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Culture Results at Pancreatic Necrosectomy: The Microbiology of Infected Pancreatic Necrosis

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Abstract

Introduction: Necrotizing pancreatitis occurs in 5-10% of patients with acute pancreatitis. Infected pancreatic necrosis (IPN) is a feared complication. Historically, causative organisms were Gram-negative bacteria, but recent international studies now report a predominance of Gram-positive bacteria. Not all the literature is consistent, and there may be regional variation. There is very limited Australian data. This study aims to report causative organisms in IPN in the Australian setting.

Materials and Methods: Retrospective medical record review of all patients who underwent pancreatic necrosectomy at a single centre (tertiary referral center in Adelaide, South Australia) between January 2005 and December 2015. Intraoperative culture specimens were reviewed and the Gram-status and antimicrobial sensitivities noted.

Discussion and Results: A total of 1296 patients were admitted for acute pancreatitis in the study period. 28 patients underwent pancreatic necrosectomy. Mean age 55.71 years (range 30-79), including twenty males and eight females. All patients had intraoperative cultures taken. 20 cultures demonstrated growth. There were 12 Gram-negative isolates (34.3%), 20 Gram-positive isolates (57.1%) and three fungal isolates (8.6%). Two bacterial isolates were antibiotic resistant organisms (one MRSA and one VRE).

Conclusion: The findings were consistent with the majority of recent international studies demonstrating a predominance of Gram-positive organisms.

Keywords: Infected pancreatic necrosis; Pancreatic necrosectomy; Necrotizing pancreatitis

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Introduction

Necrotizing pancreatitis occurs in approximately 5-10% of patients with acute pancreatitis [1]. It is frequently diagnosed by lack of enhancement of pancreatic parenchyma on contrast computed tomography (CT) scan of the abdomen. Although the necrosum is often initially sterile, a feared complication of necrotizing pancreatitis is infected pancreatic necrosis (IPN), which has an associated mortality rate of around 30% [2]. According to the revised Atlanta criteria, diagnosis of IPN is suggested radiologically by the presence of gas locules within an acute necrotic collection or walled-off necrosis on an abdominal CT scan [1]. Alternatively, diagnosis may be made by a positive culture obtained through aspiration, percutaneous drainage or at operation [1].

Historically, cultures most frequently demonstrated Gram-negative organisms [3,4]. However, since the early 1990's, multiple studies have demonstrated a shift towards a predominance of Gram-positive organisms [3,5,6]. This shift coincided with the rise in popularity of prophylactic antibiotics [3], but appears to have persisted even after prophylactic antibiotics have been dropped from treatment recommendations in the wake of evidence that their use does not reduce the incidence of infective complications in necrotizing pancreatitis [7]. A recent increase in the prevalence of antibiotic resistant organisms isolated in patients with IPN has also been reported [8]. Furthermore, there is a growing interest in the prevalence of fungal infection in IPN, which has been linked to increased mortality [9].

There may be regional differences, however, as not all centers have reported these changes. Some authors in India [10] and China [11,12] have noted a persistence of Gram-negative organisms despite the use of prophylactic antibiotics.

To the authors' knowledge, there have been no large studies that examine causative organisms,

Table 1: Number of pre-operative antimicrobial agents used per patient.

Number of preoperative antimicrobial agents received	Number of patients (n=28)
Incomplete information	1 (3.57%)
0	1 (3.57%)
1	9 (32.14%)
2	5 (17.86%)
3	3 (10.71%)
4	6 (21.43%)
5	2 (7.14%)
6	1 (3.57%)

Table 2: Preoperative antimicrobial agents.

Antimicrobial	Number of patients
Tazobactam/piperacillin	11 (42.3%)
Meropenem	11 (42.3%)
Metronidazole	10 (38.5%)
Timentin	6 (23.1%)
Gentamicin	5 (19.2%)
Ciprofloxacin	5 (19.2%)
Vancomycin	5 (19.2%)
Cephazolin	5 (19.2%)
Amoxycillin	4 (15.4%)
Ceftriaxone	3 (11.5%)
Fluconazole	2 (7.7%)
Cefuroxin	1 (3.8%)

resistance patterns and the incidence of fungal infections in Australasia. The aim of this study is to investigate the organisms isolated in IPN and their antimicrobial sensitivities in the Australian setting in order to see if the described trends in bacteriology, antibiotic resistance and fungal infection described in other regions are present.

Materials and Methods

All patients who underwent pancreatic necrosectomy between 1st January 2005 and 31st December 2015 at a tertiary referral center in Adelaide, South Australia were identified using theatre records and the center's prospective surgical inpatient audit database. Medical records, operative notes, imaging and laboratory results were accessed. Patient age, gender, date of first admission for acute pancreatitis and date of operation were recorded. In addition, all results of microscopy, culture and sensitivity testing taken at the time of pancreatic necrosectomy were recorded and tabulated. Mortality was defined as death during the same admission or within three months of the date that pancreatic necrosectomy was performed.

Antibiotic resistance was defined as the growth of methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE) or extended-spectrum beta-lactamase (ESBL) producing Gram-negatives. These organisms have been used as measures of antibiotic resistance in previous studies looking at microbiology in IPN [5,8,13].

Results

A total of 1296 patients were admitted to our center with acute pancreatitis during the study period. Of these, 28 patients underwent operative necrosectomy for necrotizing pancreatitis. The mean age was 55.71 years (range 30-79 years). Of these, 20 were males and eight were females. The aetiology was varied; five patients had pancreatitis secondary to alcohol, 17 secondary to cholelithiasis and six were idiopathic or due to miscellaneous causes. The mean time between initial presentation with pancreatitis and operative necrosectomy was 67.46 days (range 10-557 days, median 13.5 days). The technique of necrosectomy also varied; 24 underwent open procedures via a midline laparotomy or roof-top incision, two underwent video-assisted procedures and two underwent laparoscopic procedures that were later converted to open.

Indications for operative management were varied, and included pancreatic necrosectomy at the time of emergency laparotomy for peritonitis and acute clinical deterioration (six, 21.43%) and abdominal compartment syndrome (one, 3.57%), as well as planned pancreatic necrosectomy for symptomatic walled-off necrosis that was not amenable to percutaneous drainage or endoscopic necrosectomy (21, 75%).

Pre-operatively, 26 of the 28 patients received antimicrobial agents. One patient received no antimicrobial agents prior to surgery and one patient had incomplete medical records. The numbers of antimicrobial agents used per patient are recorded in Table 1 and the type of agent is recorded in Table 2. Prophylactic antibiotics are not used in our center for the treatment of necrotizing pancreatitis.

All 28 patients had intraoperative specimens sent for microscopy, culture and sensitivity. Of these, 20 (71.43%) produced a pathogen and a total of 25 organisms were isolated from these cultures. These are recorded in Table 3. Of the positive cultures, 11 were monomicrobial (39.28%) and nine (32.14%) were polymicrobial.

Altogether, 16 of the 20 cultures (80%) grew one or more colonies of Gram-positive organisms and nine (45%) demonstrated exclusively Gram-positive growth. In comparison, ten (50%) of cultures grew Gram-negative organisms and three (15%) were exclusively Gram-negative. Seven demonstrated mixed Gram-positive and Gram-negative growth.

There were two colonies of antibiotic resistant organisms grown (7.14%). MRSA was isolated in one culture and VRE was isolated in another. No ESBL-producing organisms were observed. There were three fungal isolates across the 20 positive cultures and all were Candida species.

Prior to operative pancreatic necrosectomy, 11 patients underwent percutaneous drainage under radiological guidance, one underwent endoscopic retrograde cholangiopancreatography (ERCP) and three patients underwent endoscopic cystgastrostomy.

Four patients (14.28%) died during the same admission and seven patients (25%) required subsequent surgical procedures (five relook laparotomies, one revision of surgical scar and one reversal of ileostomy). Of the patients who died, two patients had no growth on intraoperative cultures and two had polymicrobial infections (the first patient grew Enterococcus, Streptococcus and Candida krusei and the second patient grew Enterococcus, Proteus mirabilis and Candia albicans). No antibiotic resistant organisms were observed in the cultures of the patients who died.

Discussion

The most prevalent organisms isolated on culture of intraoperative specimens were Gram-positive bacteria. The most common individual organism was *Enterococcus spp*., followed by Escherichia coli and

Table 3: Organisms isolated from intra-operative specimens.

Organisms		Intra-operative specimen isolates (from 20 positive cultures)	
Gram-negatives	Escherichia coli	4	
	Klebsiella sp.	2	
	Citrobacter sp.	2	
	Serratia sp.	1	
	Proteus sp.	1	
	Stenotrophomonas maltophilia	1	
	Eikenella corrodens	1	
	Total	12 (34.3%)	
Gram-positives	Enterococcus sp.	9	(including 1 growth of VRE)
	Staphylococcus aureus	4	(including 1 growth of MRSA)
	Streptococcus viridans	3	
	Staphylococcus epidermidis	2	
	Other streptococcus sp.	2	
	Total	20 (57.1%)	
Fungi	Candida albicans	2	
	Candida krusei	1	
	Total	3 (8.6%)	

Staphylococcus aureus. These findings are consistent with most international studies, which have demonstrated a predominance of Gram-positive bacteria over the last 20 years [3,5,6,9,14], and in particular *Enterococcus* [6,9,14].

Contamination of necrotic pancreatic tissue hypothetically occurs after bacterial translocation from the gastrointestinal tract [15], most likely from the small intestine [16]. However, there is currently debate about whether contamination occurs hematogenously [6] or via lymphatics [16].

The observed change in microbiology of IPN noted over the last two decades has occurred with the rise in popularity of prophylactic antibiotic use [3]. Recently, given evidence demonstrating the ineffectiveness of prophylactic antibiotics in preventing infective complications of necrotizing pancreatitis [7,17,18], many centers (including our own) no longer use prophylactic antibiotics, opting instead for a targeted antibiotic approach where antibiotics are initiated upon evidence of infection [19].

It is likely that the previous practice of prophylactic antibiotics and the current practice of targeted use of antibiotics in necrotizing pancreatitis are at least partially responsible for the increase in Gram-positives [3]. Furthermore, in the wake of literature suggesting improved outcome with early enteral feeding [20], the practice of keeping patients fasting for prolonged periods has also been abandoned. It has been suggested the early enteral feeding improves gut barrier function and limits bacterial translocation [21]. It is possible, therefore, that this change in practice is also partially responsible for the change in flora noted over the last 15 years, although data regarding early feeding was not specifically collected in our study.

The proportion of antibiotic resistant organisms was lower than that reported by other authors [5,8,13], with only two isolates from two separate patients demonstrating significant antibiotic resistance in the intraoperative specimens taken. It is difficult to say why this has been observed, but local infection control practices and use of antibiotics in the community may play a role.

The number of fungal isolates was consistent with international literature, with three intraoperative specimens positive for fungal growth (8.6%). This is within the 7-14% described in other studies [22]. Two of the three patients who grew fungal isolates on their intraoperative cultures died during the same admission. Although data on fungal infection in IPN and mortality is conflicting [23], Schmidt "et al." [9], when looking at culture results in patients who underwent endoscopic transmural drainage and necrosectomy for IPN, found an association between the presence of fungal isolates on index culture and mortality.

Polymicrobial infections have associated with higher mortality in IPN in some studies [19]. In this study, nine of the 20 positive cultures (45%) were polymicrobial and two of these nine patients died (compared to none of the 11 patients with monomicrobial growth on intraoperative cultures).

There is very limited data on bacterial isolates from IPN in Australasia at present. A study by Jacob "et al." [22], concerning operative management of abdominal compartment syndrome and IPN in eleven patients with "acute pancreatitis in Alice Springs, Northern Territory reported a total of three positive intraoperative cultures from a total of six. Two grew both *Enterococcus spp*. and E. coli and one grew *E. coli* alone.

Various authors have recommended the use of carbapenem or quinolone antibiotics in IPN as these classes have been shown to have good penetrance of pancreatic tissue [24] and are active against both Gram-negative and Gram-positive organisms [17,19]. These recommendations would appear to be suitable for the Australian setting given our findings.

The major limitations of our study were that is retrospective and that (due to the rarity of the condition), the sample size was small. The audit database used also did not accurately record patients who underwent percutaneous drainage or endoscopic necrosectomy for necrotizing pancreatitis alone, without the need for operative

management. Inclusion of this group of patients would potentially have added further power. The majority of patients were administered antimicrobial agents pre-operatively, and the type of agents used varied widely as this study included antimicrobials initiated for all indications (such as respiratory and urinary tract infections) occurring anytime from admission to operative management. This has the potential to alter the flora grown on intra-operative culture. Furthermore, pre-operative insertion of percutaneous drains could hypothetically also alter the organisms subsequently isolated from intra-operative cultures.

Our study also demonstrated a high rate of open procedures. This is partially explained by the inclusion of emergency laparotomies for peritonitic deteriorating patients with IPN and a laparotomy for abdominal compartment syndrome.

Our findings indicate that the shift in the type organisms isolated in patients with IPN in Australia is consistent with the changes observed internationally in the last two decades. This is the first study of its kind regarding patients in Australasia that the authors are aware of and helps to demonstrate that recommendations regarding the treatment of patients with IPN (in particular recommendations regarding antimicrobial usage) are likely to be applicable to the Australasian setting also. Confirmation of these findings across other centers in the region would be useful.

Conclusion

There has been an internationally-observed change in the type of pathogens isolated from cultures in IPN over the last two decades from Gram-negative to Gram-positive organisms. Data concerning the Australian populace has been lacking, but these findings indicate that this change is consistent in Australia also. This has implications for antibiotic choice for clinicians treating patients with IPN.

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