also varied and was not always specified by authors. Bapaye et al stated salvage surgery was required in 26.2% of patients with plastic stents, however, Mukai et al reported no patients required surgical intervention for inadequate drainage. This may suggest heterogeneity between included patients or difference in practice between centres.

EUS guided drainage is regarded as first line treatment for pancreatic fluid collections requiring intervention. The use of transmural metal stents increases the probability of clinical success and reduces the frequency of adverse events when compared to plastic stents for EUS guided drainage of pancreatic fluid collections. Future, well designed prospective randomized control trials with multiple centres are required to evaluate clinical outcomes, adverse events and potential costs.

## CHAPTER THREE: Usage of transmural metal stents for endoscopic ultrasound guided drainage of pseudocysts may lead to lower reintervention rates

### Introduction

Pancreatic pseudocysts are a common complication of pancreatitis, occurring in 5-10% of patients with acute pancreatitis[74,87].Pseudocysts also occur following chronic pancreatitis trauma, surgery, transplantation or pancreatic ductal obstruction. Endoscopic transmural drainage of pseudocysts has now largely replaced surgery as the first line treatment. Other therapeutic options include endoscopic transpapillary and percutaneous drainage. EUS drainage was first described placing, in some cases multiple, plastic stents in to the pseudocyst, this developed to using biliary self-expanding metal stents. More recently purpose built fully covered self-expanding metal stents (FCSEMS) with lumen apposing wide-flanges have been introduced and are becoming more widely used[86,88] . FCSEMS have larger lumens to reduce the risk of occlusion, enhance drainage and allow single step placement but carry a risk of stent migration and bleeding[89,90].

Multiple studies have demonstrated the safety and effectiveness of FCSEMS for pseudocyst drainage[79]. There is now evidence to suggest that using FCSEMS improves clinical outcomes and reduces adverse events associated with pseudocyst drainage[57,91].

We conducted a retrospective analysis from a single centre comparing the outcomes of plastic and metal stents for pseudocyst drainage with regard to technical and clinical success, adverse events and requirement of further intervention.

### Methods

#### Patients

A prospectively maintained database of all patients undergoing EUS guided pancreatic fluid collection drainage at the Royal Liverpool University Hospital was retrospectively searched from 2010-2016. Pancreatic fluid collections (PFC) were assessed by CT, MR and EUS images according to the Atlanta and revised Atlanta criteria[6,92]. Patients with walled off necrosis (WON) were excluded from this analysis. The indications for pseudocyst drainage were infection or suspected infection, persistent pain, gastric outlet obstruction or an enlarging collection.

The management plan for each patient was agreed at the benign multi-disciplinary team meeting, attended by pancreatic surgeons, gastroenterologists and radiologists. Patients with acute pancreatitis were managed according to the IAP/APA guidelines[9].

The following patient characteristics were collected: age, gender, smoking status, chronic pancreatitis, pre-operative diabetes, duration of pseudocyst (months), indication for intervention, aetiology of pancreatitis, width of largest diameter on baseline CT scan (mm), location of collection, route and endoscopist.

**Endoscopic techniques**

The initial endoscopy was performed under moderate sedation with a linear echoendoscope. The optimum site for cystogastrotomy is decided by either identifying a clearly bulging lesion or using by EUS to identify the cavity, both in combination with analysis of radiological images. A transgastric route is preferred but a transduodenal route was used when appropriate.

For the insertion of plastic stents, the gastric or duodenal wall is punctured by needle-knife electrocautery or a cystotome. Fluid was aspirated from the cavity and sent for microbiology. Under fluoroscopic guidance a guidewire was advanced in to the collection and the tract dilated to 8-12mm with a radial expansion balloon. A 4f or 7f double pigtail stent was placed over the wire under fluoroscopic guidance in to the pseudocyst.

We used 3 metal stents over the study period, a 10mm Wallstent (Boston Scientic), 16mm Nagi stent (Taewoong Medical Co. Ltd) or 15mm Hot AXIOS stent (Boston Scientific). For FCSEMS (Wallstent and Nagi) insertion follows the same procedure as plastic stents. The Hot AXIOS stent includes an enhanced delivery system allowing single stage insertion. Fluoroscopy was not required for most Hot AXIOS stent insertions.

**Follow up**

A CT scan was arranged after 6 weeks post procedure. If the pseudocyst had resolved the stent was removed and the patient was placed in a regular clinical follow up programme for monitoring of further symptoms or recurrence.

**Outcomes**

Technical success was defined as the procedure completed with adequate deployment and positioning of the stent. Procedures that were not tolerated by the patient were not deemed

technical failures. Short term success was defined as a 50% reduction in pseudocyst size at 6 weeks on CT imaging. Long term success is defined at an 80% reduction in pseudocyst size at 6 months on cross sectional imaging with resolution of clinical symptoms. Reintervention was defined as requiring further endoscopic, surgical or percutaneous pseudocyst drainage for pseudocyst management within 12 months post index procedure. Adverse events recorded included bleeding, stent migration, stent malfunction, perforation, infection and readmission and were classified in to early (within 30 days of procedure) and late events.

Other outcomes recorded included: length of stay, length of follow-up, numbers of procedures and duration stent in situ.

**Statistical analysis**

Descriptive statistics are performed on patient characteristics and the outcome measures. Continuous variables are presented with their median and interquartile range (IQR), while categorical variables are described as frequencies and proportion percentages. Chi-square test, Fisher exact test or Wilcoxon-Mann-Whitney test were performed as appropriate in order to examine if there was any statistically significant difference in the outcomes between the two groups, at a statistically significant level of 5% (p-values > 0.05).

**RESULTS**

**Patient demographics**

*Table 1: Summary of patient characteristics by type of stent*

| | **Type of stent** | | |
|---|---|---|---|
| | **Metal** n= 38 | **Plastic** n= 36 | **p-value** |
| Age, median(IQR) | 50 ( 43 , 62 ) | 57 ( 45 , 67 ) | 0.225 |
| Gender, n(%) | | | |
| *Male* | 25 ( 66 ) | 22 ( 61 ) | 0.860 |
| Smoker, n(%) | | | |
| *Yes* | 12 ( 32 ) | 8 (22) | 0.520 |
| *No* | 26 ( 68 ) | 28 ( 78 ) | |
| Chronic Pancreatitis, n(%) | | | |
| *Yes* | 14 ( 37 ) | 10 ( 28 ) | 0.559 |
| *No* | 24 ( 63 ) | 26 (72 ) | |
| Duration pseudocyst (months), n(%) | | | |
| *1-3* | 6 ( 16 ) | 2 ( 6 ) | 0.577 |
| *3-6* | 8 ( 21 ) | 6 ( 17 ) | |
| *6-12* | 8 ( 21 ) | 8 ( 22 ) | |
| *>12* | 14 ( 37 ) | 16 ( 44 ) | |
| *Missing* | 2 ( 5 ) | 4 ( 11 ) | |
| Indication, n(%) | | | |
| *Pain/mass effect* | 31 ( 82 ) | 32 ( 89 ) | 0.357 |
| *Sepsis* | 4 ( 11 ) | 1 ( 3 ) | |
| *Missing* | 3 ( 8 ) | 3 ( 8 ) | |
| Aetiology, n(%) | | | |
| *Alcohol* | 17 ( 45 ) | 11 ( 31 ) | 0.560 |
| *Gallstones* | 12 ( 32 ) | 14 ( 39 ) | |
| *Idiopathic* | 4 ( 11 ) | 4 ( 11 ) | |
| *Other* | 1 ( 3 ) | 1 ( 3 ) | |
| *Unknown* | 4 ( 11 ) | 6 ( 17 ) | |
| CT width (mm), Median(IQR) | 94 ( 65 , 109 ) | 106 ( 83 , 130 ) | 0.100 |
| Site, n(%) | | | |
| *Body* | 19 ( 50 ) | 17 ( 47 ) | 0.593 |
| *Head* | 7 ( 18 ) | 4 ( 11 ) | |
| *Tail* | 11 ( 29 ) | 14 ( 39 ) | |
| *Missing* | 1 (3) | 1 (3) | |
| Route, n(%) | | | |
| *Transduodenal* | 4 (11) | 0 (0) | 0.116 |
| *Transgastric* | 34 (89) | 35 (97) | |
| *Missing* | 0 ( 0 ) | 1 ( 3 ) | |
| Diabetes, n(%) | | | |
| *Yes* | 8 (21) | 12 (33) | 0.298 |
| *No* | 30 (79) | 24 (67) | |

Our search identified 108 consecutive patients that underwent EUS guided drainage of pancreatic fluid collections from 2011-2016. Thirty-four patients were excluded as they met revised Atlanta criteria for WON, therefore 74 patients were included in this analysis. Thirty-six patients received a plastic stent and 38 patients received metal stents. The results in Table 1 show no significant difference between the two groups.

Patients received one of four different stents, 25 (66%) patients received a Nagi stent, 9 (24%) Wallstent, and 4 (11%) received a Hot AXIOS stent. The 34 patients who received pigtail plastic stents were split between 4fr or 7fr double pig tails.

**Treatment outcomes**

*Table 2: Summary of treatment outcomes by type of stent*

| | **Type of Stent** | | |
|---|---|---|---|
| | **Metal** n= 38 | **Plastic** n= 36 | **p-value** |
| Technical Success, n (%) | | | |
| *Yes* | 38 ( 100 ) | 35 ( 97 ) | 0.486 |
| *No* | 0 ( 0 ) | 1 ( 3 ) | |
| Short Term Success (6 weeks), n(%) | | | |
| *Yes* | 35 ( 92 ) | 27( 75) | **0.023** |
| *No* | 2 ( 5 ) | 9 ( 25 ) | |
| *Missing* | 1 ( 3 ) | 0 ( 0 ) | |
| Long Term Success (6 months), n(%) | | | |
| *Yes* | 29 ( 76 ) | 25 (69 ) | 0.369 |
| *No* | 5 ( 13 ) | 9 ( 25 ) | |
| *Missing* | 4 ( 11 ) | 2 ( 6 ) | |
| Early adverse events , n(%) | | | |
| *Yes* | 3 ( 8 ) | 12 ( 33 ) | ***0.009*** |
| *No* | 35 ( 92 ) | 24 ( 67 ) | |
| Late adverse events, n(%) | | | |
| *Yes* | 7 ( 18 ) | 2 ( 6 ) | 0.154 |
| *No* | 31 ( 82 ) | 34 ( 94 ) | |
| Overall adverse events, n(%) | | | |
| *Yes* | 20 ( 53 ) | 15 ( 42 ) | 0.477 |
| *No* | 18 ( 47 ) | 21 ( 58 ) | |
| Reintervention, n(%) | | | |
| *Yes* | 3 ( 8 ) | 11 ( 31 ) | ***0.017*** |
| *No* | 35 (92) | 25 ( 69 ) | |

Table 2 shows the treatment outcomes for plastic and metal stents. Short term success was achieved in 92% of patients with metal stents and 75% with plastic stents (p=0.023). At 6 months, there was no significant difference between the two groups. Technical success was 100% in the metal stent group and 97% for plastic stents.

Early adverse events occurred in 33% vs. 8% of patients with plastic and metal stents respectively (p= 0.009). There was no significant difference in overall or late adverse events or between specific adverse events. Stent migration was higher for metal stents (16% vs. 6%) but this did not reach significance (p=0.263). Specific adverse events are shown in table 3.

Patients with plastic stents required reintervention more frequently than those with metal stents (31% vs. 8%, p=0.017). In the plastic stent group 11 patients needed further procedures for pseudocyst management (4 surgical, 3 percutaneous, 4 further endoscopic drainage) and 3 patients with metal stents required further intervention (2 surgical and 1 endoscopic).

*Table 3: Summary of specific adverse events by type of stent*

| | **Type of stent** | | |
|---|---|---|---|
| | **Metal** n= 38 | **Plastic** n= 36 | **p-value** |
| Stent Migration | 6 ( 16 ) | 2 ( 6 ) | 0.263 |
| Readmission | 3 ( 8 ) | 8 ( 22 ) | 0.108 |
| Bleeding- primary | 3 ( 8 ) | 5 ( 14 ) | 0.474 |
| Infection | 2 ( 5 ) | 3 ( 8 ) | 0.670 |
| Perforation | 0 ( 0 ) | 1 ( 3 ) | 0.486 |
| Bleeding- delayed | 1 ( 3 ) | 1 ( 3 ) | 1.000 |

## Additional outcomes

In 24/38 (63%) of patients with metal stents and 25/36 (69%) with plastic stents pseudocyst drainage was performed as a day case procedure.

Metal stents were left in situ for 122 days (IQR 78.5, 167.5) vs. 158 days (IQR 118.5, 189) for plastic stents (p=0.048). However, the duration the stent was in-situ did not affect the procedure's success or the rate of reintervention (see table 4). There was a trend towards increased adverse events with leaving the stent in situ for a longer period of time but did this not reach statistical significance (p=0.088). There was no difference in outcomes for patients with chronic pancreatitis or those that had previously underwent pseudocyst drainage.

*Table 4: Outcomes by duration stent in situ*

| | **Stent Duration (Days)** *Median, (IQR)* | **p-value** |
|---|---|---|
| Short Term Success | | |
| No | 194.5 ( 144.2 , 433 ) | 0.100 |
| Yes | 128.5 ( 99.2 , 185.8 ) | |
| Long Term Success | | |
| No | 145.0 ( 96.0, 496.0 ) | 1.000 |
| Yes | 147.0 ( 113.5 , 189.0 ) | |
| Reintervention (overall) | | |
| No | 139 ( 104 , 189 ) | 0.566 |
| Yes | 145 ( 120.5 , 205.5 ) | |
| AE (overall) | | |
| No | 126 ( 91.2 , 166.8 ) | 0.088 |
| Yes | 147 ( 114.5 , 202 ) | |

*Only 58 patients have been included in the analysis for stent duration. 16 patients have been excluded for the following reasons: 3 passed away, 7 experienced stent migration, 3 did not remove the stent, 2 underwent surgery and 1 was lost at follow-up.*

**DISCUSSION**

Our results suggest that using metal stents instead of plastic improve the chance of achieving successful pseudocyst drainage at 6 weeks (95% vs 75%). These results are consistent with other published studies[55,57,93]. Metal stents have a larger diameter lumen than plastic stents and therefore drain the collection faster and are also less likely to become occluded.

There was no statistically significant difference in clinical success at 6 months, 76% for patients with metal stents vs 64% for plastic. Other studies have reported higher rates of long-term clinical success[94,95]. Varadarajulu et al left plastic stents in situ indefinitely for patients with pancreatic ductal disruption and reported 5% recurrence with a median follow up duration of 356 days[94]. Two other studies have found reduced recurrence in association with leaving plastic stents in situ[53,96].

Early adverse events were significantly less frequent in patients receiving metal stents (8% vs 33%). Although specific adverse events were not statistically significantly increased in the plastic stent group, bleeding, readmission, and infection were all higher in this group. Readmissions were due to pain (n=6) or infection (n=2) following drainage, this is likely to represent inferior drainage of the pseudocyst with plastic stents. Infection is a commonly reported complication after insertion of plastic stent insertion occurring in 12-14%[57,97] of cases. Bleeding was more common with plastic stents, this may be due to the routine balloon dilatation of the tract when inserting plastic stents that does not occur for FCSEMS insertion. There was no difference in total adverse events between plastic and metal stents. This is due to high rates of stent migration with metal stents (16%).

We found that more patients required further endoscopic, surgical or endoscopic procedures after insertion of a plastic stent. Indications for repeat intervention were recurrence (55%), treatment failure (27%) or infection (18%) following drainage. One of the concerns regarding the routine use of metal stents is the increased cost compared to plastic stents. Although some studies have compared the procedural costs[81,98], currently there is no cost effectiveness analysis that considers complications or follow up costs and the potential costs of managing recurrence or treatment failure. Our results suggest patients with plastic stents are significantly more likely to require further treatment for pseudocyst management, which may offset the initial increase in cost.

Metal stents were left in situ for a median duration of 17 weeks and 23 weeks for plastic stents. There was no significant difference in success or requirement for further intervention

related to the length of time the stent remained in situ. When the stent was left in for longer, adverse events were more frequent although this does not quite reach statistical significance (p=0.088). The interim analysis of a randomised controlled trial demonstrated high rates of stent related complications and the study protocol was amended to a CT scan at 3 weeks and then stent removal, brought forward from 4-6 weeks[55]. Whilst our study has not shown similar rates of adverse events we have amended our protocol to ensure metal stents are removed sooner than 18 weeks post insertion.

There are several limitations of this study. It is retrospective with the inherent bias of this study design. Another important cause of bias is due to time period that the stents were inserted. We first started inserting metal stents in 2012, however plastic stent insertion occurred after this point. This may have led to selection bias with plastic stents being used in smaller or more favourable collections. We inserted a single plastic stent; other comparative studies have used the multiple gateway technique. This has been shown to improve success in WON[53], however it is time consuming, and we think increases the incidence of procedural adverse events.

Our results suggest that metal stents have several advantages over plastic stents for the drainage of symptomatic pancreatic pseudocysts. They result in improved drainage at 6 weeks and fewer early adverse events. Importantly, patients who had metal stents inserted were less likely to require a further procedure for management of their pseudocyst. Further randomised controlled trials are required to fully address the issue.

## CHAPTER FOUR: Treatment of walled off pancreatic necrosis by indirect transluminal irrigation endoscopic necrosectomy

### INTRODUCTION

Endoscopic necrosectomy has become first line treatment in many centres, it is minimally invasive, allows effective debridement of necrotic tissue and does not require external drains. Direct endoscopic necrosectomy was first described by Baron in 1996 [42]. Multiple studies have been published describing multiple debridement techniques, however there is no current consensus as to the optimum way of performing the procedure or treatment protocol for repeat procedures[47].

LAMS allow easy endoscopic access to the cavity and debridement of necrotic tissue can be performed using endoscopic balloon, forceps, snares and retrieval baskets. Some studies using these techniques report a relatively high incidence of adverse events[49,55]. Indirect transluminal irrigation necrosectomy is a less invasive technique with no instrumentation within the cavity. Jet pump irrigation is used, through a biliary catheter if required, to flush and loosen necrotic tissue which is then debrided with suction. Small series have suggested this method reduces the rate of serious adverse events[46].

#### Aim

We report the outcomes for 50 consecutive patients undergoing indirect transluminal irrigation necrosectomy for walled off necrosis in a single tertiary centre. The purpose of this study was to assess the effectiveness and safety of this technique for managing patients with walled off necrosis with regard to treatment success, adverse events and length of hospital stay.

### METHODS

#### Patients

Patients were prospectively entered on to a database. All patients undergoing endoscopic drainage of walled off necrosis were included in this analysis. Patients with pseudocysts were excluded from this analysis. Patients with acute pancreatitis were managed according to the IAP/APA guidelines[9]. An enhanced pancreas protocol CT scan was performed within 72-96 hours from symptom onset or on admission if the diagnosis was not clear. The CT scan was repeated if there was a change in clinical condition, a significant rise in inflammatory markers or if an intervention was planned. Surgical intervention was delayed until at least 4 weeks

after onset of symptoms unless the clinical condition of the patient mandated earlier necrosectomy. Indications for intervention were infected or suspicion of infected necrosis with clinical deterioration, ongoing gastric outlet obstruction or persistent pain, vomiting or 'unwellness'[9].

The management plan for each patient was agreed at the benign multi-disciplinary team meeting, attended by pancreatic surgeons, gastroenterologists and radiologists. Clinical information and radiological images were available to enable decision making.

**Endoscopic technique**

The procedure is performed under sedation with fentanyl and midazolam with a linear echoendoscope. The optimum site for cystogastrotomy is decided by either identifying a clearly bulging lesion or using by EUS to identify the cavity, in combination with analysis of radiological images. A transgastric route is preferred but a transduodenal route was used when appropriate.

We used 3 metal stents over the study period, 11mm Evolution (Cook medical), 16mm Nagi stent (Taewoong Medical Co. Ltd) or 15mm Hot AXIOS stent (Boston Scientific). For insertion of FCSEMS (Evolution and Nagi) the cyst cavity is punctured with a 19g needle. Fluid is aspirated and sent for microbiology. Under fluoroscopic guidance a guidewire was advanced in to the collection and the tract dilated to 8-12mm with a radial expansion balloon. The stent is placed over the guidewire in to the cavity under EUS and direct vision. The Hot AXIOS stent includes an enhanced delivery system allowing single stage insertion. Fluoroscopy was not required for most Hot AXIOS stent insertions.

Minimal tissue is debrided during the initial procedure. Our unit perform 'flush' necrosectomy, the main mode of debridement is irrigation using an endoscopic jet irrigation pump allowing suction and removal of necrotic material. A plastic cap is secured to the tip of the endoscope to aid suction. The irrigation can be delivered through a biliary stent if required which delivers improved debridement if the stent has become blocked with necrotic tissue. An endoscopic balloon is sometimes used to re-establish a tract within a blocked stent or as an adjunct for the debridement. Nasocystic tubes are not routinely placed for continuous irrigation. Co-axial double pigtail stents are inserted to help maintain stent patency at the discretion of the endoscopist.

The patient returns for scheduled repeat procedures every 7 days, more frequently if there is a clinical deterioration. Cross sectional imaging in combination with endoscopic

appearance dictate the need for further necrosectomy. The stent is removed following resolution of the collection, typically at 6-8 weeks post insertion. Other collections were drained percutaneously if required, if endoscopic treatment failed then patients were considered for minimal access retroperitoneal necrosectomy or open necrosectomy as appropriate. Patients were followed up in clinic at regular intervals to assess radiological and clinical response.

**Data items and definitions**

Treatment success was defined as resolution of symptoms and discharge from hospital with at least an 80% reduction in the size of the collection. Adverse events were divided in to procedure related and non- procedure related adverse events. Procedure related adverse events were stent migration, stent malfunction, perforation, bleeding requiring intervention and superadded infection. Mortality was defined as inpatient mortality or death within 6 months of index procedure. Infected pancreatic necrosis was defined as positive pancreatic tissue or FNA cultures or gas within the collection on CT scan.

**Statistical analysis**

The descriptive statistics were performed on patient characteristics and outcome measures. The categorical variables are described using frequencies and proportion percentages, while for the continuous variables, the median and IQR are presented. Either a Fisher exact test, a Chi-square test or a Wilcoxon-Mann-Whitney test were performed appropriately to examine if there are any statistically significant differences between adverse events or treatment success. The statistically significant level was set to be 5% (p values $< 0.05$). A univariate analysis, using a logistic regression, was conducted for each variable for both the outcome variables, adverse events and treatment success. On the statistically significant variables highlighted through the univariate analysis, a multivariate logistic regression was conducted. A backward selection was conducted using an Akaike inclusion criterion (AIC), to find the most suitable model.

**RESULTS**

**Patients**

The demographics of included patients are shown in Table 1. Fifty consecutive patients underwent endoscopic necrosectomy from May 2015- June 2017 in our centre. 20% of patients were admitted to ITU prior to the procedure. Two-thirds of patients were tertiary

referrals from other centres. The median time from onset of symptoms to transluminal stent placement was 31 days (IQR 11-47). The median pre-operative modified CT severity index was 8 (IQR 8-10), classified as severe pancreatitis. Indication for intervention was confirmed or suspected infected pancreatic necrosis in 66% of patients.

*Table 1: Patient demographics*

| *Patient Demographics* | |
|---|---|
| Age, *median (IQR)* | 62 ( 50-73) |
| Male, *n (%)* | 34 (68) |
| Aetiology, n (%) | |
| ***Biliary*** | 29 (58) |
| ***Alcohol*** | 11 (22) |
| ***Idiopathic*** | 5 (10) |
| ***Other*** | 5 (10) |
| ITU pre-procedure, *n (%)* | 10 (20) |
| APACHEII score, *median (IQR)* | 7 (3-10) |
| Tertiary referral, *n (%)* | 33 (66) |
| Highest CRP day 0-7 (median, IQR) | 156 (62-250) |
| Time to intervention, days (median, IQR) | 31 (11, 47) |
| Indication for intervention, n (%) | |
| ***Infected or suspected infected pancreatic necrosis*** | 33 (66) |
| ***Persistent symptoms or gastric outlet obstruction*** | 17 (34) |
| Diameter of collection (mm), *median (IQR)* | 118 (88-149) |
| Site of collection, *n (%)* | |
| ***Head*** | 11 (22) |
| ***Body*** | 34 (68) |
| ***Tail*** | 5 (10) |
| Infected pancreatic necrosis, *n (%)* | 23 (46) |
| Modified CT severity index, median (IQR) | 8 (8, 10) |

Procedural details are reported in Table 2. The median number of procedures required for WON resolution, excluding stent removal, was 4. At the beginning of the study period Nagi stents were predominantly used, later on our preference was to use the Hot AXIOS stent. 8 patients underwent multiple stent placement, either in to a separate or loculated part of the collection or in to the same collection to enhance drainage. The median duration until stent removal was 11 weeks (77 days).

*Table 2: Procedural characteristics*

| *Procedural characteristics* | |
|---|---|
| Number of necrosectomy procedures, median, (range) | 4 (1-10) |
| Route, n (%)<br>***Transgastric***<br>***Transduodenal***<br>***Both***<br>***Not specified*** | <br>46 (92)<br>1 (2)<br>1 (2)<br>2 (4) |
| Stent used, *n (%)*<br>***Hot AXIOS***<br>***Nagi***<br>***Evolution*** | <br>30 (60)<br>19 (38)<br>1 (2) |
| Multiple gateway technique, n (%) | 8 (16) |
| Duration stent in situ (days), median (IQR) | 77 (57-91) |
| Nasocystic irrigation | 4 (8) |

Outcomes for endoscopic necrosectomy are shown in Table 3. Management of WON with endoscopic necrosectomy was successful in 84% of patients. 4 (8%) patients required additional surgical or endoscopic drainage. 4 (8%) patients died during the inpatient admission due to multiple organ failure. The total length of stay, from onset of symptoms to discharge was 54 days (IQR 29-81). The median duration of admission post index procedure was 21 days (IQR 9-42). Procedure related adverse events occurred in 22 (44%) of patients (Table 4). Stent related adverse events occurred in 17 (34%) patients; stent migration occurred in 18% and stent malfunction in 16% of patients. However, only 7 (14%) of patients required further intervention as a result of stent problems, 5 patients required a further stent insertion and 1 patient required endoscopic stent removal under general anaesthetic. In one patient the stent (hot AXIOS) became embedded and required surgical removal. Post procedure, two patients presented with signs of peritonitis and pneumoperitoneum on CT scan consistent with perforation although no definite site of perforation was seen. 12 (24%) patients were readmitted due to pancreatitis or procedure related problems.

*Table 3: Outcomes*

| *Outcomes* | |
|---|---|
| Treatment success, n (%) | 42 (84) |
| Additional drainage required, n (%) | |
| ***Surgical*** | 3 (6) |
| ***Endoscopic*** | 1 (2) |
| Total hospitalisation (days), median, (IQR) | 54 (29,81) |
| Post-operative length of stay (days), median, (IQR) | 21 (9,42) |
| Length of stay ITU (days), median (IQR) | 0 (0,0) |
| Percutaneous drain, n (%) | 15 (30) |
| Adverse events (Overall) | 33 (66) |
| ***Non-procedure related adverse events*** | 23 (46) |
| ***Procedure related adverse events*** | 22 (44) |
| Mortality | 4 (8) |
| Readmission | 12 (24) |

*Table 4: Specific adverse events*

| *Adverse event* | *Frequency (%)* |
|---|---|
| Stent migration | 9 (18) |
| Stent malfunction | 8 (16) |
| Perforation | 2 (4) |
| Bleeding requiring intervention | 1 ( 2) |
| Superadded infection | 6 (12) |
| HAP | 5 (10) |
| Persistent Sepsis & MOF | 4 (8) |
| PV Thrombosis | 3 (6) |
| SMV Thrombosis | 7 (14) |
| Persistent fistula | 1 (2) |
| Cardiac | 2 (4) |
| PE | 2 (4) |
| Other | 1 (4) |

The length of pre-operative ITU stay (1 vs 0 days, p=0.018) and modified CTSI (10 vs 8, p=0.041) were significantly higher in patients that were not managed successfully by endoscopic necrosectomy (Table 5). Univariate regression analysis found a longer ITU admission reduced the odds of treatment success (OR 0.92, 95% CI 0.874- 0.986, p=0.016) (see Table 6).

*Table 5: Demographic and Preoperative Data comparing treatment success to failure*

| Characteristics | Treatment failure (n=8) | Treatment success (n=42) | P |
|---|---|---|---|
| Gender, n (%) | | | 0.699 |
| **Female** | 3 (37.5% ) | 13 (31.0% ) | |
| **Male** | 5 (62.5% ) | 29 (69.0% ) | |
| Age, median (IQR) | 66 ( 54, 74 ) | 62 ( 50, 73 ) | 0.781 |
| Aetiology of pancreatitis, n (%) | | | 0.737 |
| **Gallstones** | 4 (50.0% ) | 25 59.5% ) | |
| **Alcohol** | 2 (25.0% ) | 9 (21.4% ) | |
| **Idiopathic** | 1 (12.5% ) | 4 ( 9.5% ) | |
| **Other** | 1 (12.5%) | 4 ( 9.5% ) | |
| Transfer from another hospital, n (%) | 5 (62.5% ) | 28 (66.7% ) | 1.000 |
| Days from start of symptoms/admission to admission into RLBUHT, median (IQR) | 25 (17, 26 ) | 28 (12, 41 ) | 0.622 |
| CT width (mm), median (IQR) | 108 (78, 124 ) | 121 ( 88, 154 ) | 0.161 |
| CT severity score, median (IQR) | 10 ( 8, 10 ) | 8 ( 8, 10 ) | ***0.041*** |
| Average Hounsfield units (density from CT scan), median (IQR) | 7 (-3, 17 ) | 14 ( 9, 19 ) | 0.635 |
| Volume of collection from CT scan, median (IQR) | 249 197, 301 ) | 275 122, 405 ) | 1.000 |
| Pre-op stay in ITU, n (%) | 3 ( 37.5% ) | 7 ( 16.7% ) | 0.331 |
| Preoperative stay in ITU (days), median (IQR) | 1 (0,4) | 0 (0,0) | ***0.018*** |
| Highest CRP (day 0-7, median (IQR) | 217 (158, 253 ) | 138 (61, 232 ) | 0.262 |
| Type of Metal Stent, n (%) | | | 0.694 |
| **Nagi** | 4 ( 50.0% ) | 15 ( 35.7% ) | |
| **Hot Axios** | 4 ( 50.0% ) | 26 ( 61.9% ) | |
| Site, n (%) | | | 1.000 |
| **Head** | 2 (25.0% ) | 10 (23.8% ) | |
| **Body** | 5 (62.5% ) | 28 (66.7% ) | |
| **Tail** | 1 (12.5% ) | 4 ( 9.5% ) | |

*Table 6: Univariate Logistic Regression: Risk factors for treatment success*

| Characteristics | Treatment success (n=42) | | |
|---|---|---|---|
| | **Odds ratio** | **95% Confidence interval** | **P** |
| Age | 0.992 | (0.943,1.044) | 0.754 |
| Transfer from another hospital | 1.200 | 0.250,5.760) | 0.820 |
| CT width (mm) | 1.014 | (0.993,1.035) | 0.183 |
| CT severity score | 0.512 | (0.260,1.010) | 0.054 |
| Average Hounsfield units (density from CT scan) | 1.053 | (0.930,1.193) | 0.413 |
| Volume of collection from CT scan | 1.001 | (0.995,1.008) | 0.662 |
| Pre-op stay in ITU (days) | 0.953 | (0.892,1.017) | 0.149 |
| Day 7 CRP | 0.997 | (0.991,1.003) | 0.389 |
| Site | | | |
| **Body** | 1.120 | (0.187,6.720) | 0.901 |
| **Tail** | 0.800 | (0.056,11.504) | 0.870 |
| Total length of stay (days) | 0.994 | (0.980,1.008) | 0.427 |
| Length of stay in RLBUHT (days) | 0.986 | (0.966,1.006) | 0.160 |
| Post-op length of stay (days) | 0.982 | (0.957,1.007) | 0.160 |
| Total APACHE II score | 0.965 | (0.877,1.062) | 0.464 |
| Infected Necrosis | 0.227 | (0.041,1.259) | 0.090 |
| Total stay in ITU (days) | 0.928 | (0.874,0.986) | ***0.016*** |
| Number of procedures | 1.048 | (0.782,1.404) | 0.754 |
| Percutaneous drainage | 0.355 | (0.076,1.667) | 0.189 |
| Adverse event | 0.600 | (0.107,3.352) | 0.561 |

Table 7 demonstrates there was no significant difference in treatment success (86.7 vs 78.9%, p=0.694) or adverse events (63.6 vs 73.7%, p=0.541) between Hot AXIOS (LAMS) and Nagi (FCSEMS) stents in this cohort of patients. The one patient who had a Evolution stent placed was not included in this analysis. Although stent migration (26.3 vs. 13.3%, p=0.238) and procedure related adverse events (57.9 vs 36.7%, p=0.282) were found to be higher for Nagi stents, this did not reach statistical significance. All 8 patients that had multiple metal stents inserted experienced adverse events (100 vs 59.5%, p=0.0.39).

*Table 7: Outcomes for Nagi and Hot AXIOS stent*

| Outcomes by type of stent | Nagi n=19 | Hot AXIOS N=30 | p |
|---|---|---|---|
| Treatment success, n (%) | 15 (78.9) | 26 (86.7) | 0.694 |
| Adverse events, (Overall) n (%) | 14 (73.7) | 19 (63.3) | 0.541 |
| Procedure related adverse event, n (%) | 11 (57.9) | 11 (36.7) | 0.238 |
| Stent migration, n (%) | 5 (26.3) | 4 (13.3) | 0.282 |

**DISCUSSION**

Our results show indirect transluminal irrigation endoscopic necrosectomy is a safe an effective approach of treatment for walled off pancreatic necrosis. An endoscopic step up approach successfully treated 84% of patients, in keeping with other studies[46,83,86]. The mortality rate was 8%, lower than reported in our previous analysis of surgical necrosectomy[20,35] and there were no deaths as a result of procedural complications.

We have reported a higher incidence of adverse events than seen in other studies[29,43,46]. However, we report both procedure related and non-procedure related complications. Other studies are limited by not reporting clinical or physiological parameters of patients [54,83]. Data for pre-operative CRP, ITU admission, APACHEII score and modified CTSI suggest severe pancreatitis in acutely unwell patients. In addition, 30% of patients required additional percutaneous drainage for extra-pancreatic or complex collections.

An important topic in current debate regarding endoscopic necrosectomy is the optimum technique for performing the procedure[48,99]. Indirect irrigation necrosectomy allows adequate debridement without the potential increased risks of entering and instrumentation within the cavity[46]. Patients undergo a planned return for repeat endoscopic necrosectomy every 7 days until there endoscopic and radiological resolution of the collection. Three patients underwent open pancreatic necrosectomy, in 2 cases this was due to unsatisfactory

clinical response to EN and in one patient following difficulty and bleeding during attempted stent placement. We did not find nasocystic catheters and irrigation helpful as they frequently became displaced and were poorly tolerated. In selected patients with large or loculated collections, we inserted two LAMS in to different positions. These patients all experienced an adverse event. 7/8 (87.5%) patients had a non-procedure related adverse event suggesting that this technique was used in the most unwell patients which led to complications rather than the technique itself. However, it is difficult with our currently relatively small numbers of patients treated with this technique to draw conclusions about its use. Multiple plastic stents have been shown to improve rates of treatment success for drainage of WON[53], however the benefit and safety of this technique with LAMS has not yet been described.

We do not use plastic stents for initial drainage of walled off necrosis as we believe the small diameter lumen is more likely to occlude and is less effective at draining debris and thick fluid. This is supported by multiple recently published studies favouring metal stent use[45,59,88,99]. Currently, there is debate about the preferred type of metal stent for WON drainage. Our results are in accordance with published studies [51,100] that found no difference in outcome between LAMS and FCSEMS, however FCSEMS used in these studies were not specifically designed for pancreatic fluid collection drainage. We found no difference in adverse events or treatment success between the two stents predominantly used, hot AXIOS (LAMS) and Nagi (FCSEMS).

Siddiqui et al reported using LAMS reduced stent occlusion and the number of procedures required for resolution of WON compared to FCSEMS, however early adverse events were significantly higher for LAMS[100]. They reported 11/86 patients experienced an early adverse event, including 3 (3.5%) perforations during stent insertion and 6 (7.0%) bleeds at stent site[100]. Bang et al observed high numbers of serious adverse events with delayed bleeding in 3/12 patients and embedded stent in 2/12 patients in a randomised controlled trial using LAMS[61]. In our experience so far, we have not found bleeding or embedded stents a significant problem. One patient had significant bleeding following LAMS insertion and required embolization and one patient required surgical removal of LAMS, in this case the stent was left in situ for longer than the unit's protocol. Two patients presented with abdominal pain and pneumoperitoneum following stent insertion and were managed successfully by conservative treatment. The design of LAMS and FCSEMS is likely to be the cause of these adverse events. Specifically designed LAMS and FCSEMS are 10-30mm in

length and were developed with shorter lengths than the biliary stents previously used. The antrum can be thicker than this and therefore it becomes difficult to oppose the two surfaces, leading to the stents becoming embedded and possible erosion in to vessels causing bleeding. The rate of stent migration (18%) is similar to previously published studies [45], however it is higher than seen in others[51,88]. This may be explained by the longer length of time the stent was left in situ (median 11 weeks) than other studies.

Indirect irrigation transluminal endoscopic necrosectomy is now our preferred treatment modality for necrotising pancreatitis requiring intervention. We report high rates of treatment success with acceptable rates of procedure or stent related adverse events.

## CHAPTER FIVE: An endoscopic approach for pancreatic necrosis may reduce length of stay compared to minimal access surgery

### INTRODUCTION

The preferred procedure for necrosectomy varies between centres and it is unclear whether an endoscopic or surgical approach is superior[38]. The position of the pancreatic fluid collection influences which approach is chosen, collections must be accessible via the stomach or duodenal wall for an endoscopic approach. Minimal access retroperitoneal pancreatic necrosectomy (MARPN) may not be possible for some right sided collections or if there is no safe percutaneous access route. The instruments available for debridement in for a surgical approach are more effective than the forceps, balloons or baskets used in endoscopic procedures. MARPN requires a drain to be left in situ with continuous saline irrigation, keeping a patient in hospital for the duration of this process which can often be several weeks. However, endoscopic procedures can be performed on an outpatient basis, allowing patients to be discharged earlier and does not result in any external drains, potentially improving quality of life and reducing fistula rates. Endoscopic necrosectomy (EN) can be performed on ITU, avoiding transfer to theatre in very unstable patients.

This is a retrospective comparative study of consecutive patients undergoing minimal access retroperitoneal necrosectomy and endoscopic necrosectomy in a single tertiary centre. The primary outcomes measure was adverse events. Secondary outcome measures were length of stay and mortality. We will also assess possible predictive factors for adverse events.

### METHODS

#### *Patients*

All patients undergoing intervention for walled off pancreatic or peripancreatic necrosis at the Royal Liverpool University Hospital were prospectively recorded on to a database. For this study we included consecutive patients admitted to hospital and underwent MARPN from January 1 2014- December 31 2015 and consecutive patients undergoing endoscopic necrosectomy from January 1 2016- June 30 2017. Discrete time periods were chosen to reduce selection bias. Patients were analysed on an intention to treat basis.

All patients with acute pancreatitis were managed in accordance with IAP/APA guidelines[9]. The type and timing of any intervention and overall management plan was agreed at the benign Multidisciplinary Team (bMDT) meeting attended by pancreatic surgeons, endoscopists and radiologists. Intervention was delayed until 4 weeks post onset of

symptoms unless the clinical condition of the patient required earlier necrosectomy or laparotomy. CT guided fine needle aspiration (FNA) was not routinely performed.

Hospital notes were interrogated and patient demographics, pre and post-operative radiology, APACHEII[101] and biochemistry results were recorded. Outcome measures recorded included treatment success, mortality, procedure specific and procedure non-specific related adverse events, hospital length of stay and ITU stay. Procedure specific adverse events were bleeding, stent malfunction, perforation, superadded infection and clinically significant stent migration. Procedure non-specific adverse events were defined as persistent fistula, hospital acquired pneumonia, myocardial infarction, other cardiac complication, persistent sepsis & multi-organ failure, pulmonary embolism, C.Difficile infection, portal vein thrombosis and SMV thrombosis. Treatment success was defined as discharge from hospital with greater than 80% reduction in size of walled off necrosis. Mortality was defined as death whilst an inpatient or within 3 months following discharge. Infected pancreatic necrosis was defined as either gas within the collection on CT imaging or positive pancreatic tissue or FNA cultures.

**Surgical and endoscopic techniques**

***MARPN***

Minimal access retroperitoneal pancreatic necrosectomy was performed as previously described[20,35]. A 12fr pigtail drain is inserted in to the cavity under CT guidance. The preferred route is via the left flank between the spleen and splenic flexure. In patients with complex or right sided collections drainage catheters were inserted anteriorly through the gastrocolic omentum or via the right flank. The patient is transferred to the operating theatre and appropriately positioned. MARPN can be performed under sedation or general anaesthetic. With fluoroscopic guidance, the pigtail catheter is exchanged for a guidewire and the tract is dilated up to 30fr using serial dilators. Using an operating nephroscope, necrotic tissue is removed piecemeal with forceps and tissue sent to microbiology. Necrosectomy during the initial procedure is limited by immature necrosis and oozing from cavity and further procedures are often required for adequate debridement. Following necrosectomy, a 28fr chest drain with a 10 or 12fr nasogastric tube sutured inside in inserted in to the cavity and saline irrigation commenced at an initial rate of 125ml/hr. Repeat MARPN are performed after 7-10 days until necrosectomy is completed and granulation tissue is visualized. A

fistulogram is performed to ensure the cavity has collapsed and the drain is downsized to a nasogastric tube. The patient is discharged with district nurse and regular clinical follow up.

***Endoscopic necrosectomy***

Endoscopic ultrasound (EUS) guided pancreatic necrosectomy has been performed in our unit from 2015 onwards. The procedure is performed under sedation with a linear echoendoscope. Puncture site is determined by EUS guidance or an obvious bulge in to the stomach, along with review of CT imaging. Cyst puncture was performed with a 19g needle and fluid aspirated and sent for culture. A fully covered self-expanding metal stent (FCSEMS) inserted in to the collection to facilitate drainage. Our preference is to use either a 16mm Nagi stent (Taewoong Medical Co. Ltd) or 15mm Hot AXIOS stent with enhanced delivery system (Boston Scientific). Fluoroscopy was not routinely used for Hot AXIOS stent insertion. We perform lavage or 'flush' necrosectomy using a water pump to irrigate the cavity and necrotic tissue and suction to move tissue in to the stomach. A plastic cap is secured to the tip of the endoscope to aid suction. A balloon is used if the stent is blocked with tissue. Instrumentation within the cavity is avoided wherever possible. Anchoring plastic stents are placed at the discretion of the endoscopist. The patient undergoes planned weekly repeat procedures until necrosectomy is complete, confirmed endoscopically and by CT imaging. The stent is removed after the cavity has collapsed, normally 6 weeks post insertion.

Additional percutaneous drains were inserted in to loculated or flank collections when clinically indicated.

**Statistical analysis**

Descriptive statistics were performed on patient characteristics and outcome measures. The categorical variables are described using frequencies and proportion percentages, while for the continuous variables, the median and IQR are presented. Either a Fisher exact test, a Chi-square test or a Wilcoxon-Mann-Whitney test were performed appropriately to examine if there are any statistically significant differences between the outcomes EN and MARPN. The statistically significant level was set to be 5% (p values $< 0.05$). A univariate analysis, using a logistic regression, was conducted for each variable for the outcome variables, mortality, adverse events, procedure specific adverse events and procedure non-specific adverse events. On all the statistically significant variables highlighted from the univariate analysis, a multivariate logistic regression was conducted. The most appropriate model was found using a backward selection on the multivariate model, using an Akaike information criterion (AIC).

## RESULTS

Forty-one consecutive patients underwent endoscopic necrosectomy in the study period and forty-three underwent MARPN. There was no difference in age, pre-operative APACHEII score and pre-operative ITU admission between the two groups. Maximum diameter of the collection was significantly higher in the MARPN patients (110mm vs 148mm, p=0.000). In the endoscopic group, 27 (65.9%) patients had a Hot AXIOS stent inserted and 14 (34.1%) had a Nagi stent.

*Table 1: Demographic and preoperative data*

| CHARACTERISTICS | | EN (n=41) | MARPN (n=43) | p |
|---|---|---|---|---|
| **Gender, n (%)** | **Male** | 29 ( 70.7% ) | 27 ( 62.8% ) | 0.647 |
| **Age, median (IQR)** | | 60 ( 49,74 ) | 53 ( 44,74 ) | 0.428 |
| **Aetiology of pancreatitis, n (%)** | | | | |
| | **Gallstones** | 21 ( 51.2% ) | 25 ( 58.1% ) | 0.830 |
| | **Alcohol** | 11 ( 26.8% ) | 6 ( 14.0% ) | |
| | **ERCP** | 2 ( 4.9% ) | 2 ( 4.7% ) | |
| | **Idiopathic** | 4 ( 9.8% ) | 1 ( 2.3% ) | |
| | **Other** | 2 ( 4.8% ) | 6 ( 14.0% ) | |
| | **Unknown** | 1 ( 2.4% ) | 3 ( 7.0% ) | |
| **Chronic Pancreatitis, n (%)** | | 6 (14.6%) | 1 (2.3%) | 0.351 |
| **Tertiary referral, n (%)** | | 26 ( 63.4% ) | 36 ( 83.7% ) | 0.232 |
| **Days to transfer, median (IQR)** | | 28 ( 17,33 ) | 25 ( 13,35 ) | 0.491 |
| **Days to intervention, median (IQR)** | | 30 ( 11,47 ) | 31 ( 21,41 ) | 0.419 |
| | **Missing** | 2 ( 4.9% ) | 0 ( 0% ) | |
| **Indication for intervention, n (%)** | | | | |
| | **Confirmed/suspected infected necrosis** | 26 ( 63.4% ) | 40 ( 93.0% ) | 0.120 |
| | **Gastric outlet /biliary obstruction or persistent symptoms** | 14 (34.1% ) | 3 ( 7.0% ) | |
| | **Missing** | 1 ( 2.4% ) | 0 ( 0% ) | |
| **Total APACHE II score, median (IQR)** | | 7 ( 2,10 ) | 8 ( 6,11 ) | 0.263 |
| **Location of collection** | | | | |
| | **Head** | 10 ( 24.4% ) | 5 ( 11.6% ) | 0.060 |
| | **Body** | 27 ( 65.7% ) | 26 ( 60.5% ) | |
| | **Tail** | 4 ( 9.8% ) | 12 ( 27.9% ) | |
| **CT width(mm), median (IQR)** | | 110 (88,141) | 148 (128,171) | 0.001 |
| **Modified CT severity index, n (%)** | | | | 0.391 |
| | **Moderate** | 10 (24.4%) | 5 (11.6%) | |
| | **Severe** | 31 (75.6%) | 38 (88.4%) | |
| **Pre-operative admission to ITU, n (%)** | | 9 (22.0%) | 16 (37.2%) | 0.357 |
| **Pre-op ITU stay (days), median (IQR)** | | 0 (0,0) | 0 (0,2) | 0.094 |

*Table 2: Postoperative outcomes*

| OUTCOME | EN (n=41) | MARPN (n=43) | p |
|---|---|---|---|
| **Total length of stay (days), median (IQR)** | 51 (22,78) | 95 (59,143) | **0.001** |
| **Length of stay in RLBUHT (days), median (IQR)** | 27 (17,53) | 71 (47,105) | **0.001** |
| **Post-operative length of stay (days), median (IQR)** | 19 (9,41) | 63 (39,86) | **0.001** |
| **Number of procedures, median (IQR)** | 3 (2,5) | 3 (2,4) | 0.205 |
| **Adverse events, n (%)** | 26 (63.4) | 38 (88.4) | 0.135 |
| **Adverse event – Procedural, n (%)** | 13 (31.7) | 9 (20.9) | 0.519 |
| **Adverse event – Procedure non-specific, n (%)** | 18 (43.9) | 36 (83.7) | **0.030** |
| **Infected Necrosis, n (%)** | 20 (48.8 ) | 38 (88.4) | **0.028** |
| **Total stay in ITU (days), median (IQR)** | 0 ( 0, 0 ) | 0 ( 0,17 ) | **0.048** |
| **Treatment success, n (%)** | 34 (82.9) | 32 (74.4) | 0.568 |
| **Percutaneous drainage, n (%)** | 12 (29.3) | 25 (58.1) | 0.101 |
| **Missing** | 0 (0) | 1 (2.3) | |
| **Mortality, n (%)** | 3 (7.3) | 9 (20.9) | 0.118 |

Treatment of pancreatic necrosis was successful for 82.9% of EN patients and 74.4% of MARPN patients (p=0.568). The total length of hospitalisation was significantly higher in the MARPN group, 51 days vs. 98 days (p<0.001). Post-operative length of stay was also significantly higher for MARPN, 21 vs. 65 days (p<0.001). Patients undergoing MARPN had a significantly longer ITU admission (p=0.048), both groups had a median stay of 0 days however the IQR was 0-17 in the MARPN group. Procedure non-specific adverse events were higher for MARPN (43.9% vs. 83.7%, p=0.030). Procedure specific adverse events occurred in 31.7% of patients undergoing EN and 20.9% of MARPN (p=0.519). Mortality was 7.3% for EN and 20.9% for MARPN (p=0.118). Confirmed infected pancreatic necrosis was higher for MARPN (88.4 vs. 48.8%, p=0.028). Table 3 shows there are no significant differences in specific post-operative complications between EN and MARPN in this cohort of patients.

*Table 3: Details of postoperative adverse events*

| ADVERSE EVENT | EN (n=41) | MARPN (n=43) | p |
|---|---|---|---|
| **Bleeding- no intervention, n (%)** | 2 (4.9% ) | 4 (9.3% ) | 1.000 |
| **Bleeding- intervention, n (%)** | 1 (2.4% ) | 2 (4.7% ) | 1.000 |
| **Persistent fistula, n (%)** | 1 (2.4% ) | 10 ( 23.3% ) | 0.102 |
| **Hospital acquired pneumonia, n (%)** | 5 ( 12.2% ) | 7 ( 16.3% ) | 0.749 |
| **Cardiac, n (%)** | 1 (2.4% ) | 8 ( 18.6% ) | 0.164 |
| **Persistent sepsis & MOF, n (%)** | 4 (9.8% ) | 7 ( 16.3% ) | 0.772 |
| **Pulmonary embolism, n (%)** | 2 (4.9% ) | 1 (2.3% ) | 0.663 |
| **Portal vein Thrombosis, n (%)** | 3 (7.3% ) | 2 (4.7% ) | 0.717 |
| **SMV Thrombosis, n (%)** | 6 ( 14.6% ) | 3 (7.0% ) | 0.565 |
| **Other , n (%)** | 6 ( 14.6% ) | 8 ( 18.6% ) | 0.771 |
| **Readmission, n (%)** | 10 ( 24.4% ) | 9 ( 20.9% ) | 0.853 |
| **Missing, n (%)** | 0 ( 0% ) | 1 (2.3% ) | |

### *Modelling – Univariate and multivariate analysis*

The results of the univariate regression analysis for adverse events and death are shown in table 4. Pre-operative ITU admission (p<0.000), duration of ITU admission (p=0.006), APACHE II score (p=0.001) and percutaneous drainage (p=0.031) significantly increased the risk of inpatient mortality. MARPN (p=0.01), tertiary referral (p=0.033) and post-operative length of stay (p=0.021), suspected or confirmed infected pancreatic necrosis (p=0.011) increased the risk of experiencing an adverse event. Multivariate logistic regression found per day increase in post-operative stay, the odds of experiencing an adverse event increased by 9.5%.

*Table 4: Univariable Logistic Regression: Risk factors for adverse events and death*

| Characteristics | Death (n=12) | | | Adverse event (n=64) | | |
|---|---|---|---|---|---|---|
| | OR | 95% Confidence Interval | P | OR | 95% Confidence Interval | P |
| **Gender (Baseline=Female) Male** | 2.826 | (0.575,13.893) | 0.201 | 1.103 | (0.383,3.172) | 0.856 |
| **Aetiology of Pancreatitis (Baseline=Gallstones) Alcohol** | 1.018 | (0.236,4.39) | 0.981 | 1.021 | (0.276,3.784) | 0.975 |
| **Other** | 0.238 | (0.028,2.035) | 0.190 | 1.006 | (0.299,3.377) | 0.993 |
| **Tertiary referral (Baseline=No)** | 0.000 | (0.000,∞) | 0.994 | 3.210 | (1.100,9.366) | ***0.033*** |
| **Days from start of symptom/admission to admission into RLBUHT** | 1.011 | (0.986,1.038) | 0.391 | 0.989 | (0.968,1.011) | 0.339 |
| **Days to intervention** | 1.004 | (0.976,1.032) | 0.803 | 0.983 | (0.961,1.006) | 0.156 |
| **Indication for intervention (Baseline=Confirmed/suspected infected necrosis) Outlet obstruction/persistent symptoms** | 0.000 | (0.000,∞) | 0.991 | 0.225 | (0.071,0.712) | ***0.011*** |
| **CT width (mm)** | 1.008 | (0.994,1.023) | 0.258 | 1.006 | (0.996,1.018) | 0.374 |
| **Modified CTSI (Baseline=Moderate) Severe** | 0.000 | (0.000,∞) | 0.992 | 1.800 | (0.533,6.075) | 0.344 |
| **Pre-op ITU stay (Baseline=No)** | 19.000 | (3.755,96.126) | ***0.000*** | 1.953 | (0.580,6.574) | 0.279 |
| **Pre-op stay in ITU (days)** | 1.041 | (0.972,1.116) | 0.252 | 1.005 | (0.932,1.084) | 0.900 |
| **Total length of stay (days)** | 1.005 | (0.993,1.017) | 0.435 | 1.009 | (0.997,1.020) | 0.132 |
| **Length of stay in RLH (days)** | 1.003 | (0.988,1.019) | 0.659 | 1.021 | (1.003,1.039) | ***0.019*** |
| **Post-op length of stay (days)** | 1.006 | (0.990,1.022) | 0.460 | 1.030 | (1.009,1.052) | ***0.006*** |
| **Infected Necrosis (Baseline=No)** | 2.500 | (0.507,12.324) | 0.260 | 3.000 | (1.057,8.515) | ***0.039*** |
| **Post-op ITU stay (Baseline=No)** | 27.727 | (5.334,144.138) | ***0.000*** | 8.636 | (1.08,69.063) | ***0.042*** |
| **Total stay in ITU (days)** | 1.049 | (1.014,1.085) | ***0.006*** | 1.045 | (0.986,1.107) | 0.140 |
| **Total APACHE II score** | 1.156 | (1.060,1.262) | ***0.001*** | 1.107 | (0.991,1.237) | 0.073 |
| **Treatment success (Baseline=No)** | 0.000 | (0.000,∞) | 0.995 | 0.000 | (0.000,∞) | 0.991 |
| **Percutaneous drainage (Baseline=No)** | 4.607 | (1.147,18.509) | ***0.031*** | 2.260 | (0.770,6.632) | 0.138 |
| **Type of surgery (Baseline=EN) MARPN** | 3.353 | (0.838,13.410) | 0.087 | 4.385 | (1.419,13.551) | ***0.010*** |

*Table 5: Multivariable Logistic Regression: Risk factors for adverse events*

| Characteristics | Adverse events (n=58) | | |
|---|---|---|---|
| | OR | 95% Confidence Interval | P |
| **Indication for intervention (Baseline=Confirmed/suspected infected necrosis) Outlet obstruction/persistent symptoms** | 0.217 | (0.050,0.938) | ***0.041*** |
| **Length of stay in RLBUHT (days)** | 0.944 | (0.877,1.016) | 0.127 |
| **Post-op length of stay (days)** | 1.095 | (1.010,1.187) | ***0.027*** |

**DISCUSSION**

Previous studies and an ongoing trial [17,29,102,103] have used plastic pigtail stents for the endoscopic intervention arm. Plastic stents have smaller lumens and are less resistant to occlusion from necrotic debris compared to newer lumen apposing metal stents. This is a comparison of endoscopic necrosectomy using fully covered self-expanding and lumen apposing metal stents with MARPN.

The mortality rate for EN was 7.3% vs 20.9% for MARPN (p=0.118). These results are in keeping with other published studies[104], but higher than our previously reported mortality for MARPN (15.3%) [20]. The difference may be due to the comparatively small sample size in the present study. Procedure non-specific adverse events were significantly more frequent for MARPN compared to EN (44 vs 84%, p=0.030). It is known that minimally invasive techniques reduce the pro-inflammatory response to surgery compared to open operations[37]. A previous RCT found endoscopic necrosectomy reduces the post-operative levels of the inflammatory cytokine IL-6 compared to a surgical step up approach [17]. This is also supported by a significantly shorter ITU stay for EN patients (IQR 0,0 vs 0, 17 days, p=0.048), suggesting improved progression following EN.

One of the key findings from our results is the reduced length of stay for EN patients. Total hospitalisation and post-operative length of stay were significantly lower when compared to MARPN (51 vs. 98 days, p<0.001 and 21 vs 65 days, p<0.001). These results are in keeping with our previously published results for MARPN (98 days)[20]. Our protocol for EN is for the first 2 procedures to be performed whilst an inpatient, and if required any further procedures can be performed on an outpatient basis providing the patient is well enough for discharge. MARPN patients are required to stay in hospital until drain irrigation has been stopped and the drain downsized, contributing to the increased length of stay. It is reassuring there was no increase in readmission for the endoscopic approach suggesting the protocol is safe (24.4% vs 20.9%, p=0.853). Multivariate analysis found per day increase in post-operative length of stay increased the risk of a procedure non-specific adverse event by 9.5%. These results suggest endoscopic necrosectomy has the potential to reduce cost per patient for management of pancreatic necrosis and reduce the morbidity burden to the patient.

The inclusion criteria and date selections were designed to reduce selection bias however the study remains limited by this as MARPN was also performed during the EN study period. MARPN can be performed out of hours more easily due to the limited availability of suitably

trained endoscopists so the most unwell patients who required urgent intervention may have been treated by MARPN. However, APACHEII score (7 vs 8, p=0.263) and pre-operative ITU admission (22% vs. 37%, p=0.357) were not significantly different between the two groups. The majority of patients undergoing intervention were referrals from other hospitals (63% and 84% for EN and MARPN respectively). Infected pancreatic necrosis was present in a significantly higher number of MARPN patients (48.8 vs 88.4%, p=0.0.028). However, 28 (68.3%) EN patients did not have pancreatic tissue or fluid sent for culture therefore this result is unlikely to be accurate.

Both EN and MARPN are safe and effective ways of managing pancreatic necrosis. Approximately 30% of patients are unsuitable for MARPN due to the collection being inaccessible percutaneously[20]. In the past these patients have been managed by open necrosectomy, associated with higher mortality rates and increased morbidity [65]. EN offers a different minimally access approach that solves many of the anatomical issues found with MARPN, with the advantages of a significantly shorter hospital admission and reduced morbidity.

## CHAPTER SIX: An outcome and cost analysis of endoscopic, minimal access and open pancreatic necrosectomy

Saunders R, Hughes F, Evans JC, Smart H, Ghaneh P, Ramesh J, Sutton R & Halloran C. 2021. Cost Analysis and Outcomes of Endoscopic, Minimal Access and Open Pancreatic Necrosectomy. Annals of Surgery Open 2: e068 - e068.

(See Supporting Papers, page 97)

### INTRODUCTION

For the last decade minimally invasive pancreatic necrosectomy has been the gold standard of management for pancreatic necrosis requiring intervention[9,29]. In recent years endoscopic transluminal drainage and necrosectomy has been developed and has been shown to be an effective alternative for appropriate patients [17,29].

Patient level information and costing systems (PLICS) will become mandatory for acute activity in NHS hospitals for the 2018/19 financial year, moving forward from reference costs[105]. Costings are derived from tracking all resources used by an individual patient during their admission and calculating the actual costs incurred. This provides several advantages over the previous reference system which was based on healthcare resource (HRG) averages and cannot be easily linked to an individual patient[106]. Patient level costs allow for more accurate comparisons between different organisations nationally and provides more accurate data for agreeing on local pricing for patient care. It is also more accessible for clinicians allowing validation of activities and costs and a potential avenue of improving care pathways[105].

Previous cost comparisons of endoscopic necrosectomy and a step up surgical approach have demonstrated a trend towards reduced cost for an endoscopic approach [29,107,108]. The aim of this retrospective study is to evaluate any potential cost benefit for a particular intervention for pancreatic necrosis by performing a clinical comparison and cost-consequence analysis using individual patient costings.

### PATIENTS & METHODS

#### *Patients*

All patients undergoing pancreatic necrosectomy at the Royal Liverpool University Hospital from 1 April 2015- 31 March 2017 were included and analysed on an intention to treat basis. Patients with admissions extending out of these times were excluded from the study. Patients were prospectively recorded on to an electronic database.

Patients were managed in accordance with current IAP/APA guidelines[9]. Intervention was delayed until 4 weeks post onset of acute necrotising pancreatitis unless the clinical condition of the patient necessitated earlier drainage or laparotomy. Every patient was discussed at the weekly benign multi-disciplinary team (MDT) meeting, attended by pancreatic surgeons, endoscopists, radiologists and specialist nurses. The overall management plan and the nature of any required intervention was agreed by the MDT. The mode of intervention was decided on a patient by patient basis, taking in to account collection and patient characteristics.

**Surgical techniques**

***Minimal access surgical step up approach***

Minimal access retroperitoneal pancreatic necrosectomy (MARPN) was performed as previously described [20,35]. Initial percutaneous drainage is performed with a 12 French pigtail catheter inserted under CT guidance. In patients with central or left sided collections, the drainage catheter is inserted via the left flank between the spleen and splenic flexure. It is possible to insert catheters anteriorly or via the right flank in patients with right sided or complex collections. MARPN can be performed under general anaesthetic or sedation. The pigtail drain in exchanged for a guidewire under fluoroscopic guidance and the tract dilated up to 30 Fr using serial dilators. A sheath is inserted in to the tract allowing the passage of an operating nephroscope. Necrosis is removed piecemeal under direct vision with minimal necrosectomy occurring on the initial procedure due to immature necrosis and to prevent bleeding. Tissue samples are sent to microbiology for culture and sensitivities. A 10 or 12 Fr nasogastric tube is sutured inside a 28 Fr chest drain and inserted in to the cavity allowing post-operative irrigation. Repeat MARPN are performed after 7-10 days until necrosectomy is complete and healthy granulation tissue is visualised. A fistulogram is performed to confirm the cavity has collapsed. The chest drain is downsized to a nasogastric tube and the patient can be discharged if fit.

***Endoscopic step up approach (EN)***

Endoscopic transluminal drainage is the initial intervention in an endoscopic step up approach. Under endoscopic ultrasound (EUS) guidance the optimum site for stent placement is established. Cyst puncture is performed with a 19 gauge needle and aspirated fluid is sent for culture. A lumen apposing metal stent (LAMS) with enhanced delivery system (Hot AXIOS, Boston Scientific) or biflanged metal stent (Nagi, Taewoong Medical Co.Ltd) are placed in to the collection. Fluoroscopy was not routinely used for Hot AXIOS stent insertion. Necrosectomy is then performed using the 'flush' method of extra-cavity lavage using jet pump irrigation and suction[46]. A cap is placed on the tip of the endoscope to aid suction. Instrumentation and debridement is avoided within the WON cavity. A radial expansion balloon or snares are used to unblock the stent if required. The patient undergoes weekly scheduled repeat necrosectomy procedures until necrosectomy is complete. Once imaging has confirmed the cavity has completely collapsed the stent is removed, preferably within 6 weeks of insertion. Multiple metal stents or anchoring plastic stents are used at the discretion of the endoscopist.

***Open necrosectomy (ON)***

Open necrosectomy was performed with post-operative closed local lavage [20,109]. At least 2 wide bore drains were placed in to the cavity through separate incisions for irrigation. Abdominal packing and second look laparotomies were not routinely performed.

For all techniques additional percutaneous drains were inserted in to flank or loculated collections when indicated.

**Statistical analysis**

Descriptive statistics were performed on patient characteristics and outcome measures. A Chi-square test or a Kruskall Wallis test was performed to test for statistical significance at the 5% level. Univariate and multivariate logistic regression modelling was also performed.

**Outcomes**

Length of stay including any admission in the referring centre was calculated. Procedure related adverse events included bleeding requiring intervention, perforation, problematic fistulae and stent related events. Clinical adverse events were defined as hospital acquired pneumonia, persistent sepsis, pulmonary embolism, cardiac events, and venous thrombus. Additional percutaneous drainage was defined as a radiological guided drain in to an extra-pancreatic collection.

**Economic analysis**

Individual patient costs were provided by the hospital finance department for 2015-2016 and 2016-17 financial years using patient-level information and costing systems (PLICS). Individual patient costs for all diagnostic tests, treatment, inpatient stay, ITU stay and outpatients were available. Endoscopy records were also interrogated to provide an accurate cost of any stents or disposable equipment used as this is not currently represented in the PLICS data.

The drugs/treatment category included drugs, high cost drugs, pharmacy costs, and transfusion services. Staff costs consisted of both medical staff and allied health professionals including physiotherapists, dieticians, occupational therapists and specialist nurses. The Clinical Negligence Scheme for Trusts (CNST) contributions were not included in the analysis.

A cost consequence analysis (CCA) was performed due to the difficulties in establishing one discrete outcome for the procedure required for cost-effectiveness analysis. A CCA is a practical method by which cost and outcome data can be structured to enable decision makers to improve the decision making process.

We performed a cost comparison of EN and MARPN as multiple studies have demonstrated that a minimal access approach is preferred compared to open necrosecromy[17,20,110], therefore OPN would not be interventional approach chosen unless there were extenuating factors which meant an open approach was necessary.

**RESULTS**

***Clinical outcomes***

In total, there were 86 patients included the analysis. There were 38 patients treated endoscopically, 35 underwent minimal access retroperitoneal necrosectomy and 13 patients were managed by open necrosectomy. Patient demographic information is shown in Table 1. There is no difference in sex, age, aetiology, number of tertiary referrals, time to intervention, or modified CT severity score between the 3 groups. There was a significant difference in maximum width of collection (113mm vs 106mm vs 147mm, $p<0.001$) and in location of collection, 91.4% of patients undergoing MARPN had WON in the body or tail and the collection in 89.5% of endoscopic patients was in the head or body. Patients undergoing

ON and MARPN had higher APACHE II scores (6 vs 9 vs 9, p=0.017) and higher CRP levels than those patients treated by EN (107 vs 278 vs 204, p=0.012).

*Table 1: Patient demographics*

| Characteristics | Sub-group | EN (N=38) | OPN (N=13) | MARPN (N=35) | Total (N=86) | P-value |
|---|---|---|---|---|---|---|
| **Gender, n (%)** | Female | 12 ( 31.6% ) | 6 ( 46.2% ) | 12 ( 34.3% ) | 30 ( 34.9% ) | 0.633 |
| | Male | 26 ( 68.4% ) | 7 ( 53.8% ) | 23 ( 65.7% ) | 56 ( 65.1% ) | |
| **Age, median (IQR)** | | 58 ( 47, 72 ) | 58 ( 55, 71 ) | 69 ( 49, 75 ) | 60 ( 49, 74 ) | 0.532 |
| **Aetiology of Pancreatitis, n (%)** | Gallstones | 23 ( 60.5% ) | 3 ( 23.1% ) | 18 ( 51.4% ) | 44 ( 51.2% ) | 0.124 |
| | ERCP | 1 ( 2.6% ) | 2 ( 15.4% ) | 1 ( 2.9% ) | 4 ( 4.7% ) | |
| | Alcohol | 8 ( 21.1% ) | 5 ( 38.5% ) | 6 ( 17.1% ) | 19 ( 22.1% ) | |
| | Idiopathic | 3 ( 7.9% ) | 0 ( 0.0% ) | 1 ( 2.9% ) | 4 ( 4.7% ) | |
| | Other | 2 ( 5.3% ) | 1 ( 7.7% ) | 4 ( 11.4% ) | 7 ( 8.1% ) | |
| | Unknown | 1 ( 2.6% ) | 2 ( 15.4% ) | 5 ( 14.3% ) | 8 ( 9.3% ) | |
| **Transfer from another hospital, n (%)** | Yes | 23 ( 60.5% ) | 9 ( 69.2% ) | 26 ( 74.3% ) | 58 ( 67.4% ) | 0.430 |
| **Days to intervention, median (IQR)** | | 31 ( 11, 46 ) | 23 ( 7, 31 ) | 30 ( 20, 45 ) | 30 ( 11, 42 ) | 0.257 |
| **CT width (mm) of collection, median (IQR)** | | 113 ( 87, 147 ) | 106 ( 75, 155 ) | 147 ( 130, 178 ) | 134 ( 102, 160 ) | **<0.001** |
| **CT severity score, n (%)** | Moderate | 9 ( 23.7% ) | 2 ( 15.4% ) | 8 ( 22.9% ) | 19 ( 22.1% ) | 0.882 |
| | Severe | 29 ( 76.3% ) | 11 ( 84.6% ) | 27 ( 77.1% ) | 67 ( 77.9% ) | |
| **Day 7 CRP, median (IQR)** | | 107 ( 55, 228 ) | 278 ( 183, 335 ) | 204 ( 107, 244 ) | 183 ( 93, 248 ) | **0.012** |
| **Preoperative ITU stay, n (%)** | Yes | 5 ( 13.2% ) | 6 ( 46.2% ) | 9 ( 25.7% ) | 20 ( 23.3% ) | **0.047** |
| **Preoperative ICU stay (days), median (IQR)** | | 0 ( 0, 0 ) | 0 ( 0, 1 ) | 0 ( 0, 0 ) | 0 ( 0, 0 ) | 0.184 |
| **Site, n (%)** | Head | 10 ( 26.3% ) | 3 ( 23.1% ) | 3 ( 8.6% ) | 16 ( 18.6% ) | **0.028** |
| | Body | 24 ( 63.2% ) | 5 ( 38.5% ) | 20 ( 57.1% ) | 49 ( 57.0% ) | |
| | Tail | 4 ( 10.5% ) | 5 ( 38.5% ) | 12 ( 34.3% ) | 21 ( 24.4% ) | |
| **Total APACHE II score, median (IQR)** | | 6 ( 2, 9 ) | 9 ( 6, 16 ) | 9 ( 5, 12 ) | 7 ( 4, 11 ) | **0.017** |

Post-operative outcomes are shown in Table 2. The median total length of stay was significantly different; 52 days for EN patients, 63 days for OPN and 74 days for MARPN (p=0.007). The post-operative length of stay was lower in the EN group compared to OPN and MARPN (19 vs 42 vs 41 days, p<0.001). In-patient mortality was 10.5% for EN, 15.4% for OPN and 22.9% for MARPN (p=0.379). In the EN cohort, adverse events occurred in 26 (68.4%) patients, 6 (46.2%) for OPN and 24 (68.6%) for MARPN. Procedure related adverse events were higher in the EN group (19 (50%) vs 2 (15.4%) vs 5 (14.3%,) p=0.002), whereas clinical adverse events were higher in the MARPN group (14 (36.8%) vs 6 (46.2%) vs 43 (50.0%), p=0.046). Confirmed infected necrosis was significantly higher for OPN and MARPN

(84.6% and 91.4% vs 36.8%, p<0.001), however only 14 (36.8%) of EN patients had tissue or fluid samples sent for culture. There was no significant difference in the number of patients requiring additional percutaneous drainage (23.7% vs 30.8% vs 45.7%, p=0.115). EN patients required a median of 4 necrosectomy procedures, 2 procedures were required for MARPN and 1 for OPN (p<0.001).

*Table 2: Postoperative descriptive statistics*

| Outcomes | EN (N=38) | OPN (N=13) | MARPN (N=35) | Total (N=86) | P-value |
|---|---|---|---|---|---|
| **Total length of stay (days), median (IQR)** | 52 ( 29, 74 ) | 63 ( 53, 79 ) | 74 ( 55, 102 ) | 63 ( 45, 85 ) | **0.007** |
| **Length of stay in RLBUHT (days), median (IQR)** | 28 ( 17, 50 ) | 48 ( 36, 58 ) | 55 ( 39, 81 ) | 42 ( 26, 64 ) | **<0.001** |
| **Postoperative length of stay (days), median (IQR)** | 19 ( 8, 41 ) | 42 ( 26, 54 ) | 41 ( 28, 70 ) | 34 ( 19, 55 ) | **<0.001** |
| **In-patient mortality n (%)** | 4 ( 10.5% ) | 2 ( 15.4% ) | 8 ( 22.9% ) | 14 ( 16.3% ) | 0.379 |
| **Adverse events (AE), n (%)** | 26 ( 68.4% ) | 6 ( 46.2% ) | 24 ( 68.6% ) | 56 ( 65.1% ) | 0.298 |
| **AE (Procedure), n (%)** | 19 ( 50.0% ) | 2 (15.4% ) | 5 ( 14.3% ) | 26 ( 30.2% ) | **0.002** |
| **AE (Clinical), n (%)** | 14 ( 36.8% ) | 6 ( 46.2% ) | 23 ( 65.7% ) | 43 ( 50.0% ) | **0.046** |
| **Infected Necrosis, n (%)** | 14 ( 36.8% ) | 11 ( 84.6% ) | 32 ( 91.4% ) | 57 ( 66.3% ) | **<0.001** |
| **Total ITU stay (days), median (IQR)** | 0 ( 0, 0 ) | 3 ( 0, 22 ) | 0 ( 0, 5 ) | 0 ( 0, 3 ) | **0.003** |
| **Percutaneous drainage, n (%)** | 9 ( 23.7% ) | 4 ( 30.8% ) | 16 ( 45.7% ) | 29 ( 33.7% ) | 0.115 |
| **Number of Necrosectomies, median (IQR)** | 4 ( 2, 5 ) | 1 ( 1, 1 ) | 2 ( 1, 3 ) | 2 ( 1, 4 ) | **<0.001** |

Table 3 shows specific complications occurring in individual groups. There was no significant difference in complications between the interventions. Incidence of problematic fistulae was lower post endoscopic necrosectomy compared to OPN and MARPN, however this did not reach statistical significance (2.6 vs 15.4 vs 14.3%, p=0.104). In the endoscopic group, stent related problems occurred in 16 (42.1%) patients.

*Table 3: Adverse events*

| Characteristics | EN (N=38) | OPN (N=13) | MARPN (N=35) | Total (N=86) | P-value |
|---|---|---|---|---|---|
| **Bleeding, n (%)** | 1 ( 2.6% ) | 1 ( 7.7% ) | 4 ( 11.4% ) | 6 ( 7.0% ) | 0.304 |
| **Fistula, n (%)** | 1 ( 2.6% ) | 2 ( 15.4% ) | 5 ( 14.3% ) | 8 ( 9.3% ) | 0.104 |
| **HAP, n (%)** | 2 ( 5.3% ) | 1 ( 7.7% ) | 5 ( 14.3% ) | 8 ( 9.3% ) | 0.420 |
| **Cardiac, n (%)** | 2 ( 5.3% ) | 0 (0.0%) | 2 ( 5.7% ) | 4 ( 4.7% ) | 1.000 |
| **Persistent Sepsis, n (%)** | 3 ( 7.9% ) | 2 ( 15.4% ) | 7 ( 20.0% ) | 12 ( 14.0% ) | 0.339 |
| **PE, n (%)** | 1 ( 2.6% ) | 0 (0.0%) | 1 ( 2.9% ) | 2 ( 2.3% ) | 1.000 |
| **PV Thrombosis, n (%)** | 2 ( 5.3% ) | 0 (0.0%) | 0 (0.0%) | 2 ( 2.3% ) | 0.636 |
| **SMV Thrombosis, n (%)** | 6 ( 15.8% ) | 1 ( 7.7% ) | 2 ( 5.7% ) | 9 ( 10.5% ) | 0.404 |
| **Readmission, n (%)** | 10 ( 26.3% ) | 3 ( 23.1% ) | 11 ( 31.4% ) | 24 ( 27.9% ) | 0.850 |
| **Perforation, n (%)** | 2 ( 5.3% ) | 0 (0.0%) | 1 ( 2.9% ) | 3 ( 3.5% ) | 1.000 |

Univariate logistic regression analysis was performed for mortality, this demonstrated that the factors associated with increased mortality in the whole cohort of patients were age (OR 1.042, 95% CI 1.001- 1.086) transfer from another centre (OR 9.419, 95% CI 1.176-75.441), APACHEII score (OR 1.13, 95% CI 1.048-1.230), pre-operative ICU stay (OR 6.896, 95% CI 2.121-22.419) and percutaneous drainage (OR 4.386, 95% CI 1.400-13.736). Multivariate logistic regression models were performed for the outcome of adverse events. They were not performed for mortality due to the small number of events. Pancreatitis secondary to alcohol (OR 0.191, 95% CI 0.046-0.799) were less likely to suffer adverse events than those with an aetiology of gallstones. A longer length ICU stay was also associated with increased adverse events (OR 1.112, 95% CI 1.008- 1.227).

*Table 4: Univariate logistic model with the outcome as mortality*

| Characteristics | Sub-group | Odd's Ratio | 95% Confidence Interval | P-value |
|---|---|---|---|---|
| **Intervention** | OPN | 5.185 | ( 0.979, 27.450) | 0.053 |
| | MARPN | 4.038 | ( 0.994, 16.405) | 0.051 |
| **Sex** | Male | 1.222 | ( 0.381, 3.917) | 0.736 |
| **Age** | | 1.042 | ( 1.001, 1.086) | **0.046** |
| **Cause of Pancreatitis** | ERCP | 7.800 | ( 0.891, 68.304) | 0.064 |
| | Alcohol | 2.080 | ( 0.491, 8.808) | 0.320 |
| | Idiopathic | 0.000 | ( 0.000, ∞ ) | 0.994 |
| | Other | 5.850 | ( 1.004, 34.100) | 0.050 |
| | Unknown | 2.600 | ( 0.408, 16.559) | 0.312 |
| **Transfer from another hospital** | Yes | 9.419 | ( 1.176, 75.441) | **0.035** |
| **Days to intervention** | | 1.005 | ( 0.985, 1.024) | 0.653 |
| **CT width (mm)** | | 1.008 | ( 0.995, 1.021) | 0.217 |
| **CT severity** | Severe | 5.192 | ( 0.640, 42.145) | 0.123 |
| **Day 7 CRP** | | 1.005 | ( 1.000, 1.010) | 0.059 |
| **Preoperative ICU stay** | | 6.896 | ( 2.121, 22.419) | **0.001** |
| **Site** | Body | 1.575 | ( 0.303, 8.190) | 0.589 |
| | Tail | 2.187 | ( 0.365, 13.100) | 0.391 |
| **Total length of stay (days)** | | 1.008 | ( 0.996, 1.020) | 0.179 |
| **Length of stay in RLBUHT (days)** | | 1.010 | ( 0.993, 1.027) | 0.244 |
| **Postoperative length of stay (days)** | | 1.012 | ( 0.995, 1.030) | 0.171 |
| **Adverse event** | Yes | 4.667 | ( 0.984, 22.138) | 0.052 |
| **Infected Necrosis** | Yes | 4.395 | ( 0.926, 20.871) | 0.062 |
| **Length of stay in ICU (days)** | | 1.092 | ( 1.038, 1.148) | **0.001** |
| **Total APACHE II score** | | 1.135 | ( 1.048, 1.230) | **0.002** |
| **Percutaneous drainage** | Yes | 4.386 | ( 1.400, 13.736) | **0.011** |
| **Number of Necrosectomy** | | 0.972 | ( 0.750, 1.258) | 0.828 |

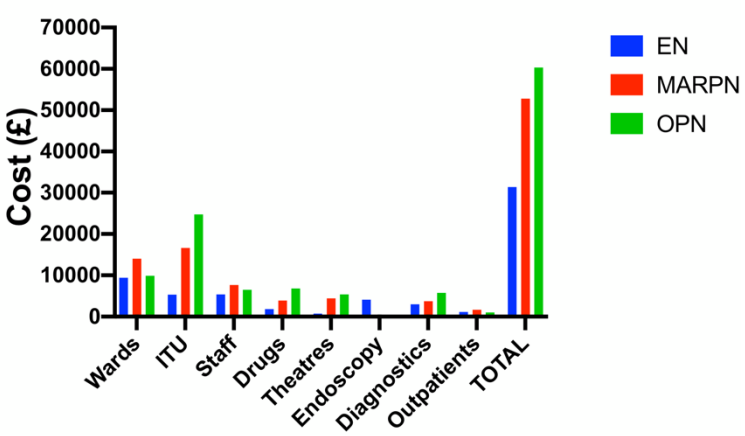
*Table 5: Multivariate logistic regression model with outcome as adverse event*

| Characteristics | Sub-group | Odd's Ratio | 95% Confidence Interval | P-value |
|---|---|---|---|---|
| **Cause of Pancreatitis** | ERCP | 0.067 | ( 0.004, 1.096) | 0.058 |
| | Alcohol | 0.191 | ( 0.046, 0.799) | **0.023** |
| | Idiopathic | 2.014 | ( 0.177, 22.848) | 0.572 |
| | Other | 0.118 | ( 0.011, 1.299) | 0.081 |
| | Unknown | 2.978 | ( 0.293, 30.309) | 0.357 |
| **Day 7 CRP** | | 1.005 | ( 0.999, 1.011) | 0.078 |
| **Length of stay in ICU (days)** | | 1.112 | ( 1.008, 1.227) | **0.034** |

***Economic outcomes***

Individual patient costs were calculated using PLICS are summarised in Table 6 and Figure 1. The average overall cost per patient was £30,981 for patients treated by EN; £52,357 for MARPN and £60,077 for OPN. The ward cost per patient was £9,430 for EN, £14,033 for MARPN and £9,890 for OPN. The costs associated with ITU stay were £5,317 for EN, £16,648 for MARPN and 24,722 for OPN.

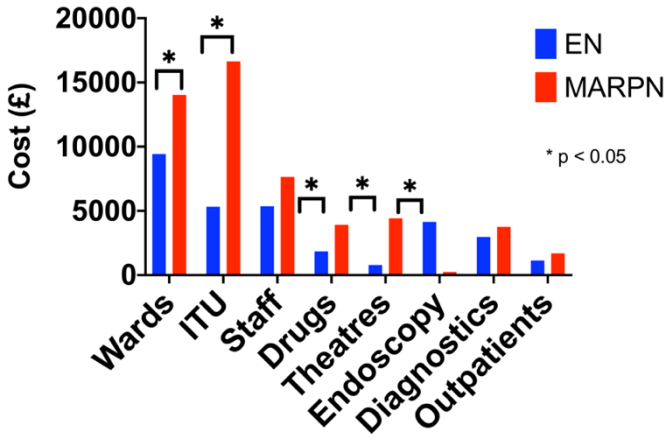
*Table 6 & Figure 1: Summary table and graph of average cost (£) per patient*




| Department | EN | MARPN | OPN |
|---|---|---|---|
| **Wards** | 9,430 | 14,033 | 9,890 |
| **ITU** | 5,317 | 16,648 | 24,722 |
| **Staff** | 5,358 | 7,648 | 6,501 |
| **Drugs/ treatment** | 1,852 | 3,910 | 6,807 |
| **Theatres** | 784 | 4,420 | 5,369 |
| **Endoscopy** | 4,135 | 245 | 0 |
| **Diagnostic tests** | 2,970 | 3,762 | 5,738 |
| **Outpatients** | 1,135 | 1,691 | 1050 |
| **TOTAL** | 30,981 | 52,357 | 60,077 |

Table 7 shows a cost comparison of EN and MARPN which demonstrates a significantly lower average total cost for EN (31,364) when compared to MARPN (£52,770) (p=0.008). The cost of ward care (£9430 vs £14,033, p=0.024) and medication (£1,852 vs £3,910, p=0.017) were also significantly lower for patients undergoing EN. The theatre costs in the MARPN group were comparable with endoscopy costs for patients managed by EN (£4,420 and £4,135).

*Table 7 & Figure 2: Comparison of average costs for EN vs MARPN (£)*




| Average costs per patient | EN | MARPN | P value |
|---|---|---|---|
| **Wards** | 9430 | 14,033 | **0.024** |
| **ITU** | 5,317 | 16,648 | 0.056 |
| **Staff** | 5,358 | 7,648 | 0.195 |
| **Medication/ treatment** | 1,852 | 3,910 | **0.017** |
| **Theatres** | 784 | 4,420 | **<0.001** |
| **Endoscopy** | 4,135 | 245 | **<0.001** |
| **Diagnostic tests** | 2,970 | 3,762 | 0.296 |
| **Outpatients** | 1,135 | 1,691 | 0.159 |
| **TOTAL** | 31,364 | 52,770 | **0.008** |

## DISCUSSION

This study has investigated the clinical outcomes and actual cost for different approaches for the management of pancreatic necrosis in a real-world setting. All patients undergoing endoscopic, minimal access or open pancreatic necrosectomy at a tertiary centre over two financial years were included in the analysis. The most important finding from this study is that patients undergoing an endoscopic approach had reduced a length of inpatient stay associated with reduced treatment costs compared to a surgical approach.

The average cost for managing a patient with MARPN is over £20,000 more expensive than for EN. The increased cost it likely to be due to the significantly longer length of stay in the MARPN patients on both a surgical ward and ICU. The increased length of stay for MARPN of approximately three weeks is thought to be related to many factors, including being performed in a sicker cohort of patients and patients required to be an inpatient throughout.

In some suitable patients EN can be performed on an outpatient basis after the initial two procedures therefore reducing inpatient stay. MARPN patients are required to remain an inpatient until drain irrigation has been discontinued and the drain has been downsized. It is reassuring that there was no increase in readmission following EN, suggesting that the protocol is safe. The finding of a reduced length of stay for endoscopic necrosectomy is consistent with previously published studies [29,107].

Open pancreatic necrosectomy was associated with higher costs than the less invasive approaches with higher ICU costs and longer ICU stays. Previously published studies have found increased morbidity with OPN compared to minimal access techniques [40 17 20]. Bakker et al observed a trend towards increased ITU stays for OPN but this did not reach statistical significance. They also reported an increased inflammatory response following open surgical necrosectomy compared to EN [17]. This may be partly responsible for the increased ITU stay and costs found for OPN. However, the OPN cohort in this analysis may have been more physiologically unstable as we report higher CRP values but comparable APACHEII scores.

This is an observational analysis with intervention decided by the MDT rather than by randomisation. Our organisation started performing endoscopic necrosectomy shortly before the time frame included in this study so the learning curve period for the technique is included in this data. As clinicians became more experienced with the technique, it was performed on a wider range of patients including those on ICU and those with less favourable collections. The pre-operative patient characteristics show that MARPN and OPN were performed in patients with higher APACHEII scores, higher CRP and more ICU admissions then EN. Therefore, it is important to acknowledge that it is therefore difficult to make direct comparisons of clinical outcomes as the groups are fundamentally different. EN requires an endoscopist trained in the procedure which is not always currently available out of hours, resulting in the patients deteriorating at these times undergoing a surgical intervention. The site of the pancreatic necrosis has implications for the approach chosen; for endoscopic necrosectomy the collection has to be accessible via the transgastric or transduodenal route, meaning collections in the tail may be inaccessible. For MARPN, collections need to be approached via the left flank, although central or right sided collections may also be accessible percutaneously in some patients.

This study gives an accurate representation of cost to the trust of treating this complex cohort of patients with long and resource heavy inpatient stays. The NHS National Tariff for

pancreatic necrosectomy for 2019/20 financial year is £21, 212, substantially less than it will cost a centre to treat the majority of these patients [111,112].

In conclusion, open and minimal access pancreatic necrosectomy were performed in a more unwell cohort of patients than endoscopic necrosectomy during the study period. However, utilising all available techniques in a hybrid bespoke manner can reduce length of stay and healthcare related costs, especially when performing endoscopic necrosectomy.

**CHAPTER EIGHT: Single-Port Retroperitoneal Pancreatic Necrosectomy: a novel approach to extra-pancreatic walled off necrosis**

Saunders R, Neoptolemos J, Hughes F, Ghaneh P & Halloran C. Single-Port Retroperitoneal Pancreatic Necrosectomy for the Treatment of Extrapancreatic Walled-Off Necrotic Collections. 2021. Annals of Surgery 2: e019.

(See Supporting Papers, page 97)

**INTRODUCTION**

Multiple techniques have been described for the management of pancreatic and peripancreatic necrosis. A step up endoscopic or minimal access surgical approach is the gold standard in management [9]. However, some WON collections are not accessible by these methods and are difficult to manage, typically those in or extending down the paracolic gutters. These collections have been traditionally managed by percutaneous drainage using small diameter pigtail catheters inserted under radiological guidance. Different techniques have been described for managing collections not adequately treated by percutaneous drains including open necrosectomy or open cut down and debridement. There are now several reports and case series of transcutaneous endoscopic necrosectomy with placement of a self-expanding metal stent [113,114],

We have developed Single-Port Retroperitoneal Pancreatic Necrosectomy (SPRPN), a novel method for managing these difficult collections. A Single Incision Laparoscopic Surgery (SILS$^{TM}$) port is placed in to the collection and a SILS specific articulating grasper is used for debridement of necrotic tissue. We gained provisional funding and approval to undertake SPRPN in a test cohort of patients This study reports our initial experience with this technique in 7 consecutive patients.

**METHODS**

***Patients***

We retrospectively analysed the first 7 patients to undergo SPRPN from 2016-19. Acute pancreatitis was managed according to IAP/APA guidelines [16]. A CT scan was performed 72-96 hours post admission, earlier of there was diagnostic uncertainty. All patients were discussed at the benign MDT meeting prior to intervention, attended by pancreatic surgeons,

endoscopists, radiologists and specialist nurses. Intervention was reserved for patients with documented or suspicion of infected pancreatic necrosis or those with persistent pain or other symptoms after an extended period of hospitalisation. Infected necrosis was defined as positive tissue cultures or gas in the collection on CT imaging. A repeat CT was performed if there was clinical deterioration, a significant rise in inflammatory markers or for planning possible intervention. SPRPN was used in patients with symptomatic flank or paracolic gutter collections not responding to percutaneous catheter drainage and with accessible collections. Patients were followed up regularly in outpatient clinic following discharge.

***Technique***

Percutaneous drains were inserted in to the collection by CT or ultrasound guidance in the radiology department. Percutaneous catheter drains (PCD) were flushed with 10 ml saline twice daily. If the patient responded adequately conservative management was continued, however if not then SPRPN was performed. SPRPN was performed in theatre under general anaesthetic by a single pancreatic surgeon. A ureteric stent is inserted prior to necrosectomy to protect against ureteric injury. The percutaneous drain was used to guide the site of incision. The 3 channel SILS port (Medtronic/Covidien, Connecticut, USA) was inserted using an open cut down technique. A 0 degree nephroscope was inserted through one port and an articulating grasper (CILS-Clinch) through another. Saline irrigation was used when necessary. Debridement was performed under direct vision. Tissue samples were collected and sent for culture and sensitivities. Two large bore irrigating drains were placed in the cavity allowing continuous post-operative irrigation, initially at a rate of 125ml/hr and reduced according to clinical response. Patients underwent further necrosectomy procedures if clinically indicated by ongoing sepsis or non-resolution of the collection.

**RESULTS**

Patient and collection characteristics are shown in Table 1.

*Table 1: Patient demographics*

| Patient Number | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|
| **Age** | 24 | 59 | 63 | 40 | 71 | 68 | 58 |
| **Gender** | Female | Female | Female | Male | Male | Male | Female |
| **Aetiology** | ERCP | ERCP | Gallstones | ETOH | ERCP | Gallstones | ETOH |
| **Collection size (mm)** | 113 x 110 x 124 | 98 x 85 x 142 | 92 x 59 x 63 | 128 x 73 x 112 | 92 x 97 x 300 | 298 x 207 x 316 | 70 x 72 x 113 |
| **Location of WON** | Right paracolic | Right paracolic | Right paracolic | Right paracolic + Right upper quadrant | Left paracolic+ groin + pancreatic tail | Horseshoe | Left paracolic |
| **Transfer to regional centre** | Yes | Yes | No | Yes | Yes | No | Yes |
| **Co-morbidity** | None | None | None | None | None | Cold agglutin disease | None |
| **Infected necrosis** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Multiple organ failure** | Yes | No | No | Yes | No | No | No |

We have managed 7 patients with a median (IQR) age of 59 (40-68) with SPRPN. Infected pancreatic necrosis was confirmed in all patients by tissue culture. Two patients had multiple organ failure and were admitted to ITU for supportive management prior to intervention. Five patients were transferred from other hospitals to our supra-regional centre. The aetiology was gallstones in 2 patients, alcohol in 2 patients and post ERCP trauma in 3 patients. Two of these patients also had a perforation in the second part of the duodenum. Two patients had multi-organ dysfunction syndrome. The median (IQR) dimensions (width x depth x height) of the collections drained were 98 (92-128) x 85 (72-110) x 124 (112-130).

Procedural details and outcomes are shown in Table 2. SPRPN was performed a median (IQR) of 23 (19-34) days post onset of acute pancreatitis. The first patient required two procedures as part of the learning curve, all subsequent patients were managed with one. Complications were experienced in 4 patients. Patient 2 had multiple collections and required a percutaneous drain in to a collection in the tail of the pancreas. She had multiple septic episodes and died from portal vein occlusion and sepsis seven months following admission. Patient 4 had an infarcted right colon due to the inflammatory occlusion of mesenteric vessel. This was noted after the initial necrosis was cleared and was converted to an open

necrosectomy and extended right hemicolectomy. Two patients required further PCD insertion on subsequent admissions, not at the site of the original collections. The overall median (IQR) length of stay was 98 (61-133) including the hospital stay in the referring hospital prior to transfer. The post-operative length of stay was 47 (19-102) days. The median (IQR) time from admission to PCD was 23 (19-34) days. The median (IQR) time to resolution of the collection on imaging was 42 (36-49) days.

*Table 2: Procedure details and outcomes*

| **Patient Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|
| **Time to percutaneous drain (d)** | 33 | 29 | 62 | 34 | 19 | 23 | 7 |
| **Time from PCD to SPRPN (d)** | 12 | 2 | 7 | 17 | 30 | 73 | 2 |
| **Number of sessions** | 2 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Complications** | No | Death (PV occlusion + sepsis) | No | OPN + Right hemicolectomy DVT arm from PICC | UTI from stent | Adhesions, cholangitis | No |
| **Length of stay (days)** | 61 | 133 | 88 | 98 | 108 | 217 | 19 |
| **Post-operative length of stay (days)** | 23 | 102 | 19 | 47 | 59 | 120 | 13 |
| **Time to resolution (days)** | 37 | 42 | 36 | 83 | 49 | 45 | 11 |
| **Length of follow up (mo)** | 39 | 6 | 30 | 24 | 19 | 10 | 9 |

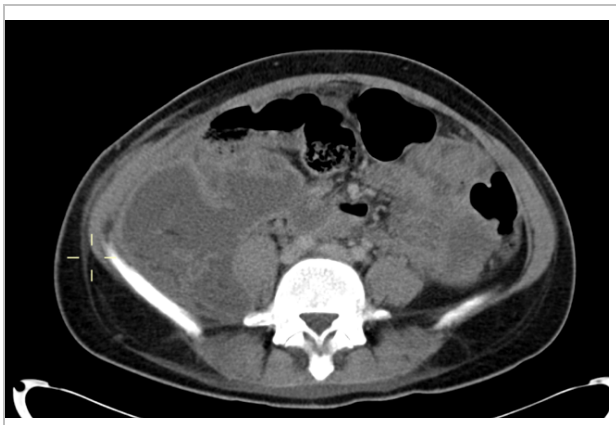


Fig 1a. Patient 1 pre-operative

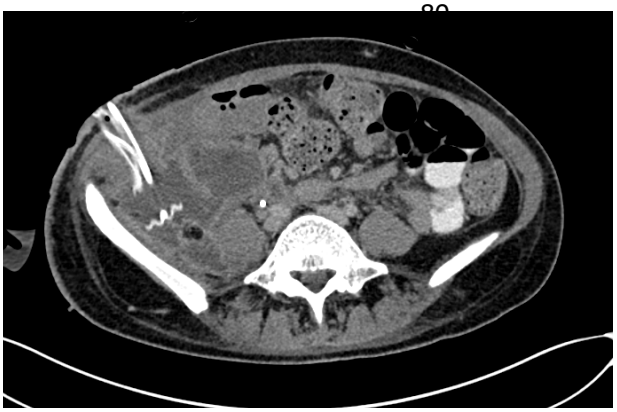


Fig 1b. Patient 1 post-operative

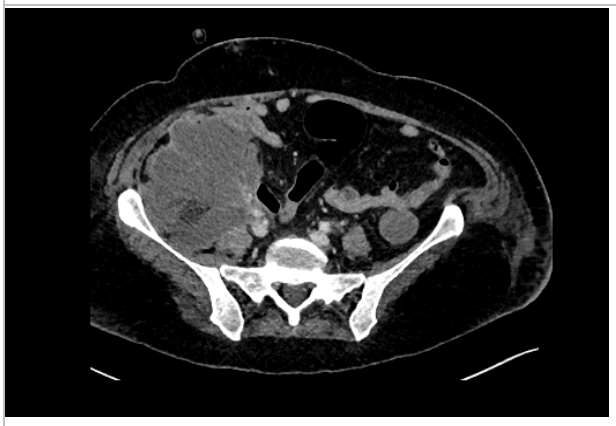


Fig 1c. Patient 2 pre-operative

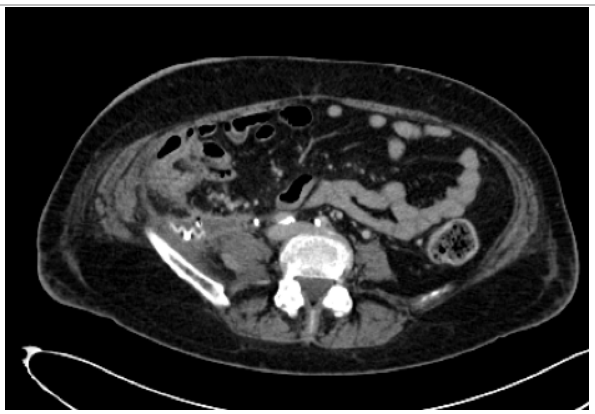


Fig 1d. Patient 2 post-operative

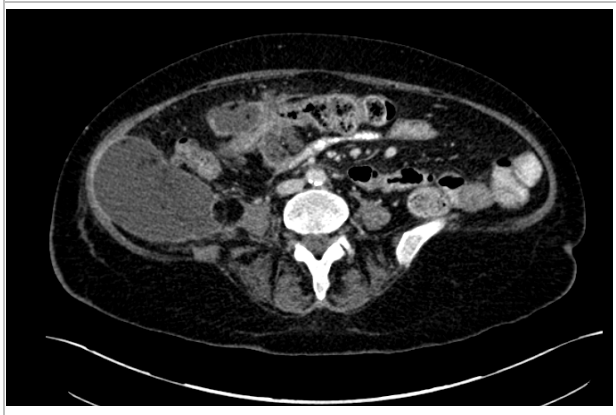


Fig 1e. Patient 3 pre-operative

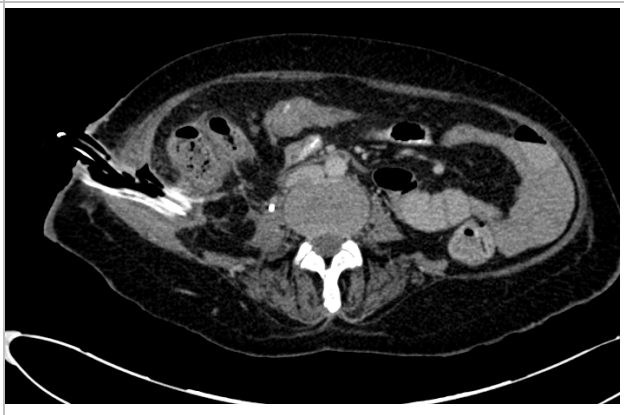


Fig 1f. Patient 3 post-operative

*Figure 1: Pre and post SILS necrosectomy CT images from 3 patients, all showing adequate resolution of right paracolic gutter walled off necrosis.*

**DISCUSSION**

In most cases walled off necrosis is pancreatic or peripancreatic and can be accessed percutaneously and stepped up to minimal access pancreatic necrosectomy; or endoscopically allowing placement of a self-expanding metal stent and necrosectomy if required. Extra-pancreatic collections can be problematic and require intervention in a small number of patients. As with pancreatic collections, a step-up approach is recommended with placement of a percutaneous catheter drain under radiological guidance as the initial step. If this does not provide adequate clinical response then options include open necrosectomy, open cut down and debridement or percutaneous endoscopic necrosectomy. We report our results for SPRPN, a novel minimally invasive technique for managing these difficult patients. Minimally invasive intervention have been shown to reduce the stress response to surgery[17,37], potentially of benefit in these extremely unwell patients.

We report the first 7 patients to be treated by SPRPN. The necrotic collection was cleared with one procedure in all but the index case. Given the high morbidity associated with severe acute pancreatitis it is not unexpected that 4 patients experienced complications, with one patient dying following a portal vein thrombosis on a second admission.

We suggest there are several advantages of SPRPN over percutaneous endoscopic necrosectomy. There is superior visualisation of the cavity using a laparoscope over an endoscope, facilitating debridement. Surgical instruments are better for handling and debriding tissue than endoscopic instruments, a problem also limiting transluminal endoscopic necrosectomy. Metal stents are left in situ after percutaneous endoscopic necrosectomy, potentially leading to persistent fistulae[115].

There are limitations to this study and the generalisability of the results. Only seven patients were treated with SPRPN during the study period, we intervene on approximately 50 patients per year so these very highly selected patients[20]. Patient selection is extremely important and will evolve as our experience of the technique grows. The proximity of the ureters to the collection and the depth of the collection limit the extent of necrosectomy possible. The appropriate expertise is required, and other treatment options should be available.

A potential development of the technique would be to perform MARPN using a SILS port, replacing an operating nephroscope providing the collection was accessible. This would hopefully allow improved debridement and visualisation of the necrotic cavity. A small case

series of 3 patients successfully managed by SILS retroperitoneal necrosectomy suggests this is possible [116]. The articulating graspers available for use enable more effective debridement as more angulation is possible, allowing access to a greater area for debridement. This may translate to patients requiring fewer MARPN procedures leading to reduced length of stay and reducing costs.

In conclusion, we have shown SPRPN to be a safe and effective option for treating flank and paracolic pancreatic walled off necrosis. It is now part of the armamentarium and hybrid pathway for the management of patients with pancreatic necrosis in our centre.

**CHAPTER NINE: Conclusions and algorithm for the management of infected pancreatic necrosis**

Pancreatitis is a common cause for a hospital admission within the United Kingdom and has a global incidence of 34 per 100, 000 [3]. Pancreatic and peripancreatic fluid collections are one of the possible complications of pancreatitis and have been the focus of this thesis. The revised Atlanta criteria defines pancreatic fluid collections according to their duration post onset of pancreatitis and whether they are associated pancreatic or peripancreatic necrosis[6].

As surgical techniques and technology have developed, minimally invasive options are now available for managing pancreatic fluid collections. The most recent change in management of pancreatic fluid collections has been the introduction of endoscopic approaches [117]. In our unit, EUS guided inserted of plastic pigtail stents was first used for the drainage of symptomatic pancreatic pseudocysts. More recently larger diameter self-expanding metal stents or lumen apposing metal stents have been used to drain these collections. We found that using metal stents increased the likelihood of achieving successful drainage of the pseudocyst at six weeks following the procedure (95% vs 75%, p= 0.023) and also reduced the need for further surgical, percutaneous or endoscopic drainage (8 vs 31%, p=0.017).

A systematic review and meta-analysis of the outcomes following drainage of pancreatic fluid collections with plastic and metal stents was performed. This again demonstrated superior clinical success when metal stents were used (93.8% vs 86.2%, RR 1.08 (95% CI 1.02-1.14), p=0.009). Adverse events were also reduced with metal stents (10.2% vs 25%, RR0.42 (95% CI 0.18-0.75), p=0.006). This study was limited by the included studies being largely retrospective and heterogeneity in methods and outcomes[91]. Despite not being represented in the included studies there has been concern in other studies of high rates of adverse events with lumen apposing metal stents, in particular delayed bleeding and buried stent syndrome[61].

Endoscopic treatment of pancreatic necrosis was first described in 1996 [42] and has now become first line treatment in many centres. It is minimally invasive, allows debridement of necrotic tissue and does not require external drains unlike MARPN or OPN. In the first fifty patients treated by EN in our institution, treatment was successful in 42 (84%), the mortality was 4 (8%) and 22 (44%) of patients experienced procedural related adverse events. The rate of adverse events is likely to be partly due to the learning curve, however stent related adverse events are common in other published studies [54,61]. An advantage of a metal stent is

the larger diameter allows passage of the endoscope in order to perform flush necrosectomy and access the cavity if required [46].

Prior to the introduction of endoscopic necrosectomy we performed a step-up approach with minimal access retroperitoneal necrosectomy. After analysing the initial results with EN, we then compared it to our results over the same period with MARPN. A minimal access surgical step up approach remains the gold standard approach with regard to supporting literature [29,38,117]. This prospective review of 84 patients found a significantly reduced length of stay for EN compared to MARPN (51 vs 95 days, p=0.001), however there was no difference in mortality or adverse events. This is supported by results from randomised controlled trials [29,107] . Despite multiple technical advances, few studies have demonstrated improved mortality following pancreatic necrosectomy. This is likely to be due to the severity of the disease process and no option for intervention affects the early phase of pancreatitis.

The NCEPOD report on acute pancreatitis recommended the introduction of tertiary centres for the management of pancreatitis[11]. As demonstrated in previous studies published from our institution, these patients have significant morbidity associated with pancreatitis, long ITU stays and long overall hospital admissions[20]. To evaluate the cost to the trust of managing these patients, a cost consequence analysis was performed. The patient level individual costs data (PLICS) was used to provide an accurate cost of managing individual patients over 2 financial years. Clinical outcomes were also recorded and analysed. This analysis again found a reduced length of stay for EN, compared to MARPN and OPN. There was no difference in mortality or morbidity but the lack of randomisation of patients limits further interpretation of this. We found the mean overall cost for patients treated by EN was £30, 981, £52, 357 for MARPN and £60, 077 for OPN (p=0.008[118]). This data can be used to inform commissioning. The NHS tariff for pancreatic necrosectomy for the study period was £21, 212[111].

The NHS National Tariff Payment System informs the planning and payment for services and procedures performed by NHS providers. The method in which these tariffs are set is complex and involves multiple steps. National Cost Collection and hospital episodes statistics (HES) data are used and in 2022/23 PLICS data has been used to calculate tariff prices for the first time [119]. National prices can be adjusted through local modifications if they do not adequately cover efficient costs for a provider but need to be approved by NHS Improvement. In order to agree a locally determined price for pancreatic necrosectomy, the trust would need to demonstrate to commissioners that it would provide quality, cost-

effective care in the best interests of patients [120]. This can be easily evidenced by this work, our previously published patient outcomes and recently published trials [29,38,107].

In order to develop an algorithm for the management of infected pancreatic necrosis, a review of the available interventional techniques was undertaken. International guidelines for the management of pancreatitis recommend delaying intervention for at least 4 weeks following the onset of pancreatitis to allow the collection to "wall off"[16]. Previous studies, all be it largely with open necrosectomy as the intervention found inferior outcomes with increased mortality following early necrosectomy [121].

Following the widespread adoption of the "step up approach" [20,24], catheter drainage either by a percutaneous or transgastric route has become the preferred first line intervention. It allows source control until definitive intervention can be performed. It has also been shown that patients undergoing PCD as initial management experience fewer complications than those undergoing primary necrosectomy [15]. In terms of practice within the UK, percutaneous drainage may be performed in the referring centre to stabilise a patient prior to transfer to the tertiary pancreatitis centre. Although this needs to be considered carefully, particularly if the tract is going to be used for further procedures. Despite being the least invasive intervention, PCD is associated with morbidity in approximately 20% of patients with bleeding and pancreatic fistulae being the most common [21, 22].

All patients in which intervention is being considered should have a contrast enhanced CT scan[16]. This demonstrates the site and size of the pancreatic fluid collection and whether there are any extra pancreatic collections present. If the collection is in close proximity to the stomach or duodenum then it should be accessible for EUS guided catheter drainage. Minimal access retroperitoneal pancreatic necrosectomy is most commonly performed for collections on the left side of the abdomen with access provided between the splenic flexure and lower pole of the spleen. However more central and right sided collections can also be accessed for this technique providing there is an appropriate route avoiding abdominal viscera[20].

In the algorithm, EUS necrosectomy should be performed as the preferred procedure providing the collection is accessible via endoscopy. Our data has shown the length of stay is significantly shorter following endoscopic necrosectomy when compared to OPN or MARPN. A small randomised control trial found that an endoscopic step up approach reduces post-operative IL-6 levels compared to a surgical step up approach[17], however in current trial

evidence and our own results this has not translated in to a reduction in mortality [29,118]. One trial did find reduced complications following endoscopic necrosectomy with a composite end point of major complications or death within 6 months[107], however this currently has not been replicated by others. As complications are thought to be similar between EN and MARPN, we feel the reduction in length of stay warrants it being the first line intervention where possible. Current NICE guidance supports this approach, albeit with the recommendation coming from the results of only one randomised control trial that was available at the time of last publication in 2018[13].

Following initial endoscopic or percutaneous catheter drainage the physiological parameters of the patient are closely monitored by the clinical team and regular blood tests including inflammatory markers are obtained. A repeat CT scan is performed after 7-10 days. If the patient deteriorates clinically or is failing to improve then further intervention is performed. If an endoscopic drain was placed, then the patient will undergo endoscopic flush necrosectomy. Whilst if a percutaneous drain was inserted the step up is to MARPN. The patient then enters the phase of monitoring and repeat imaging prior to consideration of repeat intervention if required.

Walled off pancreatic necrosis can be pancreatic, peripancreatic or extrapancreatic[6]. In patients with extrapancreatic collections, commonly the right or left paracolic gutter, percutaneous drains can be inserted to achieve source control[46,122]. These collections can be difficult to access with conventional approaches. We have shown that Single Port Retroperitoneal Necrosectomy is an effective technique for managing these patients who do not respond adequately to simple percutaneous drainage and should be considered in the management of these patients.

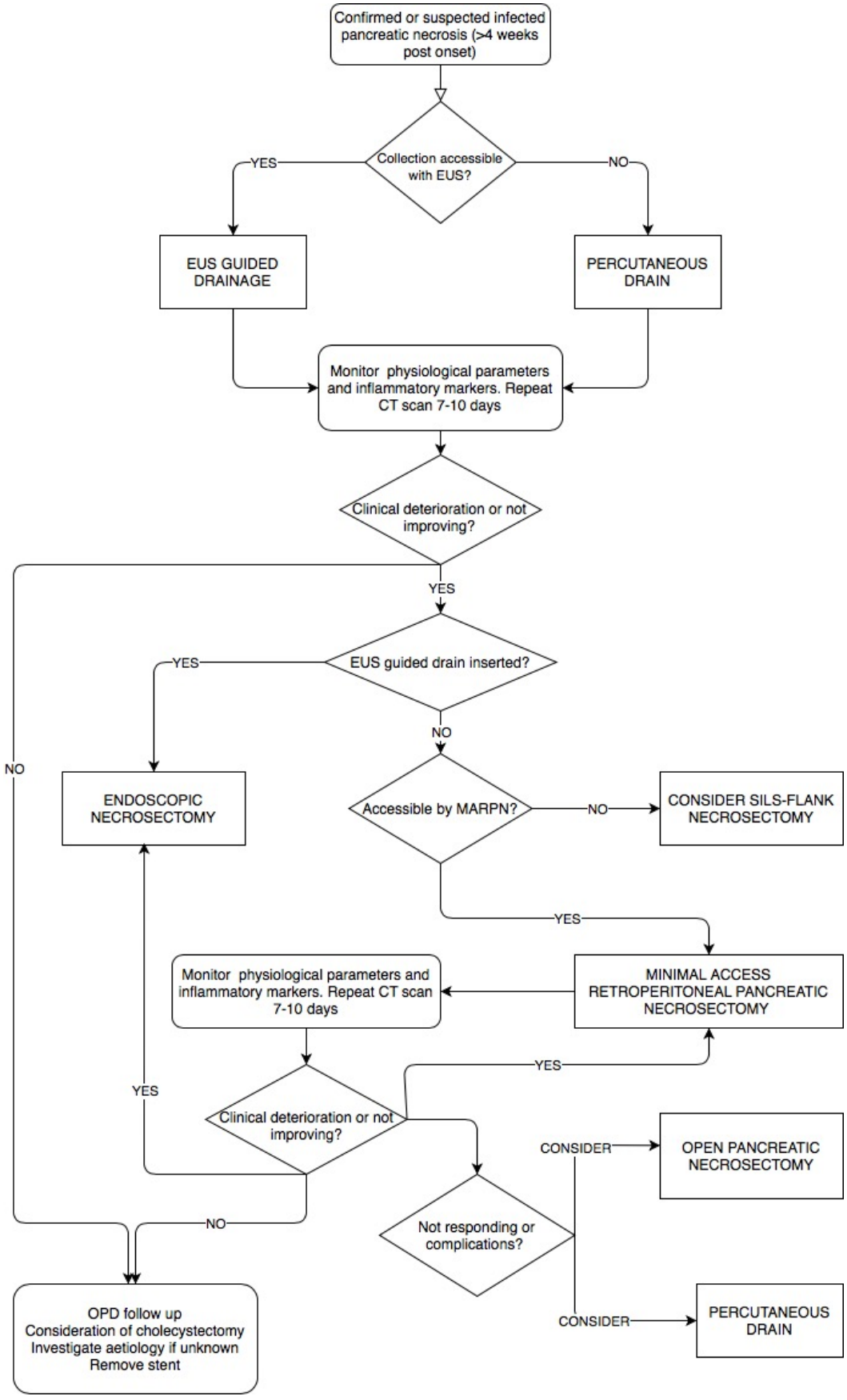
Open necrosectomy was historically the gold standard for managing infected pancreatic necrosis but is becoming rarer given the evidence of the increased mortality and morbidity following OPN compared to a step up approach[20,24,38]. However, OPN remains a valuable procedure and is now often only performed when the collections are not accessible by other routes, as salvage surgery or following complications of a minimally invasive approach.

Post-discharge from hospital the patient will be followed up in outpatient's clinic. Consideration needs to be given to treating the cause of pancreatitis[11]; discussion of laparoscopic cholecystectomy; alcohol cessation or further investigations if the aetiology is

still unclear. If endoscopic necrosectomy and stent placement was undertaken, then the stent will be removed within six weeks to reduce the risk of complications.

The algorithm is intended to help guide management of these complex patients with infected pancreatic necrosis, but it is accepted that these patients can be difficult to manage and deteriorate quickly. It is not always possible in clinical practice to follow an algorithm and staffing and organisational factors also have an impact on what intervention will be performed. We recommend a hybrid, bespoke management plan for every patient requiring intervention for pancreatic necrosis considering possible interventions and tailoring care to the individual clinical picture.

*Figure 1: Algorithm for the management of infected pancreatic necrosis*



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**SUPPORTING PAPERS**

**Cost Analysis and Outcomes of Endoscopic, Minimal Access and Open Pancreatic Necrosectomy.** R Saunders, F Hughes, J Evans, H Smart, P Ghaneh, J Ramesh, R Sutton, C Halloran. Annals of Surgery Open. 2021 Jun 1; 2 (2):e068

**Single-Port Retroperitoneal Pancreatic Necrosectomy for the Treatment of Extrapancreatic Walled- Off Necrotic Collections**. R Saunders, JP Neoptolemos, F Hughes, P Ghaneh, CM Halloran. Annals of Surgery Open. 2021 Mar 2; 1: e019.

**A systematic review and meta-analysis of metal versus plastic stents for drainage of Pancreatic fluid collections: metal stents are advantageous.** R Saunders, S Cicconi, J Evans, VS Yip, M Raraty, P Ghaneh, R Sutton, JP Neoptolemos, C Halloran. Surgical Endoscopy. May 2019;33(5):1412-142

Original Study

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# Cost Analysis and Outcomes of Endoscopic, Minimal Access and Open Pancreatic Necrosectomy

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**Objectives:** To assess both individual patient and institutional costs as well as outcomes in patients with pancreatic necrosis who underwent either endoscopic, minimal access or open pancreatic necrosectomy. These data can be used to evaluate clinical effectiveness with a view to informing local healthcare providers.

**Background:** Intervention for infected pancreatic necrosis is associated with a high morbidity, mortality, and long hospital stays. Minimal access surgical step-up approaches have been the gold standard of care; however, endoscopic approaches are now offered preferentially.

**Methods:** All patients undergoing endoscopic (EN), minimal access retroperitoneal (MARPN), and open (OPN) necrosectomy at a single institution from April 2015 to March 2017 were included. Patients were selected for intervention based on morphology and position of the necrosis and on clinical factors. Patient-level costing systems were used to determine inpatient and outpatient costs.

**Results:** Eighty-six patients were included: 38 underwent EN, 35 MARPN, and 13 OPN. Preoperative APACHEII was 6 versus 9 versus 9 ($P$ = 0.017) and CRP 107 versus 204 versus 278 ($P$ = 0.012), respectively. Postoperative stay was 19 days for EN versus 41 for MARPN versus 42 for OPN ($P$ = 0.007). Complications occurred in 68.4%, 68.6%, and 46.2% ($P$ = 0.298), whereas mortality was 10.5%, 22.9%, and 15.4% ($P$ = 0.379), respectively. Mean total cost was £31,364 for EN, £52,770 for MARPN ($P$ = 0.008), and £60,346 for OPN. Ward and critical care costs for EN were lower than for MARPN (ward: £9430 vs £14,033, $P$ = 0.024; critical care: £5317 vs £16,648, $P$ = 0.056).

**Conclusions:** EN was at least as safe and effective as MARPN and OPN and was associated with markedly reduced hospital stay and cost, although some markers of disease severity were higher in patients undergoing MARPN and OPN. These results support EN as the preferred approach to necrosectomy, but hybrid utilization of all available techniques remains integral to optimal outcomes.

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## INTRODUCTION

Acute pancreatitis is a potentially fatal condition that results in approximately 100 acute admissions per year for most acute hospitals in the United Kingdom.[1] Approximately 20% of patients will develop pancreatic necrosis as a complication of acute pancreatitis with infected pancreatic necrosis subsequently occurring in 30% to 70% of this group.[2,3] The resultant mortality is between 20% and 30%.[4–9] In most cases of infected pancreatic necrosis, intervention is required.[10,11]

For the last decade, minimally invasive pancreatic necrosectomy has been the gold standard of management for pancreatic necrosis requiring intervention.[10,12] More recently, endoscopic transluminal drainage and necrosectomy have been developed and shown to be an effective alternative for appropriate patients.[12,13] Open necrosectomy is a more invasive treatment approach and, overall, its use has declined as it has been confirmed to be associated with a higher incidence of morbidity and mortality.[6,14,15] Current evidence is inconclusive regarding the advantages of an endoscopic approach compared to minimally invasive surgical interventions in terms of clinical outcomes.[16] The TENSION trial concluded that an endoscopic step-up approach was not superior to a surgical step-up approach[12]; however, a smaller trial found that an endoscopic approach reduced major complications and increased quality of life.[17]

Patient-level information and costing systems (PLICS) have become mandatory for acute activity in NHS hospitals from the 2018/2019 financial year, moving forward from reference costs.[18] Costings are derived from tracking all resources used by an individual patient during their admission and calculating the actual costs incurred. This provides several advantages over the previous reference system which was based on healthcare

resource group (HRG) averages and cannot be easily linked to an individual patient.[19] HRGs are groupings of clinically similar events or treatments that are judged to use comparable levels of healthcare resource.[20] Patient-level costing allows for more accurate comparisons between different organizations nationally and provides more accurate data for agreeing on local pricing for patient care. It is also more accessible for clinicians, allowing validation of activities and costs and a potential avenue of improving care pathways.[18]

Previous cost comparisons of endoscopic necrosectomy and a step-up surgical approach have demonstrated a trend toward reduced cost for an endoscopic approach.[12,17,21] The aim of this study was to evaluate any potential cost benefit for a particular intervention for pancreatic necrosis by performing a clinical comparison and cost-consequence analysis using individual patient costings.

## METHODS

### *Patients*

All patients undergoing pancreatic necrosectomy at the Royal Liverpool University Hospital from April 1, 2015, to March 31, 2017, were included and analyzed on an intention to treat basis. Patients with admissions extending out of these times were excluded from the study. This tight time frame was chosen to accommodate whole patient episodes in which procedures were undertaken within a negotiated block contract, with a fixed budget agreed by NHS commissioners. Patients were prospectively recorded on to an electronic database.

All patients were managed in accordance with current IAP/APA guidelines.[10] Intervention was delayed until 4 weeks post onset of acute necrotizing pancreatitis unless the clinical condition of the patient necessitated earlier drainage or laparotomy. Every patient was discussed at the weekly benign multidisciplinary team (MDT) meeting, attended by pancreatic surgeons, endoscopists, radiologists and specialist nurses. The overall management plan and the nature of any required intervention was agreed by the MDT. The mode of intervention was decided on a patient-by-patient basis, following review of the individual's condition and the position of the necrosis. However, if the clinical condition changed, patients were treated accordingly to their emergent situation. Specific indications for intervention included clinical suspicion or documented infected necrosis, ongoing nonimproving organ failure, ongoing gastric or biliary obstruction. APACHE II scores were calculated before the initial intervention performed.

### *Necrosectomy Techniques*

#### *Endoscopic Approach*

Endoscopic (EN) transluminal drainage was the initial intervention in an endoscopic step-up approach. Under endoscopic ultrasound (EUS) guidance the optimum site for stent placement was established. Cyst puncture was performed with a 19-gauge needle and aspirated fluid was sent for culture. A lumen apposing metal stent (LAMS) with enhanced delivery system (Hot AXIOS; Boston Scientific) or biflanged metal stent (Nagi; Taewoong Medical Co. Ltd) was placed into the collection. Fluoroscopy was not routinely used for Hot AXIOS stent insertion. Necrosectomy was then performed using the "flush" method of extracavity lavage using jet pump irrigation and suction.[22] A cap was placed on the tip of the endoscope to aid suction. Instrumentation and debridement of the cavity was avoided within the cavity. A radial expansion balloon or snares were used to unblock the stent if required. The patient underwent weekly scheduled repeat necrosectomy procedures until necrosectomy was complete; these were undertaken as an outpatient if the patient was sufficiently well. Once imaging confirmed the cavity had completely collapsed, the stent was removed, preferably within 6 weeks of insertion. Multiple metal stents or anchoring plastic stents were used at the discretion of the endoscopist.

#### *Minimal Access Retroperitoneal Pancreatic Necrosectomy*

Minimal access retroperitoneal pancreatic necrosectomy (MARPN) was performed as previously described.[6,7] Initial percutaneous drainage was performed with a 12-French pigtail catheter inserted under CT guidance. In patients with central or left-sided collections, the drainage catheter was inserted via the left flank between the spleen and splenic flexure. It was possible to insert catheters anteriorly or via the right flank in patients with right-sided or complex collections. MARPN was performed under general anesthetic or sedation. The pigtail drain was exchanged for a guidewire under fluoroscopic guidance and the tract dilated up to 30 Fr using serial dilators. A sheath was inserted into the tract allowing the passage of an operating nephroscope. Necrosis was removed piecemeal under direct vision with a minimal necrosectomy on the initial procedure due to immature necrosis and to prevent bleeding. Tissue samples were sent to microbiology for culture and sensitivities. A 10- or 12-Fr nasogastric tube was sutured inside a 28-Fr chest drain and inserted into the cavity allowing postoperative irrigation. Repeat MARPNs were performed every 7–10 days until necrosectomy was complete and healthy granulation tissue was visualized. A fistulogram was performed to confirm the cavity had collapsed. The chest drain was downsized to a nasogastric tube and the patient was discharged when sufficiently fit.

#### *Open Pancreatic Necrosectomy*

At laparotomy, the necrotic area was exposed by transection of the gastrocolic and duodenocolic ligaments or through the space of Riolan adjacent to the ligament of Treitz, allowing blunt dissection then debridement of necrotic tissue. At least 2 wide bore drains were placed into the cavity through separate incisions and the cavity managed by closed continuous local lavage.[6,23] Abdominal packing and second look laparotomies were not routinely performed.

For all techniques, additional percutaneous drains were inserted in to flank or loculated collections when indicated.

### *Statistical Analysis*

Descriptive statistics were performed on patient characteristics and outcome measures. A Chi-square test or a Kruskall–Wallis test was performed to test for statistical significance at the 5% level. Univariate logistic regression and multivariate logistic regression modeling including all factors with $P < 0.1$ in univariate analysis were also performed.

### *Outcomes*

Length of stay including any admission in the referring center was calculated. Procedure-related adverse events (AEs) included bleeding requiring intervention, visceral perforation, problematic fistulae, and stent-related events. AEs were separated into clinical AEs: hospital acquired pneumonia, persistent sepsis, pulmonary embolism, cardiac events, and venous thrombosis and procedural AEs: bleeding, perforation, fistulae, stent migration, and stent malfunction. Additional percutaneous drainage was defined as a radiological guided drain placed into an extrapancreatic collection.

### *Economic Analysis*

Individual patient costs were provided by the hospital finance department for 2015–2016 and 2016–2017 financial years

using PLICS. Individual patient costs for all diagnostic tests, treatment, inpatient stay, critical care stay, and outpatients were available from the Trust finance department. Endoscopy records were also interrogated to provide an accurate cost of any stents or disposable equipment used, as this is not currently represented in the PLICS data.

The drugs/treatment category included drugs, high-cost drugs, pharmacy costs, and transfusion services. Staff costs consisted of both medical staff and allied health professionals including physiotherapists, dieticians, occupational therapists and specialist nurses. The Clinical Negligence Scheme for Trusts (CNST) contributions were not included in the analysis.

A cost consequence analysis (CCA) was performed due to the difficulties in establishing one discrete outcome for the procedure required for cost-effectiveness analysis. A CCA is a practical method by which cost and outcome data can be structured to enable decision makers to improve the decision-making process.

We performed a statistical analysis of the comparative costs of EN versus MARPN versus OPN, and a subsequent cost comparison analysis of EN versus MARPN. Multiple studies have demonstrated that a minimal access approach is to be preferred over an open approach,[6,13,24] unless there are extenuating factors necessitating an open approach; therefore, a separate analysis to compare these 2 interventions was performed to help inform our practice. Such extenuating circumstances include rapid clinical deterioration, sepsis, requiring organ support, or suspected additional intra-abdominal pathology such as visceral perforation or pancreatitis associated visceral infarction.

## RESULTS

### *Clinical Outcomes*

In total, 86 patients were included the analysis: 38 patients underwent EN, 35 underwent MARPN, and 13 underwent OPN. Patient demographic information is shown in Table 1. There were no differences in sex, age, etiology, number of tertiary referrals, time to intervention, or modified CT severity score between the 3 groups. There was, however, a significant difference in the maximum width of collections (113 vs 147 vs 106 mm for EN, MARPN, and OPN, respectively, $P < 0.001$) and in the location of necrosis. Of 35, 32 (91.4%) patients undergoing MARPN had necrosis in the body or tail, whereas 34 (89.5%) of 38 patients undergoing EN had necrosis in the head or body. Patients undergoing OPN and MARPN had higher APACHE II scores (6 vs 9 vs 9, $P = 0.017$) and higher CRP levels than those patients treated by EN (107 vs 204 vs 278, $P = 0.012$).

Postoperative outcomes are shown in Table 2. The median (IQR) total length of stay was significantly different: 52 (29, 74) days for EN patients, 74 (55, 102) days for MARPN, and 63 (53, 79) days for OPN ($P = 0.007$). The postoperative length of stay was lower in the EN group compared to MARPN and OPN (19 vs 41 vs 42 days, $P < 0.001$). In-patient mortality was 4 (10.5%) for EN, 8 (22.9%) for MARPN, and 2 (15.4%) for OPN ($P = 0.379$). Overall AEs occurred in 26 (68.4%) patients undergoing EN, 24 (68.6%) for MARPN, and 6 (46.2%) for OPN. Procedural-related AEs were higher in the EN group ($P = 0.002$), whereas clinical AEs were higher in the MARPN group ($P = 0.046$). Confirmed infected necrosis was significantly higher for MARPN and OPN [32 (91.4%) and 11 (84.6%) versus 14 (36.8%) for the EN group], $P < 0.001$, but only 14 patients undergoing EN had samples sent for culture, all of whom had positive cultures. The common organisms found on culture were *Escherichia coli*, *Enteroccocus* species, *Klebsiella* species, and *Candida albicans*. There was no difference in difference in microbiota cultured between groups. There was no significant difference in the number of patients requiring additional percutaneous drainage ($P = 0.115$). The median (IQR) number of necrosectomies were 4 (2, 5) for EN, 2 (1, 3) for MARPN, and 1 for OPN ($P < 0.001$).

Table 3 shows specific complications occurring in individual groups. There was no significant difference in complications between the interventions. The incidence of persistent pancreatic fistulae was lower after EN compared to MARPN or OPN; however, this did not reach statistical significance ($P = 0.104$). In the endoscopic group, stent-related problems occurred in 16 (42.1%) patients.

Univariate logistic regression analysis (see Supplemental Table 1, http://links.lww.com/AOSO/A38) was performed for mortality. This demonstrated that the factors associated with increased mortality in the whole cohort of patients were age [odds ratio (OR) 1.042, 95% confidence interval (CI) 1.001–1.086] transfer from another center (OR 9.419, 95% CI 1.176–75.441), APACHEII score (OR 1.13, 95% CI 1.048–1.230), preoperative ICU stay (OR 6.896, 95% CI 2.121–22.419), and percutaneous drainage (OR 4.386, 95% CI 1.400–13.736). Multivariate logistic regression models (see Supplemental Table 2, http://links.lww.com/AOSO/A39) were performed for the outcome of AEs. They were not performed for mortality due to the small

**TABLE 1.**

**Patient Demographics**

| Characteristics | Subgroup | EN (N = 38) | MARPN (N = 35) | OPN (N = 13) | Total (N = 86) | *P* |
|---|---|---|---|---|---|---|
| Gender, n (%) | Female | 12 (31.6%) | 12 (34.3%) | 6 (46.2%) | 30 (34.9%) | 0.633 |
| | Male | 26 (68.4%) | 23 (65.7%) | 7 (53.8%) | 56 (65.1%) | |
| Age, median (IQR) | | 58 (47, 72) | 69 (49, 75) | 58 (55, 71) | 60 (49, 74) | 0.532 |
| Etiology of Pancreatitis, n (%) | Gallstones | 23 (60.5%) | 18 (51.4%) | 3 (23.1%) | 44 (51.2%) | 0.124 |
| | ERCP | 1 (2.6%) | 1 (2.9%) | 2 (15.4%) | 4 (4.7%) | |
| | Alcohol | 8 (21.1%) | 6 (17.1%) | 5 (38.5%) | 19 (22.1%) | |
| | Idiopathic | 3 (7.9%) | 1 (2.9%) | 0 (0.0%) | 4 (4.7%) | |
| | Other | 2 (5.3%) | 4 (11.4%) | 1 (7.7%) | 7 (8.1%) | |
| | Unknown | 1 (2.6%) | 5 (14.3%) | 2 (15.4%) | 8 (9.3%) | |
| Transfer from another hospital, n (%) | Yes | 23 (60.5%) | 26 (74.3%) | 9 (69.2%) | 58 (67.4%) | 0.430 |
| Days to intervention, median (IQR) | | 31 (11, 46) | 30 (20, 45) | 23 (7, 31) | 30 (11, 42) | 0.257 |
| CT width (mm) of collection, median (IQR) | | 113 (87, 147) | 147 (130, 178) | 106 (75, 155) | 134 (102, 160) | **<0.001** |
| CT severity score, n (%) | Moderate | 9 (23.7%) | 8 (22.9%) | 2 (15.4%) | 19 (22.1%) | 0.882 |
| | Severe | 29 (76.3%) | 27 (77.1%) | 11 (84.6%) | 67 (77.9%) | |
| Day 7 post admission RLUH CRP, median (IQR) | | 107 (55, 228) | 204 (107, 244) | 278 (183, 335) | 183 (93, 248) | **0.012** |
| Preoperative ITU stay, n (%) | Yes | 5 (13.2%) | 9 (25.7%) | 6 (46.2%) | 20 (23.3%) | **0.047** |
| Site, n (%) | Head | 10 (26.3%) | 3 (8.6%) | 3 (23.1%) | 16 (18.6%) | **0.028** |
| | Body | 24 (63.2%) | 20 (57.1%) | 5 (38.5%) | 49 (57.0%) | |
| | Tail | 4 (10.5%) | 12 (34.3%) | 5 (38.5%) | 21 (24.4%) | |
| Total APACHE II score, median (IQR) | | 6 (2, 9) | 9 (5, 12) | 9 (6, 16) | 7 (4, 11) | **0.017** |

Significant results are indicated in bold.

**TABLE 2.**

**Postoperative Descriptive Statistics**

| Outcomes | EN (N = 38) | MARPN (N = 35) | OPN (N = 13) | Total (N = 86) | *P* |
|---|---|---|---|---|---|
| Total length of stay (d), median (IQR) | 52 (29, 74) | 74 (55, 102) | 63 (53, 79) | 63 (45, 85) | **0.007** |
| Length of stay in RLBUHT (d), median (IQR) | 28 (17, 50) | 55 (39, 81) | 48 (36, 58) | 42 (26, 64) | **<0.001** |
| Postoperative length of stay (d), median (IQR) | 19 (8, 41) | 41 (28, 70) | 42 (26, 54) | 34 (19, 55) | **<0.001** |
| In-patient mortality, n (%) | 4 (10.5%) | 8 (22.9%) | 2 (15.4%) | 14 (16.3%) | 0.379 |
| 90-d mortality, n (%) | 4 (10.5%) | 8 (22.9%) | 3 (23.1%) | 15 (17.4%) | 0.323 |
| AEs, n (%) | 26 (68.4%) | 24 (68.6%) | 6 (46.2%) | 56 (65.1%) | 0.298 |
| AE (procedure), n (%) | 19 (50.0%) | 5 (14.3%) | 2 (15.4%) | 26 (30.2%) | **0.002** |
| AE (clinical), n (%) | 14 (36.8%) | 23 (65.7%) | 6 (46.2%) | 43 (50.0%) | **0.046** |
| Infected necrosis, n (%) | 14 (36.8%) | 32 (91.4%) | 11 (84.6%) | 57 (66.3%) | **<0.001** |
| Total ITU stay (d), median (IQR) | 0 (0, 0) | 0 (0, 5) | 3 (0, 22) | 0 (0, 3) | **0.003** |
| Percutaneous drainage, n (%) | 9 (23.7%) | 16 (45.7%) | 4 (30.8%) | 29 (33.7%) | 0.115 |
| No. necrosectomies, median (IQR) | 4 (2, 5) | 2 (1, 3) | 1 (1, 1) | 2 (1, 4) | **<0.001** |

Significant results are indicated in bold.

**TABLE 3.**

**Adverse Events**

| Characteristics | EN (N = 38) | MARPN (N = 35) | OPN (N = 13) | Total (N = 86) | *P* |
|---|---|---|---|---|---|
| Bleeding, n (%) | 1 (2.6%) | 4 (11.4%) | 1 (7.7%) | 6 (7.0%) | 0.304 |
| Fistula, n (%) | 1 (2.6%) | 5 (14.3%) | 2 (15.4%) | 8 (9.3%) | 0.104 |
| HAP, n (%) | 2 (5.3%) | 5 (14.3%) | 1 (7.7%) | 8 (9.3%) | 0.420 |
| Cardiac, n (%) | 2 (5.3%) | 2 (5.7%) | 0 (0.0%) | 4 (4.7%) | 1.000 |
| Persistent sepsis, n (%) | 3 (7.9%) | 7 (20.0%) | 2 (15.4%) | 12 (14.0%) | 0.339 |
| PE, n (%) | 1 (2.6%) | 1 (2.9%) | 0 (0.0%) | 2 (2.3%) | 1.000 |
| PV thrombosis, n (%) | 2 (5.3%) | 0 (0.0%) | 0 (0.0%) | 2 (2.3%) | 0.636 |
| SMV thrombosis, n (%) | 6 (15.8%) | 2 (5.7%) | 1 (7.7%) | 9 (10.5%) | 0.404 |
| Readmission, n (%) | 10 (26.3%) | 11 (31.4%) | 3 (23.1%) | 24 (27.9%) | 0.850 |
| Perforation, n (%) | 2 (5.3%) | 1 (2.9%) | 0 (0.0%) | 3 (3.5%) | 1.000 |

number of events. Patients with pancreatitis secondary to alcohol (OR 0.191, 95% CI 0.046–0.799) were less likely to suffer AEs than those with an etiology of gallstones. A longer length ICU stay was also associated with increased AEs (OR 1.112, 95% CI 1.008–1.227).

### *Economic Outcomes*

Individual patient costs were calculated using PLICS are summarized in Table 4 and Figure 1. The mean overall cost per patient was £30,981 for patients treated by EN, £52,357 for MARPN, and £60,077 for OPN ($P$ = 0.006). Similarly, the ward and intensive care costs were £9430 and £14,033; £9890 ($P$ = 0.089) and £5317; £16,648 and £24,722 for EN, MARPN, and OPN, respectively ($P$ = 0.001).

Table 5 and Figure 2 show a cost comparison of EN and MARPN which demonstrates a significantly lower average total cost for EN (£30,981) when compared to MARPN (£52,537) ($P$ = 0.004). The cost of ward care (£9430 vs £14,033, $P$ = 0.035) and medication (£1852 vs £3910, $P$ = 0.006) were also significantly lower for patients undergoing EN. The operating room costs in the MARPN group were comparable with endoscopy costs for patients managed by EN (£4420 and £4135).

## DISCUSSION

This study has investigated the actual cost alongside clinical outcomes for different approaches for the management of pancreatic necrosis in a real-world setting. All patients undergoing EN, MARPN, or OPN at a tertiary center over 2 financial years,

**TABLE 4.**

**Summary Table of the Average Cost (£) per Patient for EN, OPN, and MARPN**

| Department | EN (£) | MARPN (£) | OPN (£) | *P* |
|---|---|---|---|---|
| Wards | 9430 | 14,033 | 9890 | 0.089 |
| ITU/critical care | 5317 | 16,648 | 24,722 | **0.001** |
| Staff | 5358 | 7648 | 6501 | 0.298 |
| Drugs/treatment | 1852 | 3910 | 6807 | **0.024** |
| Theaters | 784 | 4420 | 5369 | **0.001** |
| Endoscopy | 4135 | 245 | 0 | **0.001** |
| Diagnostic tests | 2970 | 3762 | 5738 | 0.378 |
| outpatients | 1135 | 1691 | 1050 | 0.611 |
| TOTAL | 30,981 | 52,357 | 60,077 | **0.006** |

Significant results are indicated in bold.

HAP, hospital acquired pneumonia; PE, pulmonary embolus; PV, portal vein; SMV, superior mesenteric vein.

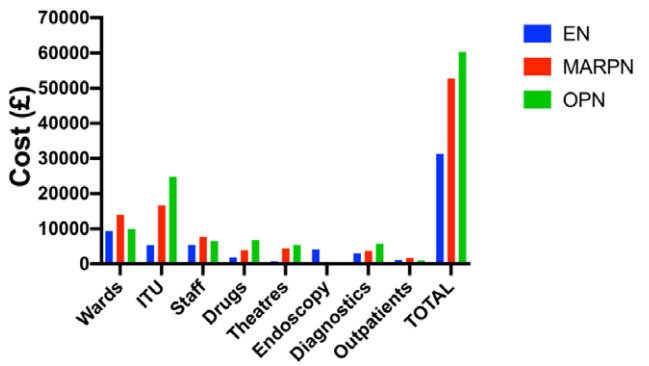


**FIGURE 1.** Graph showing average cost (£) per patient for EN, OPN, and MARPN.

**TABLE 5.**

**Cost Comparison for EN vs MARPN (£)**

| Average Costs per Patient | EN (£) | MARPN (£) | *P* |
|---|---|---|---|
| Wards | 9430 | 14,033 | **0.035** |
| ITU | 5317 | 16,648 | **0.025** |
| Staff | 5358 | 7648 | 0.168 |
| Medication/ treatment | 1852 | 3910 | **0.006** |
| Theaters/OR | 784 | 4420 | **0.001** |
| Endoscopy | 4135 | 245 | **0.001** |
| Diagnostic tests | 2970 | 3762 | 0.148 |
| Outpatients | 1135 | 1691 | 0.551 |
| Total | 30,981 | 52,537 | **0.004** |

Significant results are indicated in bold.

within a block UK NHS financial contract period, were included in the analysis. The results give an accurate representation of current costs for treating this complex cohort of patients with long and resource heavy inpatient stays. The most important finding is that patients undergoing EN had outcomes equivalent to those undergoing MARPN or OPN, with reduced inpatient stays and reduced treatment costs. Despite the less severe disease profile of patients undergoing EN; however, the average cost of EN was £30,981, whereas the NHS National Tariff for pancreatic necrosectomy for the 2019/2020 financial year was only £21,212, substantially less than it costs a center to treat the majority of these patients.[25,26] Those responsible for commissioning and allocating resources for health services should ensure that these essential costs are met.

The average cost for managing a patient with MARPN was over £20,000 more expensive than for EN. The increased cost is largely due to the significantly longer length of stay of the MARPN patients on both a surgical ward and ICU. The increased length of stay for MARPN of approximately 3 weeks is likely to be related to many factors, including being performed in a sicker cohort of patients and the need to prolong hospital stay until drain irrigation has been discontinued and drain downsized. Contrastingly, our protocol for EN is an initial transgastric drainage, followed by flush necrosectomy at 7 days; clinically well and suitable patients can then be discharged, without the need for irrigation, with EN performed on a weekly outpatient basis until the necrotic collection has resolved. It is reassuring that there was no increase in readmission following EN, suggesting that the protocol is safe. The finding of a reduced length of stay for endoscopic necrosectomy is consistent with previously published studies.[12,17]

OPN was associated with higher costs than the less invasive approaches, as OPN was associated with higher ICU costs and longer ICU stays. Previously published studies have found increased morbidity with OPN compared to minimal access techniques.[6,7,13,24,27] Bakker et al[13] observed a trend toward increased ITU stays for OPN, but this did not reach statistical significance; they also reported an increased inflammatory response following open surgical necrosectomy compared to EN. This may be partly responsible for the increased ITU stay and costs found for OPN. However, the OPN cohort in our analysis may have been more physiologically unstable initially, as we report higher CRP values and APACHEII scores for the OPN compared to the EN patients.

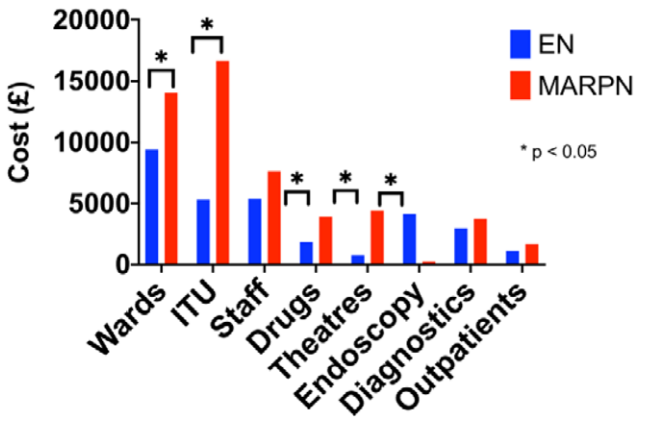


**FIGURE 2.** Comparison of average costs for EN vs MARPN (£).

This study is an observational analysis with intervention decided by the MDT rather than by randomization. We started performing EN shortly before the time frame included in this study, so the learning curve period for the technique is included in these data. As clinicians became more experienced with the technique, it was performed on a wider range of patients, including those on ICU and those with less favorable collections. The preoperative patient characteristics show that MARPN and OPN were performed in patients with higher APACHEII scores, higher CRP and associated with more ICU admissions then EN, limiting direct comparisons. Any patient who deteriorated was reassessed and the plan of intervention adjusted accordingly. Patients waiting for EN (who required a specialist endoscopist) or patients waiting for MARPN (who required an interventional radiology guidewire/drain placement as part of the procedure), in whom appropriate infra-structure was not immediately available and in whom it was felt life was in danger, underwent surgical intervention. Judgments of best care are commonplace in tertiary units, dealing with inter-regional transfers at high volume.

The site of the pancreatic necrosis has implications for the approach chosen; for EN, the collection has to be accessible via the transgastric or transduodenal route, whereas collections in the tail may be inaccessible. For MARPN, collections have to be approached via the flanks, although central or right-sided collections may also be accessible percutaneously in some patients.

Treatment algorithms have not been widely used for pancreatic necrosis, given the heterogeneity of the disease and variations in local expertise. One group is continuing to develop an algorithm to define the role of surgical approaches by time from onset of pancreatitis and hemodynamic status.[28] We feel the optimal way to approach pancreatic necrosis is to use a treatment algorithm taking into account the location of the necrosis and physiological condition of the patient to determine the management approach. This includes percutaneous drains, endoscopic, minimal access, and complex minimal access including single-port necrosectomy,[29] open necrosectomy or a combination of the above. Our work is ongoing.

## ACKNOWLEDGMENTS

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Brief Clinical Report

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# Single-Port Retroperitoneal Pancreatic Necrosectomy for the Treatment of Extrapancreatic Walled-Off Necrotic Collections

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## INTRODUCTION

Endoscopic or minimally invasive step-up approaches are considered the gold standard of treatment for pancreatic collections or necrosis,[1,2] with multiple techniques described.[3–6] Unfortunately, extrapancreatic necrosis, which is separate and remote from the pancreas, is often not adequately accessible by standard methods, typically when either in or extending down the paracolic gutters.[7,8] Overall, the management of extrapancreatic necrosis is not well addressed in the literature. Traditionally, treatment is by percutaneous drainage using relatively small diameter pigtail catheters inserted under radiologic guidance. Results are often unsatisfactory meaning open necrosectomy is required to debride the area, which in turn requires large incisions and sometimes multiple reoperations.

We have developed single-port retroperitoneal pancreatic necrosectomy (SPRPN), a novel method for managing extrapancreatic necrosis. A SILS port is placed into the necrotic collection and an articulating grasper (SILS Clinch) is used for debridement of necrotic tissue, providing a 300° operational arc around the port. This study reports our initial experience with this technique in 7 consecutive patients.

## METHODS

### *Patient Population*

Definitions used were that of the Atlanta criteria.[9] Acute pancreatitis was managed according to International Association of Pancreatology/American Association of Pancreatology guidelines.[10] All patients were discussed by the multidisciplinary team, attended by pancreatic surgeons, gastroenterologists, endoscopists, and interventional radiologists. Intervention was reserved for patients with documented or suspicion of infected pancreatic necrosis or those with persistent pain or symptoms after an extended period of hospitalization. Infected necrosis was defined as positive tissue cultures or gas in the collection on computerized tomography (CT) imaging. Repeat CT was performed if there was clinical deterioration, a significant rise in inflammatory markers or for planning possible intervention. SPRPN was used in patients with symptomatic extra-pancreatic walled-off necrosis (WON) in either the flank or the paracolic gutters, or complex collections that would otherwise require an open necrosectomy. Patients were followed up regularly in outpatient clinic following discharge.

### *Technique*

Percutaneous drains (PCDs) were radiologically inserted into the necrotic collection. SPRPN was performed under general anesthetic. Ureteric stents were inserted prior to necrosectomy to protect against ureteric injury and to prevent traction of the collapsing cavity from kinking the ureters. The 3-channel SILS port (Medtronic/Covidien, CT) was inserted using an open cut down technique, where a 3-cm incision was centered over the PCD insertion point. A zero-degree nephroscope was inserted through one port and an articulating grasper (SILS-Clinch) through another. Continuous 0.9% saline irrigation was used through the nephroscope to expand the cavity. Near complete necrosectomy, so as to avoid hemorrhage, was undertaken by direct vision. Tissue samples were sent to microbiology for culture and sensitivities. A 10 or 12 Fr nasogastric tube was sutured to a corrugated drain and inserted into the cavity allowing postoperative irrigation and drainage, initially at a rate of 125 ml/h and reduced according to clinical response. Patients underwent further CT scans or necrosectomy procedures if clinically indicated by ongoing sepsis or nonresolution of the collection.

## RESULTS

Between December 2016 and September 2019, 7 patients with a median (interquartile range [IQR]) age of 59 (40–68) years underwent SPRPN (Table 1). Five patients were transferred from district hospitals to our supraregional center. The etiology was gallstones in 2 patients, ethanol in 2 patients and endoscopic retrograde cholangiopancreatography (ERCP) related in 3 patients of which 2 also had perforation of the second part of the duodenum. All patients had severe pancreatitis, all had infected necrosis, and 2 patients had multiorgan dysfunction syndrome. All patients had WON, 4 patients had predominantly right-sided collections, 2 predominantly left-sided collections, and 1 with a complex horseshoe collection involving both paracolic gutters. The median (IQR) dimensions of the collections (width × depth

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**TABLE 1.**

**Clinical Characteristics of Patients**

| | | Patients | | | | | | | Summary Statistic | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Patient Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **Median** | **IQR** |
| Demographics | Age (y) | 24 | 59 | 63 | 40 | 71 | 68 | 58 | 59 | 40–68 |
| | Sex | F | F | F | M | M | M | F | — | — |
| | Etiology | Post-ERCP* | Post-ERCP* | Gall Stones | Ethanol | Post-ERCP | Gall stones† | Ethanol | — | — |
| | Smoker | N | Y | N | N | N | N | N | — | — |
| | Transfer to regional center | Y | Y | N | Y | Y | N | Y‡ | — | — |
| | MODS | Y | N | N | Y | N | N | N | — | — |
| | Infected necrosis | Y | Y | Y | Y | Y | Y | Y | — | — |
| | Severity of pancreatitis | Severe | Severe | Severe | Severe | Severe | Severe | Severe | — | — |
| | Comorbidity | None | None | None | None | None | Cold agglutin disease | None | — | — |
| | | | | | | | | | Median | IQR |
| Imaging findings | Focus of WON | Right Paracolic | Right Paracolic | Right Paracolic | Right Paracolic and Right Upper Quadrant | Left Paracolic and Left Groin | Horseshoe | Left Paracolic | | |
| | Pancreatic necrosis | N | N | N | N | Pancreatic tail (30%) | N | N | - | - |
| | Width (mm) | 113 | 98 | 92 | 128 | 92 | 298 | 70 | 98 | 92–128 |
| | Depth (mm) | 110 | 85 | 59 | 73 | 97 | 207 | 72 | 85 | 72–110 |
| | Height (mm) | 124 | 142 | 63 | 112 | 300 | 316 | 113 | 124 | 112–300 |
| | | | | | | | | | Median | IQR |
| Outcomes | Overall length of Stay (d) | 61 | 133 | 88 | 98 | 108 | 217 | 19 | 98 | 61–133 |
| | Time to PCD (d) | 23 | 29 | 62 | 34 | 19 | 23 | 7 | 23 | 19–34 |
| | Time from PCD to SPRPN (d) | 12 | 2 | 7 | 17 | 30 | 73 | 2 | 12 | 2–30 |
| | Number of sessions | 2 | 1 | 1 | 1 | 1 | 1 | 1 | — | — |
| | Postoperative length of stay (d) | 23 | 102 | 19 | 47 | 59 | 120 | 13 | 47 | 19–102 |
| | Postoperative time to resolution (d) | 37 | 42 | 36 | 83 | 49 | 45 | 11 | 42 | 36–49 |
| | Follow-up (mo) | 39 | 6 | 30 | 24 | 19 | 10 | 9 | 19 | 9–30 |
| | Complications | N | Death (PV occlusion and sepsis) | N | Open Necrosectomy and right hemicolectomy DVT arm from PICC | UTI from stent | Adhesions, cholangitis | N | — | — |

All summary parameters are median (IQR). Severity of pancreatitis and definitions are defined by the Revised Atlanta Classification.[9]

*ERCP-induced pancreatitis with retroduodenal perforation.

†Required ERCP for cholangitis.

‡Seen as outpatient and electively admitted.

DVT indicates deep venous thrombosis; F, female; infected necrosis, infected necrosis was defined as positive tissue cultures or gas in the collection on computerized tomography imaging; IQR, interquartile range; M, male; MODS, multiorgan dysfunction syndrome; N, no; PICC, peripherally inserted central catheter; Y, yes.

× height) were 98 mm (92–128) × 85 mm (72–110) × 124 mm (112–300). The first patient underwent 2 procedures as part of the learning curve, while the remaining patients underwent only 1 procedure each. The fourth patient had an infarcted right colon secondary to the inflammatory occlusion of mesenteric vessels, which was noted after the initial necrosis was cleared and was converted to an open necrosectomy with extended right hemicolectomy. Two patients required further PCD on subsequent admissions for further attacks of pancreatitis, unrelated to the original collections.

The overall median (IQR) length of stay for this cohort was 98 (61–133) days, which included patient stay in the district hospitals prior to transfer. The median (IQR) time from hospital admission to PCD was 23 (19–34) days and time from PCD to SPRPN was 12 (2–30) days. The median (IQR) time of postoperative stay was 47 (19–102) days and time to collection resolution was 42 (36–49) days. The second patient died on a second admission from portal vein occlusion and sepsis related to other underlying disease. Three further patients had complications, namely peripherally inserted central catheter line deep venous thrombosis, urinary sepsis, and biliary sepsis requiring ERCP.

## DISCUSSION

We report the initial experience of 7 patients undergoing SPRPN for infected walled-off extra pancreatic necrosis. A SILS port has previously been described for direct access to pancreatic necrosis in 3 patients,[5] its use into extrapancreatic collections is novel. Our patients were superselected, representing a serious clinical challenge but ultimately with a successful outcome using a 3-cm incision. Necrosis was cleared after only 1 procedure in all but the index case. Although the excess consumable costs are around $1040, overall savings might be seen in terms of reduced length of stay and surgical procedures.

Given the generally poor condition of these patients, it is unsurprising that 4 patients had complications. The second patient died from infected ascites following a portal vein thrombosis on a second admission. The fourth patient was seen to have infarcted their right colon from mesenteric artery inflammatory occlusion, seen once the necrosis was removed from the area, necessitating an open necrosectomy and extended right hemicolectomy.

The successful management of severe pancreatitis requires a personalized hybrid approach using a combination of available approaches. The technique described here should be considered an addition to the group of complex-minimal access procedures, which can be used in place of traditional open necrosectomy for difficult placed extrapancreatic WON.

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# A systematic review and meta-analysis of metal versus plastic stents for drainage of pancreatic fluid collections: metal stents are advantageous

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## Abstract

**Background** The use of fully covered metal stents (FCSEMS) and specifically designed lumen apposing metal stents for transmural drainage of pancreatic fluid collections has become widespread. A systematic review published in 2015 did not support the routine use of metal stents for drainage of pancreatic fluid collections. However, recent studies have shown conflicting data; therefore a systematic review and meta-analysis was performed.

**Method** We conducted a database search for original comparative studies between plastic and metal stents. The random effects model was used to calculate pooled risk ratios (RR) with 95% confidence intervals (CI). Outcomes analysed were clinical success, adverse events and requirement of further intervention.

**Results** The search identified 936 studies, 7 studies with 681 (340 metal, 341 plastic) patients met inclusion criteria and were included in the meta-analysis. Clinical success was achieved in 93.8% versus 86.2% in the metal and plastic groups, respectively, RR 1.08 [95% CI 1.02–1.14]; $p=0.009$. Adverse events were reduced for metal stents when compared with plastic (10.2% vs. 25.0%), RR 0.42 [95% CI 0.22–0.81]; $p=0.010$. Metal stent usage reduced bleeding (2.8% vs. 7.9%), RR 0.37; [95% CI 0.18–0.75]; $p=0.006$. Further intervention was required in 12.4% of patients in the metal stent group versus 26.7% for plastic stents, RR 0.54; [95% CI 0.22–1.29]; $p=0.165$.

**Conclusions** The use of metal stents for drainage of pancreatic fluid collections is associated with improved clinical success, fewer adverse events and reduced bleeding compared to plastic stents.

**Keywords** Pancreatic fluid collection · Metal stents · Plastic stents · Endoscopic ultrasound intervention · Pancreatic pseudocyst · Drainage

Pancreatic and peri-pancreatic fluid collections (PFC) are common following an insult to the pancreas [1, 2]. It is important to differentiate between those, which are purely fluid, and those that contain necrotic tissue when considering appropriate treatments. The revised Atlanta Classification states that acute peri-pancreatic fluid collections (APFC) are homogenous, do not have a well-defined wall and can be multiple. They occur within the first 4 weeks of non-necrotic interstitial oedematous pancreatitis. Most APFC remain

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sterile and resolve spontaneously without intervention, they do not by themselves constitute severe acute pancreatitis [3]. Pancreatic pseudocysts are peri-pancreatic fluid collections surrounded by a well-defined wall with no solid material and markedly increased amylase activity. A pancreatic pseudocyst usually arises after more than 4 weeks of the start of an attack and are nearly always associated with chronic pancreatitis. A pseudocyst is extremely rare in acute pancreatitis and use of the term pancreatic pseudocyst in the setting of acute pancreatitis may fall into disuse [3]. A pseudocyst may occur in acute necrotising pancreatitis secondary to a disrupted main pancreatic duct, whereby parenchymal necrosis of the neck or body isolates a viable distal remnant [3, 4].

Acute necrotising pancreatitis may feature acute necrotic collections (ANC), which have mixed heterogeneous contents with no definable wall or capsule. Walled-off necrosis (WON), which may be intrapancreatic or extrapancreatic, has mixed fluid and solid components as well as a defined capsule and requires at least 4 weeks following the onset of necrotising pancreatitis to mature [3].

Although many PFCs will resolve spontaneously, intervention is indicated in cases when infection is present or if the collection is persistently symptomatic [3, 5]. Management options for PFCs include percutaneous, endoscopic, minimal access and open surgical techniques [6–8]. A recent randomised trial has shown equal efficacy between surgery and endoscopic drainage of pseudocysts but found reduced length of hospital stay and reduced costs for endoscopic intervention [9]. Thus, endoscopic management is now often regarded as first-line management of PFCs with multiple studies demonstrating its safety and high success rates [10, 11].

Endoscopic drainage of PFCs traditionally involves creating a fistula and placement of plastic stents to enable resolution by transluminal drainage. Natural progression led to the use of fully covered self-expanding metal stents (FCSEMS), initially designed for biliary stenting and latterly specifically designed FCSEMS as well as lumen apposing metal stents (LAMS) [10, 12]. Metal stents have the advantage of large diameter lumens, which facilitate better drainage, particularly when there is debris or necrotic tissue present. They also allow easy and safe access to the cavity for direct endoscopic necrosectomy if required [13]. However, metal stents are significantly more expensive than plastic stents and some early reports raised safety concerns regarding their use, notably delayed bleeding and embedded stents [14]. With high success rates using plastic stents published, some centres do not see the benefit of metal stents, particularly for pseudocyst drainage [10].

A systematic review published in 2015 concluded that there was no evidence to support the routine use of metal stents for drainage of pancreatic fluid collections [15]. Since then, however, several studies comparing plastic double pigtail stents and FCSEMS/LAMS have been published in the literature.

The aim of this systematic review and meta-analysis is to review these recently published studies to assess clinical success rates, adverse events and requirement of further intervention, when treating PFC of any description.

## Materials and methods

### Eligibility criteria

The inclusion criteria for qualitative and quantitative analysis were comparative studies between plastic double pigtail stents and metal stents for drainage of both walled-off necrosis (WON) and pseudocysts. Randomised controlled trials, prospective and retrospective studies were all eligible for inclusion as preliminary searches demonstrated few randomised controlled trials. Studies that used LAMS, FCSEMS and biliary self-expanding metal stents were all included. Only English language adult studies were included. No date criteria were set. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [16] and the protocol was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO, CRD42017071101).

### Information sources

MEDLINE, Pubmed and SCOPUS databases were searched, with the final search conducted on 20/10/17. References of included studies were also screened.

### Search

The search terms were “pseudocyst” OR “pancreatic fluid collection” OR “walled-off necrosis” AND “endoscopy” OR “endoscopic ultrasound” OR “EUS” AND “stent”.

### Study selection

Search results were combined on the Covidence software platform. Duplicate records were removed. Two reviewers (RSa, JR) independently scanned the title and abstract of all records identified during the search. Full-text articles were retrieved and reviewed if it was not clear from the abstract if inclusion criteria were met. We included studies irrespective of whether they reported all outcome measures. Studies not meeting the inclusion criteria were excluded with the reason for exclusion recorded.

### Data collection process

Data were extracted independently in a standardised table by two reviewers (RSa, SC). Agreement was reached by consensus.

### Data items

The following characteristics were extracted from the studies: study design, number of centres, location of centres, date of studies, total number of participants, mean age, sex, type of PFC, type of metal stent, type and number of plastic stent, follow-up period and size of PFC.

The primary outcome measure recorded was clinical success, defined as resolution of pancreatic fluid collection. Secondary outcome measures were adverse events and rate of reintervention. Other outcomes recorded were technical success, recurrence, length of stay and stent migration.

### Statistics

Random effects modelling was undertaken for each of the outcomes of interest. The effect size between metal and plastic stents was described in terms of individual and pooled risk ratios with 95% confidence intervals and weighting estimated using the Mantel–Haenszel method. Forest plots were generated and study heterogeneity was investigated using the $I^2$ statistic. An $I^2$ exceeding 50% was considered to indicate significant heterogeneity. Sensitivity analyses were performed on the outcomes when heterogeneity or outlier studies were found. The effect size between metal and plastic stents was also explored for pseudocyst and WON separately. Funnel plots were used to explore the presence of publication bias and Egger's regression test for assessing their asymmetry. We considered $p$ values $< 0.05$ to be statistically significant. All the analyses were performed in Stata 14 (StataCorp, College Station, Texas, USA), using the command *Metan* for fitting random effects models and producing forest plots.

## Results

### Study selection

The database search returned 1768 articles, 936 remained after duplicates were removed (see Fig. 1). Twelve full-text articles were reviewed and five were excluded; four were not comparative studies and another was from the same centre as an included study [17, 18] and it was unclear if the data were duplicated. Seven studies were included in the analysis [17, 19–24]. It is important to state that patient allocation to study group was by stent, rather than by type of pancreatic fluid collection.

### Study characteristics

The characteristics of included studies are shown in Table 1. Patient demographic information and characteristics are summarised in Table 2. The outcome measures of individual studies are summarised in Table 3.

### Synthesis of results

#### Clinical success

The results for the primary outcome measure of clinical success are shown in Fig. 2. The seven papers included in this analysis contained a total of 681 patients, 340 and 341 had metal and plastic stents, respectively. Overall, 93.8% of patients in the metal stent group and 86.2% in the plastic stent group achieved clinical success. The pooled risk ratio (RR) suggests an increase in clinical success when metal stents are used compared to plastic stents (1.08 [95% CI 1.02–1.14], $p = 0.009$; $I^2 = 25.4\%$).

There was heterogeneity of definition of clinical success between studies, summarised in Table 4. Five studies defined success using both radiological and clinical criteria. One study assessed clinical improvement only and one study reported radiological resolution. For the Ang et al., we included final clinical success for the quantitative analysis, for Dayyeh et al., we included the results that regarded concomitant percutaneous drainage as a failure of endoscopic drainage for better consistency across studies.

Subgroup analysis was undertaken and found four studies specific for WON, comprising 186 and 150 for metal and plastic stent groups, respectively (see Fig. 3). Only two studies were suitable for analysis for pseudocysts, including 119 patients with metal and 132 with plastic stents. For WON, clinical success was achieved in 91.4% of the metal stent group and 80.7% of patients with plastic stents. The pooled risk ratio suggests superiority of metal stents but does not reach significance (1.11 [95% CI 0.98–1.24], $p = 0.089$; $I^2 = 48.6\%$). Similarly, clinical success in the pseudocyst group occurred in 98.3% of those patients with metal stents and 89.4% of those with plastic stents. The pooled risk ratio (1.10 [95%CI 1.03–1.17], $p = 0.005$; $I^2 = 0.0\%$) suggests placing metal stents increases clinical success in patients with a pseudocyst, however, interpretation is limited due to the small number of studies included.

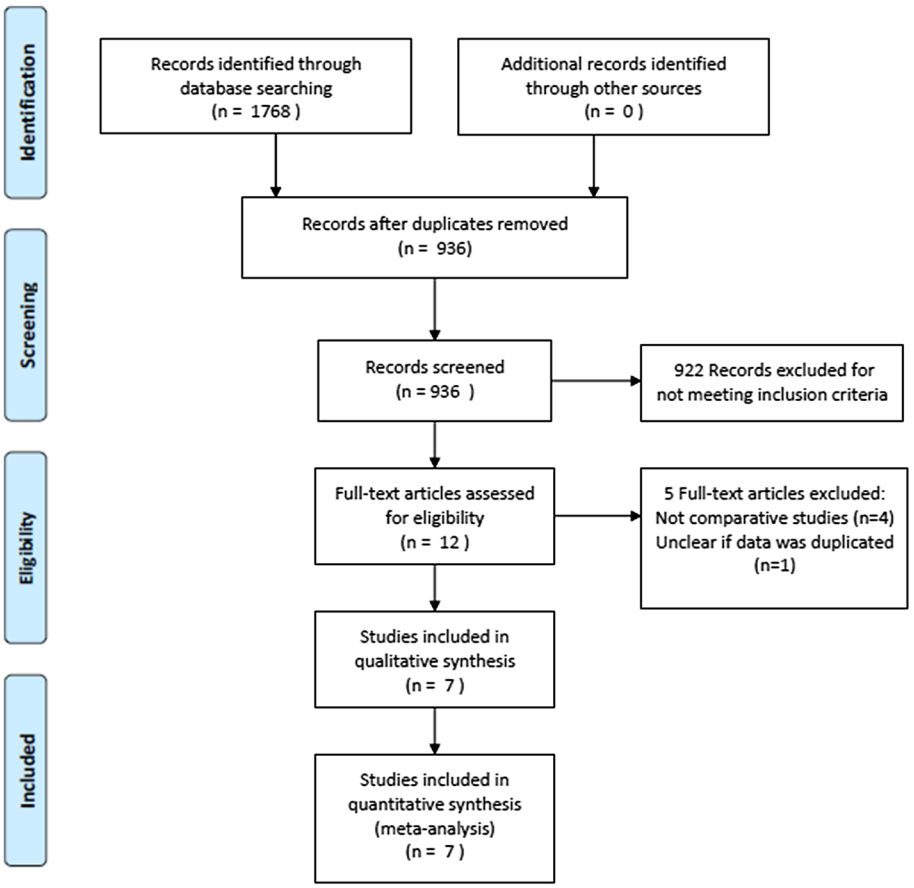


**Fig. 1** PRISMA flow chart of search [16]

**Table 1** Characteristics of included studies

| Author Year | Study type | Number of patients (%) | | PFC type (%) | | Metal stent type (diameter mm) | Plastic stent size (number of stents) |
|---|---|---|---|---|---|---|---|
| | | Plastic stent | Metal stent | Pseudocyst | WON | | |
| Ang et al. 2016 [24] | Retrospective 2 centre | 37 (76) | 12 (24) | 31 (63) | 18 (37) | Nagi (16 mm) | (1–2) |
| Bang et al. 2016 [19] | Retrospective case control | 40 (67) | 20 (33) | 21 (35) | 39 (65) | Hot AXIOS (15 mm) | 7f 4 cm (2) |
| Bapaye et al. 2016 [20] | Retrospective | 61 (46) | 72 (54) | – | 133 (100) | Nagi (16 mm) | 7f (2–4) |
| Dayyeh et al 2017 [23] | Retrospective | 36 (38) | 58 (62) | – | 94 (100) | Axios (15 mm), Niti-s (18 or 20 mm) | 7f or 10f (2 or more) |
| Lee et al. 2014 [22] | *RCT | 25 (50) | 25 (50) | 14 (28) | 36 (72) | BONA-Soo (8 mm) | 7f (2–3) |
| Mukai et al. 2014 [21] | Retrospective | 27 (39) | 43 (61) | – | 70 (100) | Axios (10 or 15 mm) Niti-s (16 mm) Hanaro (12 mm) | 7f (1–2) |
| Shariaha et al 2015 [24] | Retrospective 2 centre cohort | 118 (51) | 112 (49) | 230 (100) | – | Wallflex Gore Viabl (10 mm) | 10f (2) |

*In Lee et al., five patients were lost to follow-up (3 and 2 in plastic and metal stents, respectively). Therefore, the number of patients used for calculating clinical success, reintervention and recurrence was 45 (22/23)

## Adverse events

The adverse events reported in individual studies are summarised in Table 5. A total of 592 patients from six studies were considered for this analysis; 284 in the metal and 308 in the plastic stent group (see Fig. 4). Adverse events were noted in 10.2% of the metal and 25.0% in plastic stent group. The pooled risk ratio demonstrated a 58% reduced risk of

**Table 2** Patient demographics and characteristics in included studies

| Author Year | Mean age, years | | Male (%) | | Mean PFC size (mm) | | PFC infection (%) | | Nasocystic drainage (%) | | Median follow-up duration (months) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal |
| Ang et al. 2016 [24] | *Cross-over of stent summary presented | | *Cross-over of stent summary presented | | *Cross-over of stent summary presented | | – | – | Not routine | | – | |
| Bang et al. 2016 [19] | 52.9 | 50.7 | 62.5 | 55.0 | 109.3 | 120.0 | – | – | 20.0 | 5.0 | 26.5 | 5.3 |
| Bapaye et al. 2016 [20] | 40.7 | 43.9 | 88.5 | 86.1 | 117.1 | 100.9 | – | – | Yes | | Until stent removal | |
| Dayyeh et al. 2017 [23] | 59.7 | 52.7 | 77.7 | 77.6 | 128.0 | 134.0 | 44.4 | 39.7 | No | | – | |
| Lee et al. 2014 [22] | 51.6 | 53.7 | 76.0 | 88.0 | 89.0 | 84.0 | 32.0 | 44.0 | If debris/pus | | – | |
| Mukai et al. 2014 [21] | 55.9 | 54.4 | 77.8 | 86.0 | 77.1 | 105.6 | 59.3 | 53.4 | 92.6 | 25.6 | – | |
| Sharaiha et al. 2015 [17] | 52.2 | 53.2 | 69.5 | 55.4 | 97.8 | 98.6 | – | – | No | | 16 | |

*Ang et al. reports a cross-over summary of patient characteristics. Initial stent placement was plastic in 37 patients and metal in 12, 4 patients with plastic stents went on to have metal stents inserted at a further procedure

experiencing adverse events when a metal stent was used compared to plastic (0.42 [95% CI 0.22–0.81], $p=0.010$; $I^2=42.9\%$). Results from Dayyeh et al. were not included as the summaries were reported for each adverse event separately. Random effects models for stent migration and perforation were fitted, however, no significant effect size between the two types of stents was identified.

The outcome of bleeding was analysed separately (see Fig. 5). The six papers included in the analysis contained a total of 626 patients, 322 of which treated with metal stents and 304 with plastic stents. Bleeding was reported for 2.8% and 7.9% of patients treated with metal and plastic stents, respectively. The pooled Risk Ratio indicates that the use of metal stents reduced the risk of bleeding by 63% compared to plastic stents (0.37; [95% CI 0.18–0.75], $p=0.006$; $I^2=0.0\%$). The results do not show heterogeneity, suggesting bleeding risk was consistent across the publications. Results from Bang et al. were not included as it does not specifically report bleeding adverse events.

Subgroup analysis was undertaken and found three studies reporting adverse events for WON separately and were included in the analysis, 128 patients had metal stents included and 114 for plastic (see Fig. 6). Adverse events occurred in 8.6% of patients with metal stents and 26.3% of the plastic stent group. The pooled risk ratio (0.52 [95%CI 0.10–2.79], $p=0.442$; $I^2=82.4\%$) does not suggest a significant reduction in adverse events for either plastic or metal stents for patients with WON. Two studies with 119 and 132 patients with metal and plastic stents, respectively, were likewise reported for pseudocysts. Adverse events occurred in 15.1% of patients with metal stents and 30.3% of those with plastic stents. The pooled risk ratio (0.50 [0.31–0.82], $p=0.006$; $I^2=0.0\%$) suggests that inserting a metal stent reduced the risk of experiencing an adverse event in patients with pseudocysts.

The infection rate post stent insertion for metal stents was 5.4% and 13.2% for plastic stents. The pooled risk ratio (0.53 [95% CI 0.23–1.20], $p=0.127$; $I^2=41.9\%$) does not suggest a difference between the groups. The severity of post-procedural infection was not well defined within the studies [17, 24]. One study reported a single mortality from uncontrolled sepsis [21], another reported 2/58 (3%) of metal 2/36 and (6%) of plastic stent patients required transfer to intensive care for sepsis management [23]. In three studies, either surgical or endoscopic intervention was required for control of infection [19, 20, 22]. Bang et al. stated 3/20 (15%) and 5/40 (12.5%) patients in the metal and plastic groups, respectively, developed post-procedural infection, four patients were managed with further endoscopic procedures and three by surgical techniques but this is not specified by stent type [19]. Bapaye et al. reported 2/72 (2.8%) patients with metal and 16/61 (26.2%) with plastic stents developed infection

**Table 3** Summary table of outcome measures

| Author Year | Technical success (%) | | Clinical success (%) | | Adverse events (%) | | PFC recurrence (%) | | Reintervention (%) | | Mean length of stay (days) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal |
| Ang et al. 2016 [24] | 100.0 | 100.0 | 94.6 | 100.0 | 13.5 | 0.0 | – | | 35.1 | 8.3 | – | |
| Bang et al. 2016 [19] | 100.0 | 100.0 | 92.5 | 95.0 | 15.0 | 20.0 | 0.0 | 0.0 | 30.0 | 25.0 | 9.2 | 9.3 |
| Bapaye et al. 2016 [20] | 100.0 | 100.0 | 73.8 | 94.4 | 36.1 | 5.6 | 0.0 | 0.0 | 26.2 | 2.8 | 8.0 | 4.1 |
| Dayyeh et al 2017 [23] | – | | 75.0 | 82.8 | Summaries of specific AE presented | | – | | – | | 8.0* | 4.0* |
| Lee et al. 2014 [22] | 100.0 | 100.0 | 90.9 | 87.0 | 8.0 | 0.0 | 0.0 | 4.5 | 9.1 | 13.0 | – | |
| Mukai et al. 2014 [21] | 100.0 | 100.0 | 92.6 | 97.7 | 18.5 | 7.0 | – | | 25.9 | 23.3 | 28.7 | 22.5 |
| Sharaiha et al. 2015 [17] | 92.0 | 98.0 | 89.0 | 98.2 | 31.4 | 16.1 | 3.4 | 0.9 | – | | – | |

*Dayyeh et al. summarised median length of stay

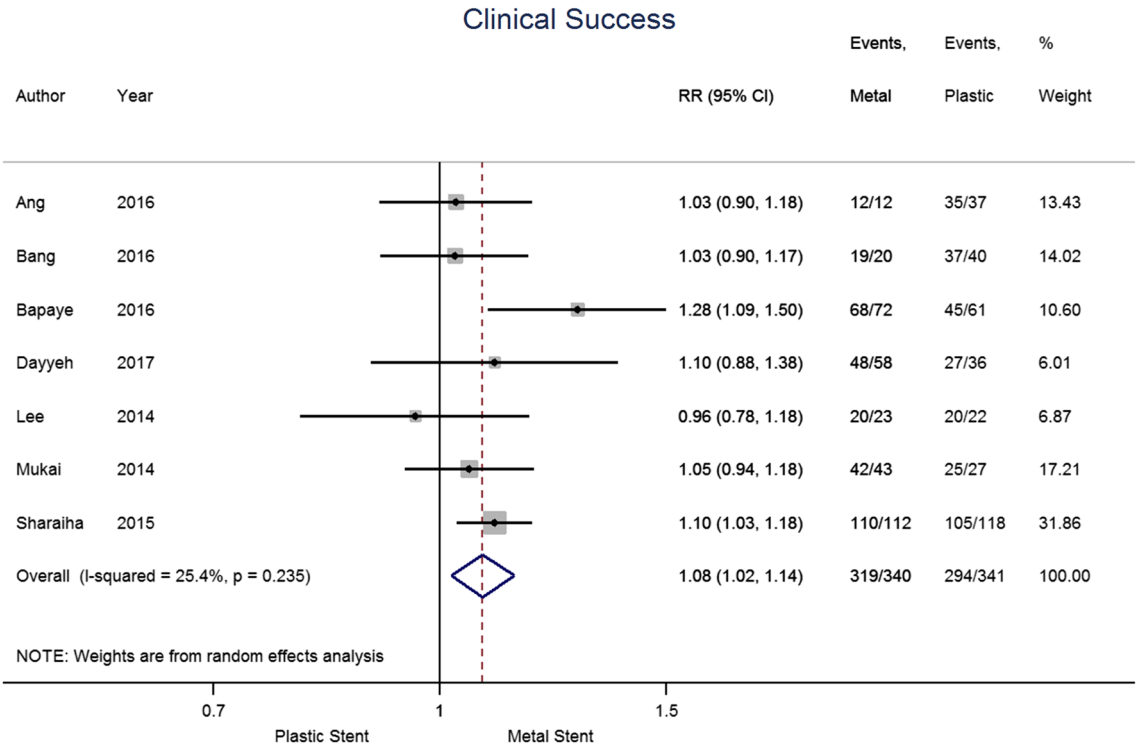


**Fig. 2** Forest plot for individual and pooled risk ratio of clinical success

**Table 4** Definitions of clinical success

| Author Year | Definition clinical success |
|---|---|
| Ang et al. 2016 [24] | Size < 2 cm on imaging and resolution of symptoms |
| Bang et al. 2016 [19] | Size < 2 cm on imaging with resolution of symptoms at 8 weeks |
| Bapaye et al. 2016 [20] | Symptom resolution and complete resolution on imaging at end of treatment period |
| Dayyeh et al. 2017 [23] | Complete clinical amelioration of acute index symptoms and resolution on imaging |
| Lee et al. 2014 [22] | Size < 2 cm on CT performed every 4 weeks with resolution of symptoms |
| Mukai et al. 2014 [21] | Resolution of symptoms |
| Sharaiha et al. 2015 [17] | Resolution at 12 months on imaging |

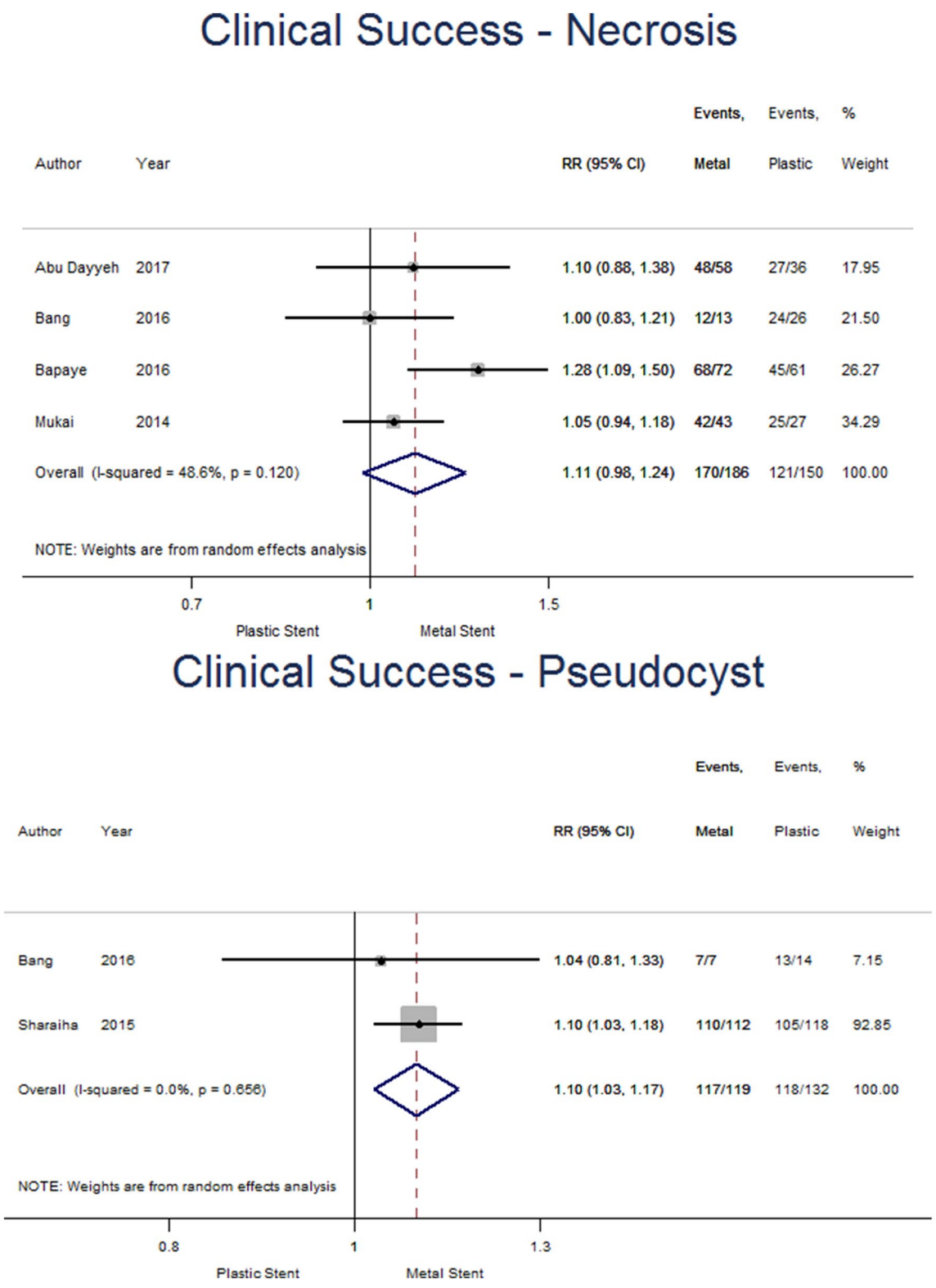


**Fig. 3** Forest plot showing individual and pooled risk ratios of clinical success for pseudocysts and walled-off necrosis

**Table 5** Frequency of specific adverse events

| Author year | Bleeding (%) | | Stent migration (%) | | Infection (%) | | Perforation (%) | | Tract dilatation (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | Metal | Plastic | metal |
| Ang et al. 2016 [24] | 5.4 | 0.0 | Cross-over of stent summary presented* | | 2.7 | 0.0 | 2.7 | 0.0 | 8.0 | 8.0 |
| Bang et al. 2016 [19] | – | | 2.5 | 10.0 | 12.5 | 15.0 | – | | 12.0–15.0 | – |
| Bapaye et al. 2016 [20] | 8.2 | 2.8 | 3.3 | 2.8 | 26.2 | 2.8 | – | | 18.0 | 6.0 |
| Dayyeh et al. 2017 [23] | 19.4 | 6.9 | 19.4 | 20.7 | 5.6 | 3.4 | 8.3 | 1.7 | 15.0–18.0 | 15.0–18.0 |
| Lee et al. 2014 [22] | 4.0 | 0.0 | 4.0 | 0.0 | 8.0 | 12.0 | – | | 8.0 | When resistance encountered |
| Mukai et al. 2014 [21] | 11.1 | 0.0 | 3.7 | 4.7 | – | | 0.0 | 2.3 | 15.0–20.0 | – |
| Sharaiha et al. 2015 [17] | 5.1 | 2.7 | 0.8 | 0.9 | 13.6 | 5.4 | 4.2 | 1.8 | 10.0 | 10.0 |

*Ang et al. reports stent migration for stent cross-over

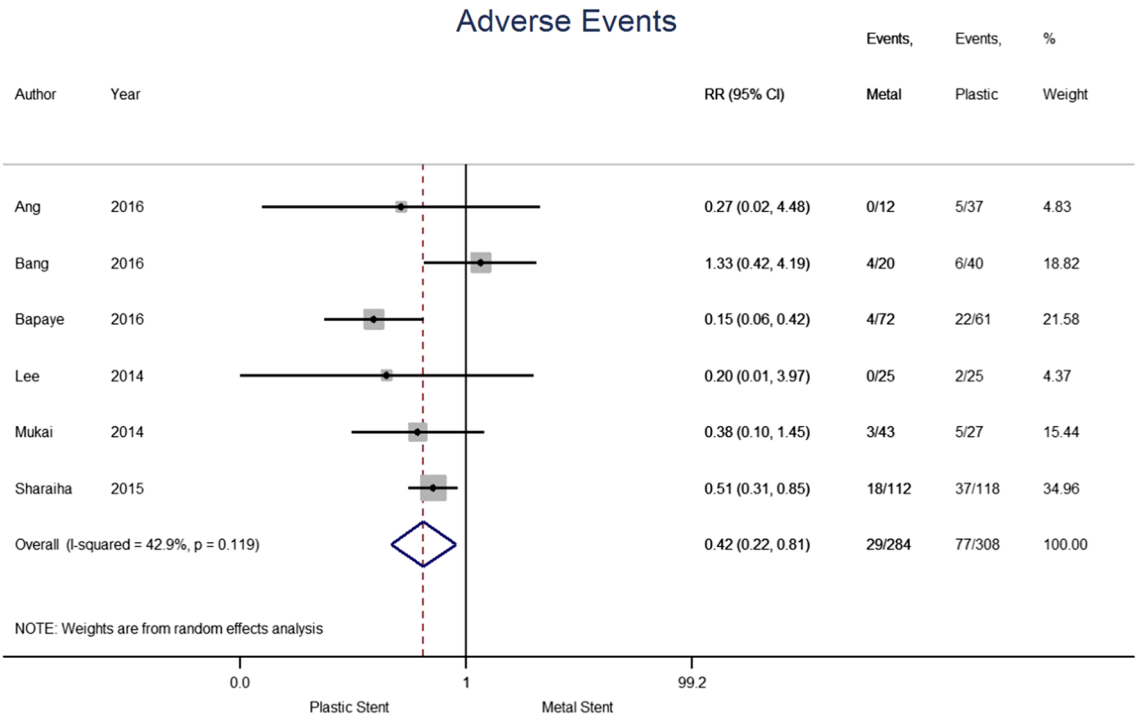


**Fig. 4** Forest plot for individual and pooled risk ratio of adverse events

that were all managed surgically [20]. In the study by Lee, 2/25 (8%) of metal and 3/25 (12%) of the plastic group were found to have post-procedural infection and were all managed with further endoscopic drainage [22].

### Reintervention

Reintervention data were available from five studies (see Fig. 7), therefore the analysis contains 357 patients, 170 and 187 in metal and plastic stent groups, respectively. The percentage of patients requiring reintervention was 12.4% among those treated with metal stent and 26.7% in the plastic stent group. The pooled risk ratio suggests a higher risk of reintervention when plastic stent were used, however, treatment effect failed to reach statistical significance (0.54; [95% CI 0.22–1.29], $p = 0.165$; $I^2 = 59.6\%$).

The stated definitions for reintervention were a need for repeat endoscopy or surgery due to persistent symptoms associated with residual PFC that had not reduced by > 50% in size [24], if symptoms or inflammation continued despite drainage and additional sessions of direct endoscopic necrosectomy [21], additional transmural drainage and/or

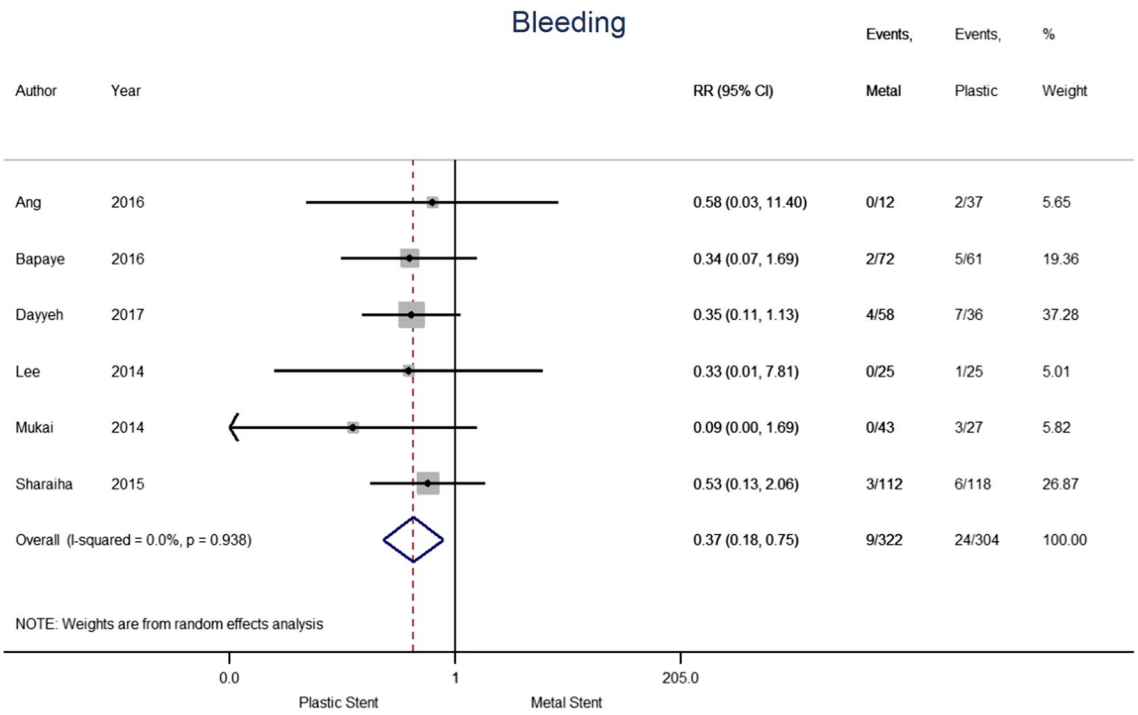


**Fig. 5** Forest plot for individual and pooled risk ratio of bleeding

endoscopic necrosectomy [19] and salvage surgical intervention [20].

Sharaiha et al. and Dayyeh et al. were not included as reintervention rates were not reported fully. Sharaiha et al. stated that 52 (22%) patients required further interventions for pseudocysts within first month. Furthermore, it reported a significant difference in short-term intervention ($p=0.008$) but does not include actual numbers or clarify which stent was superior [17].

Subgroup analysis was undertaken and found three studies specified reintervention in WON (see Fig. 8). 128 and 114 patients had metal and plastic stents inserted, respectively. 21.1% of those in the metal group and 22.9% in the plastic group required reintervention. The pooled risk ratio (0.65 [95% CI 0.16–2.60], $p=0.543$; $I^2=84.8\%$) does not suggest a superiority for either stent. Only one study was suitable for inclusion in the pseudocyst analysis so meta-analysis was unable to be performed.

### Publication bias, subgroup and sensitivity analyses

The Bapaye study was a consistent outlier in the quantitative analysis. Sensitivity analyses performed without this study, confirmed the same findings of the main analyses and showed a considerable drop in heterogeneity. There was no significant difference in methodology or reporting to explain this and no reason to exclude it from the analysis.

Funnel plots to assess publication bias for outcomes are presented in supplementary information. The graphs do not reflect any publication bias and Egger's regression tests for asymmetry yielded statistically non-significant p-values.

## Discussion

This meta-analysis demonstrates superior clinical success and reduced adverse events for use of metal stents when compared to plastic for endoscopic transluminal drainage of pancreatic fluid collections. Previous meta-analysis by Bang et al. showed no difference in the efficacy and adverse events between plastic and metal stents for

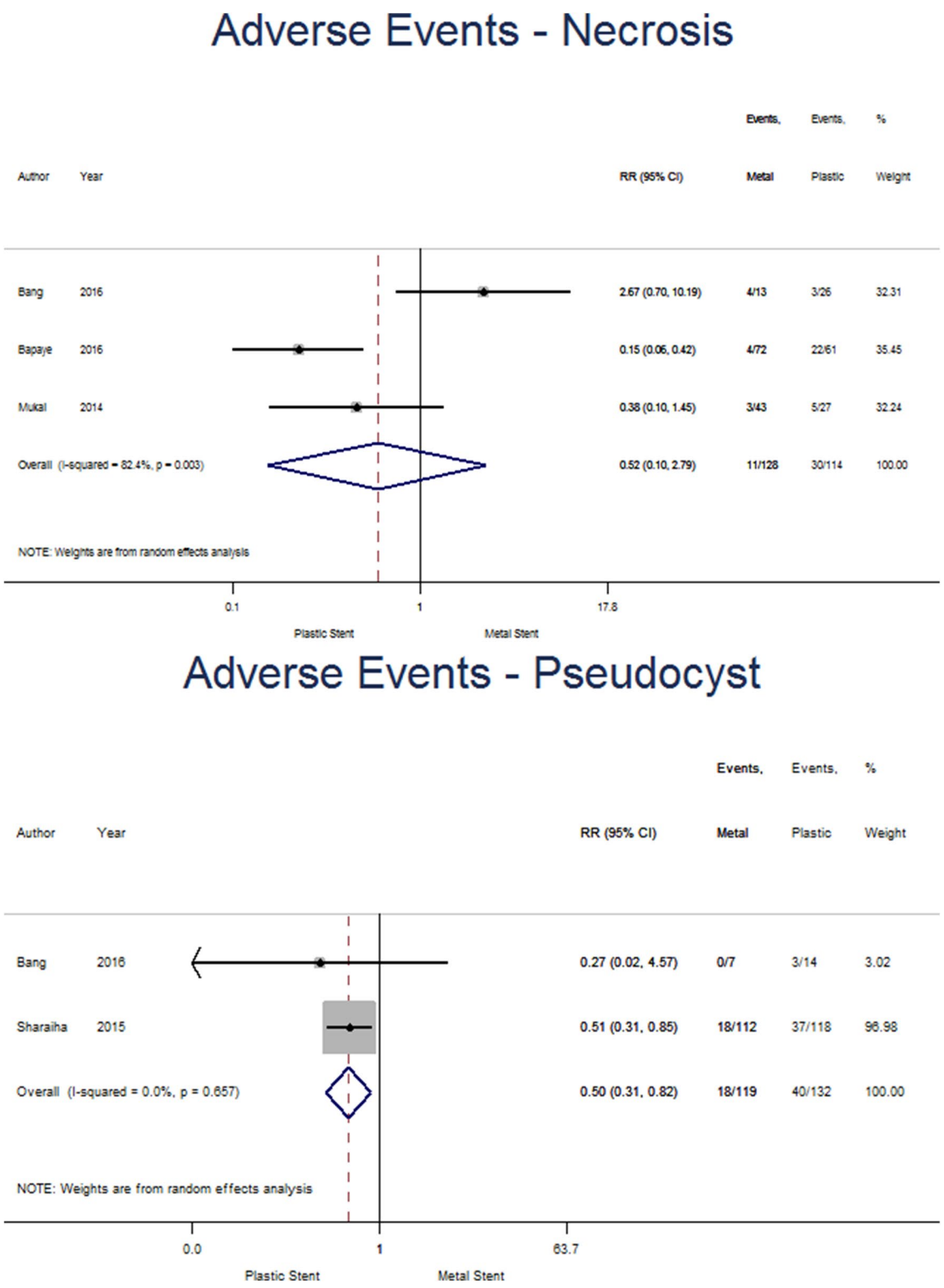


**Fig. 6** Forest plot showing individual and pooled risk ratios for adverse events for pseudocysts and walled-off necrosis

drainage of PFCs [15]. The majority of these data were derived from the use of specifically designed, large calibre, covered metal stents with lumen apposing flanges, unlike the previous review. It is likely that the improved outcomes

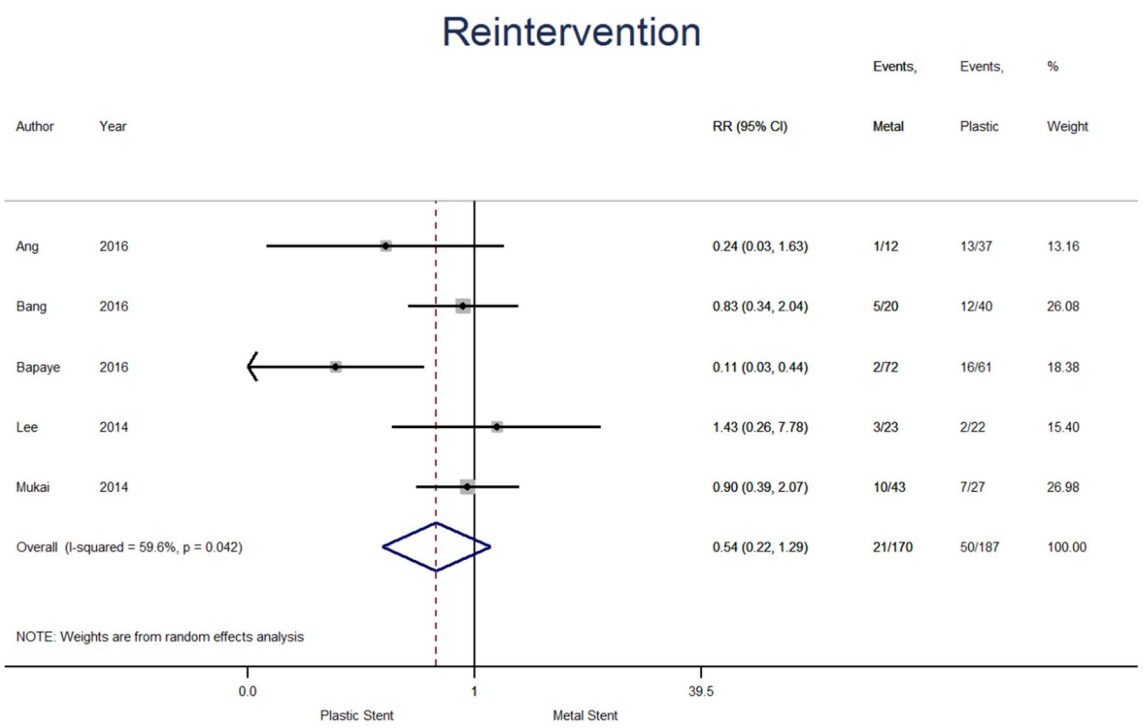


**Fig. 7** Forest plot for individual and pooled risk ratio for reintervention

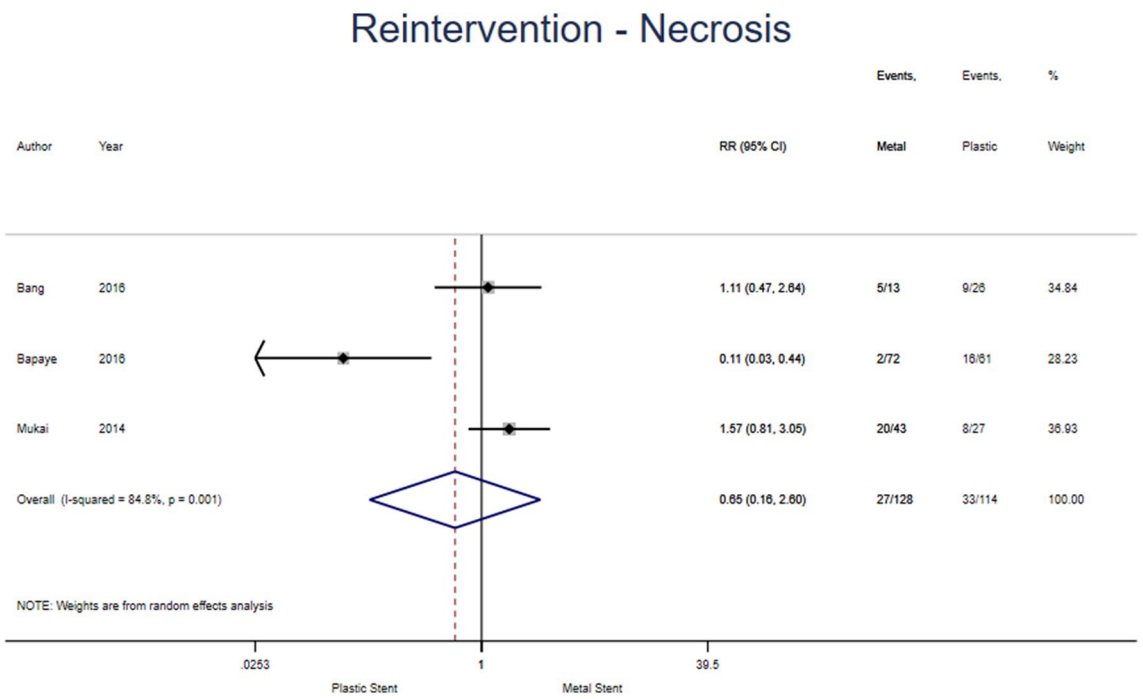


**Fig. 8** Forest plot showing individual and pooled risk ratios for reintervention in walled-off necrosis

of metal stents in this review are as a result of these stents as they are tailored for PFC drainage.

The fistula created by balloon dilatation enables plastic stent placement and drainage of fluid, however, this may be insufficient due to spontaneous closure of the fistula around the stent. Plastic stents have substantially smaller lumens than metal stents leaving them more susceptible to blockage or occlusion, even in pseudocysts or WON

with minimal debris. Although the use of plastic or metal stents was not found to reduce infection post drainage, metal stents can facilitate drainage of both liquid and the viscous necrotic debris, leading to the higher rates of successful drainage. Patients are not always routinely investigated by EUS prior to intervention; this is reflected in these studies where PFC's were frequently diagnosed by CT or MR imaging. CT imaging has a low sensitivity for assessing necrosis so there is diagnostic uncertainty when judging a collection to be a pseudocyst or WON. Recent guidance suggests that MRI or ultrasound assessment may be required to accurately characterise the collection [3].

There are several limitations of this systematic review and meta-analysis. All but one included studies are retrospective studies with the inherent bias associated with this methodology [17, 19–23]. There was a discrepancy in type and quality of included studies leading to the synthesis of results of variable reliability [25, 26]. There were also differences between definitions for the outcomes reported. Different types of metal stent were used both in individual and across studies; it is not currently clear in published literature if there is any demonstrable clinical advantage of a particular stent. In two studies there is a discrete time point where practice changed and metal stents were used routinely; however, in four studies, plastic stents continued to be used for PFCs with certain characteristics leading to conceivable selection bias [21]. Furthermore, the sample sizes of some studies are relatively small and correspond to extended periods of time. The number of studies included in the meta-analyses is also quite limited and therefore meta-regression was not performed for exploring further the cause of heterogeneity.

All these studies were designed to investigate a difference in outcomes between stents not between types of PFC. There are limitations in combining pseudocysts and WON for data analysis and potential limitations in the classification of PFC within individual studies. The revised Atlanta criteria were introduced in 2012, therefore it is likely that patients were classified differently over the period the studies were ongoing. However, in the studies included except for Mukai et al. [21], patients have short or no length of stay recorded and no clinical details suggesting these are not acutely unwell patients with infected pancreatic necrosis but rather patients being treated on a semi-elective basis. The subgroup analyses for drainage of pseudocysts in terms of clinical success and adverse events suggest that metal stents remain advantageous over that of plastic stents. Similar subgroup analyses for drainage of WON with metal stents are less convincing, with clinical success almost reaching significance, while adverse events or reintervention show no difference between metal or plastic stents. However, these subgroup analyses are limited by the very small numbers of studies which state these indications separately and therefore it is difficult to draw conclusions based on these data. Finally, the cost incurred was not evaluated in this analysis.

Our analysis showed that patients were 58% less likely to experience an adverse event with metal compared to plastic stents. Inserting plastic stents, particularly multiple plastic stents can be technically demanding and time consuming which may in part explain the increased risk [22]. Bleeding was significantly more common in patients with a plastic stent (2.8 vs. 7.9%, $p = 0.006$), this may be due to the greater dilatation required for plastic stent insertion. Dilatation of the tract prior to stent insertion for plastic stents ranged from 8 to 20 mm and 0–18 mm for metal stents in studies included in this review. The majority of studies used multiple plastic stents inserted, which has previously been shown to improve treatment success compared to using a single stent [27].

Delayed bleeding in patients with metal stents was reported in one study [20]. An interim analysis for a randomised control trial by Bang et al. also reported significant delayed bleeding in 3 of 12 patients with LAMS [14]. This required a change in the trial protocol to remove stents earlier than initially planned. Investigators described buried stent syndrome in 2/12 patients and 1/12 patient with a biliary stricture secondary to a stent [14]. However, high rates of adverse events have not been seen in other cohorts of patients with LAMS [28]. The experience with LAMS is still early and more multicentre, prospective randomised data are required to accurately quantity the risk; elucidate causes for the risk and suggest potential solutions. It is likely that the delayed bleeding and buried stent problems seen with LAMS are due to its design rather than procedural steps in stent insertion.

There was no significant difference in the rate of reintervention between plastic and metal stents. This could be due to type 2 error as two of the largest studies were not included in the analysis and it was a relatively rare event for the sample size. Reported reintervention rates ranged from 2.8 to 35.1% between studies. The type of reintervention required also varied and was not always specified by authors. Bapaye et al. stated that salvage surgery was required in 26.2% of patients with plastic stents; however, Mukai et al. reported no patients required surgical intervention for inadequate drainage. This may suggest heterogeneity between included patients or difference in practice between centres.

EUS-guided drainage is regarded as first-line treatment for pancreatic fluid collections requiring intervention. The use of transmural metal stents increases the probability of clinical success and reduces the frequency of adverse events when compared to plastic stents for EUS-guided drainage of pancreatic fluid collections. Future, well-designed prospective randomised control trials with multiple centres are required to evaluate clinical outcomes, adverse events and potential costs.

## Compliance with ethical standards

**Disclosures** Prof. Neoptolemos discloses personal fees from AMGEN and Mylan; grants from Taiho Pharma (Japan), KAEL GemVax (Korea), AstraZeneca, Clovis Oncology and Ventana, Pharma Nord and NUCANA; personal fees from Boehringer Ingelheim Pharma GmbH & Co. KG, Novartis Pharma AG, KAEL GemVax, and Astellas. Prof. Sutton discloses grants from Cypralis Research, GlaxoSmithKline, Innovate UK (with Cypralis Ltd) and Merck/MSD: Supply of drug for trial (other aspects of trial funded by UK MRC and NIHR). Dr Ramesh is a Consultant for Boston Scientific. Miss Saunders, Miss Cicconi, Dr Evans, Mr Yip, Mr Raraty, Prof Ghaneh and Mr Halloran have no conflicts of interest or financial ties to disclose.



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