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The microbiology of infected pancreatic necrosis

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ABSTRACT

Background: Acute pancreatitis (AP) continues to cause significant morbidity and mortality, especially when it leads to infected pancreatic necrosis (IPN). Modern treatment of IPN frequently involves prolonged courses of antibiotics in combination with minimally invasive therapies. This study aimed to update the existing evidence base by identifying the pathogens causing IPN and therefore aid future selection of empirical antibiotics.
Methods: Clinical data, including microbiology results, of consecutive patients with IPN undergoing minimally invasive necrosectomy at our institution between January 2009 and July 2016 were retrospectively reviewed.
Results: The results of 40 patients (22 males and 18 females, median age 60 years) with IPN were reviewed. The etiology of AP was gallstones, alcohol, dyslipidemia and unknown in 31, 2, 2 and 5 patients, respectively. The most frequently identified microbes in microbiology cultures were *Enterococcus faecalis* and *faecium* (22.5% and 20.0%) and *Escherichia coli* (20.0%). In 19 cases the cultures grew multiple organisms. The antibiotics with the least resistance amongst the microbiota were teicoplanin (5.0%), linezolid (5.6%), ertapenem (6.5%), and meropenem (7.4%).
Conclusion: The carbapenem antibiotics, ertapenem and meropenem provide good antimicrobial cover against the common, mainly enteral, microorganisms causing IPN. Culture and sensitivity results of acquired samples should be regularly reviewed to adjust prescribing and monitor for emergence of resistance.

Introduction

The clinical course of acute pancreatitis (AP) varies in the extreme. Whilst some patients require only simple analgesia and investigation of the cause, others develop multi-organ failure with significant morbidity and mortality [1]. During the first 14 days of the condition, mortality is most often the result of a systemic inflammatory response and tends not to involve microbial infections. Thereafter, mortalities are mostly associated with infective complications including infected pancreatic necrosis (IPN) [2]. This occurs in only 6% of cases of AP but can result in 32%–50% mortality [1,3].

Current management of IPN takes a much more conservative approach than the previously favored laparotomy and open debridement. Guidelines currently recommend a step-wise approach to treatment utilizing antibiotics, endoscopic or percutaneous drainage, minimal access debridement and thus reserve open surgery as the last resort [4]. This strategy involves diligent antibiotic usage, initially empirically but subsequently targeted to the antimicrobial sensitivity results [5]. In order to guide initial antimicrobial therapies, we aimed to identify the prevalent microorganisms causing IPN at our institution, and their antimicrobial sensitivity profiles. We have analyzed our results in the context of the existing literature to enhance current management strategies.

Methods

We retrospectively analyzed the patients with IPN treated in our tertiary institution. The precipitating episode of AP was treated in line with the British Society of Gastroenterology guidelines [6]. Antibiotics were initiated if there were clinical or biochemical signs of sepsis, or radiographic evidence of IPN. This was predominantly piperacillin/tazobactam in line with the hospital antibiotic policy. Routine fine needle aspiration of pancreatic necrosis for diagnostic purposes was not undertaken at our institution. IPN

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Table 1
Micro-organisms identified from IPN.

Microbes	Frequency isolated (%)	Frequency associated with a poly-microbial culture (%)
Enterococcus faecalis	9 (22.5)	8 (88.9)
Enterococcus faecium	8 (20.0)	3 (37.5)
E. coli	8 (20.0)	4 (50.0)
Pseudomonas aeruginosa	5 (12.5)	4 (80.0)
Coagulase negative staphylococcus	5 (12.5)	3 (60.0)
Anaerobes	5 (12.5)	5 (100.0)
Enterobacter spp.	4 (10.0)	3 (75.0)
Coliform	3 (7.5)	2 (66.7)
Staphylococcus epidermis	3 (7.5)	2 (66.7)
Staphylococcus aureus	3 (7.5)	1 (33.3)
Viridans group streptococci	2 (5.0)	2 (100.0)
Morganella morganii	2 (5.0)	1 (50.0)
Enterococcus spp.	2 (5.0)	1 (50.0)
Klebsiella oxytoca	2 (5.0)	2 (100.0)
Klebsiella pneumoniae	2 (5.0)	2 (100.0)
Proteus mirabilis	1 (2.5)	1 (100.0)
Serratia marcescens	1 (2.5)	1 (100.0)
Staphylococcus haemolyticus	1 (2.5)	1 (100.0)

was diagnosed according to the revised Atlanta guidelines, by the presence of extra-luminal, peri-pancreatic air with associated hypo-perfusion of the pancreas on contrast enhanced computed tomography (CT) [7].

In accordance with current consensus, radiologically guided percutaneous drainage of collections was withheld until at least 4 weeks after the initial attack of pancreatitis unless there was evidence of worsening sepsis or IPN [4]. Samples from this drain were sent for microbiological analysis, however, the main purpose of this drainage was to facilitate minimal access retroperitoneal pancreatic necrosectomy (MARPN). MARPN is a technique carried out under a general anesthetic to debride devitalised, infected pancreatic tissue through the radiologically placed, left flank drain channel only. The two surgeons performing the technique in our unit used a standardized method with a rigid cystoscope and optical biopsy forceps. MARPN can be repeated multiple times until only healthy tissue remains. Tissue samples removed during the procedure were processed by the microbiology department, according to the laboratory standard operating procedures. Antibiotic regimens were regularly reviewed and updated in light of any results from microbiology sample analysis.

All patients undergoing MARPN between 1 January 2009 and 31 July 2016 at our institution were included in this study. Electronic hospital and pathology records were interrogated to identify the relevant microbiology samples from the first MARPN procedure, and to detail the episode of AP. This included the etiology of AP and also any empirical antibiotic usage. This study excluded patients who had open pancreatic debridement for bleeding, perforated viscous or those without features of IPN on CT.

Results

In total, our tertiary unit managed 110 patients with complicated severe necrotizing pancreatitis during the study period. This included 5 patients who underwent open surgery directly, 62 patients treated using percutaneous drainage alone and 43 patients underwent MARPN for suspected IPN. Of these 43 patients, 3 had negative tissue cultures and hence they were excluded from the analysis. The resulting 22 male patients and 18 female patients had a median age of 60 years (22–82 years). The commonest cause of AP was gallstones (77.5%) with alcohol and dyslipidemia causing 2 cases (5.0%) each. The etiology was undetermined in 5 patients, of which 2 suffered inpatient mortality and hence had not yet undergone complete investigation. Overall, 15 patients died (37.5%) as a result of the complications of AP, and they had a median survival of 106 days (range 29–217). The median time from the onset of AP to a diagnosis of IPN was 24 days (range 6–93), and from AP to radiological drainage was 29 days (range 9–95). Antibiotics given prior to MARPN included: 15 patients received meropenem, 11 piperacillin/tazobactam, 5 gentamicin, 4 imipenem, 4 teicoplanin and 1 co-amoxiclav. Antimicrobial combination therapy was common with 6 patients also received vancomycin, 5 metronidazole and 3 flucloxacillin. The antibiotics were also prescribed with the anti-fungal, fluconazole in 21 patients.

Table 2
The top 5 antibiotics with the most and the least microbial resistance.

Antibiotic	Resistance against all microbes (%)
Top 5 antibiotics with the most microbial resistance	
Ampicillin	92.3
Erythromycin	82.4
Amoxicillin	75.0
Clarithromycin	68.4
Flucloxacillin	62.5
Top 5 antibiotics with the least microbial resistance	
Vancomycin	8.3
Meropenem	7.4
Ertapenem	6.3
Linezolid	5.6
Teicoplanin	5.0

The micro-organisms identified from IPN culture samples are displayed in Table 1. Poly-microbial cultures were seen in 19 cases. All cultures were obtained from tissue samples except 2 patients as no tissue samples were received for analysis. In these cases, the microbiological findings from the initial percutaneous aspirate were used instead. Antibiotics with the most and the least microbial resistance are summarised in Table 2. Other frequently used antibiotics included amoxicillin/clavulanic acid (resistance seen in 60.0% of cultures tested), gentamicin (30.0%) and ciprofloxacin (26.3%).

Discussion

AP is an inflammatory condition with multiple etiologies; alcohol and gallstones are the most common in this series and others [6]. It is likely that all cases of AP share a common intracellular pathway that, once initiated, leads to activated pancreatic enzymes causing auto digestion and cell apoptosis within the pancreas [8]. Damage to the pancreatic ducts can exacerbate this situation and result in local fluid collections. Both the devitalized, necrotic pancreatic tissue and the peri-pancreatic fluid collections can act as a focus for infection with microbes migrating via hematogenous or lymphatic routes, or by ascension through the gastrointestinal tract. The disruption of the normal gut barrier is thought to be the major source of bacteria in AP and the greater the extent of pancreatic necrosis, the higher the prevalence of IPN [9–12].

A systematic search of the literature using Embase and MEDLINE databases, revealed a small number of studies that have previously documented the microbial spectrum seen in IPN [13–20]. The results of these studies are displayed in parallel with the results from our study in Table 3. All the studies indicate a high frequency of poly-microbial infections with an overall predominance of *Enterococci, staphylococci* and *Escherichia coli* bacteria. Conversely, *proteus* and *pseudomonas* species were identified relatively infrequently. It should be noted that the data collection of these studies spans a large time period (1976–2016) and therefore results are susceptible to the effects of changing clinical practice and antibiotic usage [21]. The international distribution of the studies could also alter the etiology of AP and the prevalent microbiota. It makes the generalization of these previous results to current, local populations debatable and illustrates the importance of up to date research.

The results of our study clearly show a predominance of gastrointestinal flora in line with previous studies. The spectrum of bacteria supports the model of endogenous spread of microbes into necrotic pancreatic tissue and we have also demonstrated the poly-microbial nature of IPN [13–20]. We recognize that these results, whist expected, may have been affected by confounding factors in a relatively small cohort study. One should ideally take into consideration factors such as the location of the necrosis (head or tail of pancreas), the etiology of AP, the use of enteral feeding, biliary instrumentation (cholecystectomy or ERCP) and recent broad spectrum antibiotic usage. The current study was not with large enough sample size to draw any conclusions regarding these variables and unfortunately there is also a paucity of evidence in the literature. A Finnish study did explore the effects of etiology and highlighted that IPN occurred more frequently in patients with biliary pancreatitis (17/23) than alcoholic pancreatitis (15/47), but found the commonest microbes remained *E. coli, staphylococci* and *Candida* species in both groups [22].

The retrospective nature of our study results in some limitations. Controlling for antibiotic exposure is very difficult, especially when accepting patients from peripheral hospitals. There was also a reliance upon the available historical pathology department reports and they did not always include a comprehensive list of antibiotic results for every pathogen. This inter-sample variation could manifest as an under estimation of sensitivity and resistance rates. However, the recorded results are likely to be the strongest results and thus likely to be most clinically relevant.

A strength of our methodology was avoiding fine needle aspiration and therefore decreasing the chances of iatrogenic contamination. About 15% of our cohort had sterile aspirates on initial aspiration and subsequently had positive tissue cultures at MARPN. This could represent sampling error or simply that the sample was taken early in the disease course. A study by Besselink et al. [23] has shown that there is an increased risk of developing IPN in pancreatic necrosis following the prolongation of a percutaneous catheter is *in-situ*. This is unlikely to have influenced our data as, on further analysis, the median time from percutaneous drainage to MARPN was only 4 days in our study.

Carbapenem antibiotics, specifically meropenem and ertapenem, were the most efficacious in our study. The low rate of resistance to them is interesting considering 37.5% of patients received meropenem empirically. Antibiotic resistance is a concern in this patient group given both the prolonged treatment courses involved, and the poly-microbial flora present. Gloor et al. [24] identified 21% of IPN had microbial resistance to the previously

Table 3
Comparison of microbial results from relevant studies.

Studies	Country	*n*	Mono/poly-microbial infection	Organism identified (%)							
				E. coli (%)	*Pseudomonas* spp. (%)	*Enterobacter aeorgenes*	*Klebsiella* spp.	*Proteus*	*Staphylococcus* spp. (%)	*Enterococcus* spp.	Anaerobes
Beger et al. [13]	Germany	45	87% / 13%	53	11	36	7	11	11	3	11
Bassi et al. [14]	Italy	93	–	20	15	–	5	10	14	–	15
Fedorak et al. [15]	USA	21	43% / 57%	24	14	5	14	5	5	33	9
Bradley [16]	USA	71	52% / 48%	47	10	20	14	–	1	3	–
Buchler et al. [17]	Switzerland	28	36% / 64%	11	4	–	9	–	36	13	2
Garg et al. [18]	India	27	68% / 32%	25	27	6	–	–	8	6	–
Isenmann et al. [19]	Germany	92	–	33	4	–	17	–	26	36	5
Cacopardo et al. [20]	Italy	20	–	50	15	5	–	–	15	10	–
Current study (2018)	UK	40	48% / 52%	20	13	3	10	3	30	48	13

used prophylactic antibiotics prescribed after the diagnosis of pancreatic necrosis (14 day course of imipenem/cilastatine). Similar to our data, a study by Maravi-Poma et al. [25] found imipenem had resistance in 32% of the microbes causing pancreatic infections. Ciprofloxacin has become notorious for its resistance and whilst not an issue in our cohort, its use is associated with an increase in ciprofloxacin resistance in both intra- and extra-pancreatic infections [26].

Antibiotic choice needs to be based on the *in vitro* antimicrobial sensitivity results, but also take into consideration bioavailability *in vivo*. Pancreatic necrosis, by definition has no vascular supply and as such antimicrobial penetration is expected to be minimal. However, a number of studies have disproved this detecting significant level of antibiotics in samples of necrotic pancreatic tissue, namely, piperacillin/tazobactam, metronidazole, imipenem, ciprofloxacin and olfoxacin [27–29]. The broad bactericidal effects of ertapenem against common intra-abdominal pathogens justify its use in IPN with the added advantage of once daily dosing [30].

Multiple meta-analyses have moved the debate on from giving prophylactic antibiotics to all cases of AP, but they seem to suggest that their use in necrotizing pancreatitis can decrease pancreatic infection rate and the length of hospital stay [31,32]. A Cochrane review concluded that in its patient group, prophylactic imipenem in cases of pancreatic necrosis decreased IPN rate but did not change overall mortality rate [33].

A final consideration in patients with IPN should be the prevalence of simultaneous fungal infection. Critically unwell patients and patients on long-term antibiotics, are prone to fungal infections and in patients with IPN this is approximately 24% [19,24,34]. The true significance of this is disputed as the study by Gloor et al. [24] did not find any correlation with mortality. It is our current practice to prescribe fluconazole as it has been shown to achieve an effective concentration in pancreatic tissue and there is evidence to suggest a reduction in invasive fungal infections [35,36].

In conclusion, current management strategies for the treatment of IPN rely on appropriate antibiotics.

Microbiology results from our cohort of patients suggest that the main pathogens in IPN are *Enterococci* spp. and *Escherichia. coli*. Given the sensitivity profiles observed, and the individual antibiotic characteristics, the most appropriate empirical antibiotic treatment is meropenem. There should be regular collaboration between surgical, critical care and microbiology teams. This would ensure that antibiotic regimens cover local microbial and antimicrobial sensitivity profiles and that they react to new information.

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Contributors

ASB proposed the study. BIB and HM performed the data collection. MNG and HM undertook the literature search. MNG undertook analysis of the data and wrote the first draft. All authors and contributed to the interpretation of the study and re-drafting. MNG is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 2010;139:813–820.
[2] Gloor B, Müller CA, Worni M, Martignoni ME, Uhl W, Büchler MW. Late mortality in patients with severe acute pancreatitis. Br J Surg 2001;88:975–979.
[3] van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254–1263.
[4] Working Group IAP/APA Acute Pancreatitis Guidelines IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1–15.
[5] van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491–1502.
[6] Working Party of the British Society of Gastroenterology Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. Gut 2005;54:iii1–iii9.
[7] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–111.
[8] Gukovsky I, Pandol SJ, Mareninova OA, Shalbueva N, Jia W, Gukovskaya AS. Impaired autophagy and organellar dysfunction in pancreatitis. J Gastroenterol Hepatol 2012;27:27–32.
[9] Wu LM, Sankaran SJ, Plank LD, Windsor JA, Petrov MS. Meta-analysis of gut barrier dysfunction in patients with acute pancreatitis. Br J Surg 2014;101:1644–1656.
[10] Fritz S, Hackert T, Hartwig W, Rossmanith F, Strobel O, Schneider L, et al. Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. Am J Surg 2010;200:111–117.
[11] Isenmann R, Rau B, Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. Br J Surg 1999;86:1020–1024.
[12] Noor MT, Radhakrishna Y, Kochhar R, Ray P, Wig JD, Sinha SK, et al. Bacteriology of infection in severe acute pancreatitis. JOP 2011;12:19–25.
[13] Beger HG, Bittner R, Block S, Büchler M. Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology 1986;91:433–438.
[14] Bassi C, Falconi M, Girelli R, Nifosi F, Elio A, Martini N, et al. Microbiological findings in severe pancreatitis. Surg Res Commun 1989;5:1–4.
[15] Fedorak IJ, Ko TC, Djuricin G, McMahon M, Thompson K, Prinz RA. Secondary pancreatic infections: are they distinct clinical entities? Surgery 1992;112:824–831.
[16] Bradley EL 3rd. A fifteen year experience with open drainage for infected pancreatic necrosis. Surg Gynecol Obstet 1993;177:215–222.
[17] Büchler MW, Gloor B, Müller CA, Friess H, Seiler CA, Uhl W. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg 2000;232:619–626.
[18] Garg PK, Khanna S, Bohidar NP, Kapil A, Tandon RK. Incidence, spectrum and antibiotic sensitivity pattern of bacterial infections among patients with acute pancreatitis. J Gastroenterol Hepatol 2001;16:1055–1059.
[19] Isenmann R, Schwarz M, Rau B, Trautmann M, Schober W, Beger HG. Characteristics of infection with Candida species in patients with necrotizing pancreatitis. World J Surg 2002;26:372–376.
[20] Cacopardo B, Pinzone M, Berretta S, Fisichella R, Di Vita M, Zanghì G, et al. Localized and systemic bacterial infections in necrotizing pancreatitis submitted to surgical necrosectomy or percutaneous drainage of necrotic secretions. BMC Surg 2013;13:S50.
[21] Pavlidis P, Crichton S, Lemmich Smith J, Morrison D, Atkinson S, Wyncoll D, et al. Improved outcome of severe acute pancreatitis in the intensive care unit. Crit Care Res Pract 2013;2013:897107.
[22] Räty S, Sand J, Nordback I. Difference in microbes contaminating pancreatic necrosis in biliary and alcoholic pancreatitis. Int J Pancreatol 1998;24:187–191.
[23] Besselink MG, van Santvoort HC, Bakker OJ, Bollen TL, Gooszen HG. Draining sterile fluid collections in acute pancreatitis? Primum non nocere!. Surg Endosc 2011;25:331–332.
[24] Gloor B, Müller CA, Worni M, Stahel PF, Redaelli C, Uhl W, et al. Pancreatic infection in severe pancreatitis: the role of fungus and multiresistant organisms. Arch Surg 2001;136:592–596.
[25] Maraví-Poma E, Gener J, Alvarez-Lerma F, Olaechea P, Blanco A, Domínguez–Muñoz JE, et al. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. Intensive Care Med 2003;29:1974–1980.

[26] Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;126:997–1004.
[27] Büchler M, Malfertheiner P, Friess H, Isenmann R, Vanek E, Grimm H, et al. Human pancreatic tissue concentration of bactericidal antibiotics. Gastroenterology 1992;103:1902–1908.
[28] Otto W, Komorzycki K, Krawczyk M. Efficacy of antibiotic penetration into pancreatic necrosis. HPB (Oxford) 2006;8:43–48.
[29] Bassi C, Pederzoli P, Vesentini S, Falconi M, Bonora A, Abbas H, et al. Behavior of antibiotics during human necrotizing pancreatitis. Antimicrob Agents Chemother 1994;38:830–836.
[30] Borbone S, Cascone C, Santagati M, Mezzatesta ML, Stefani S. Bactericidal activity of ertapenem against major intra-abdominal pathogens. Int J Antimicrob Agents 2006;28:396–401.
[31] Mourad MM, Evans R, Kalidindi V, Navaratnam R, Dvorkin L, Bramhall SR. Prophylactic antibiotics in acute pancreatitis: endless debate. Ann R Coll Surg Engl 2017;99:107–112.
[32] Xu T, Cai Q. Prophylactic antibiotic treatment in acute necrotizing pancreatitis: results from a meta-analysis. Scand J Gastroenterol 2008;43:1249–1258.
[33] Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev 2010;12:CD002941.
[34] Trikudanathan G, Navaneethan U, Vege SS. Intra-abdominal fungal infections complicating acute pancreatitis: a review. Am J Gastroenterol 2011;106:1188–1192.
[35] Shrikhande S, Friess H, Issenegger C, Martignoni ME, Yong H, Gloor B, et al. Fluconazole penetration into the pancreas. Antimicrob Agents Chemother 2000;44:2569–2571.
[36] Cortegiani A, Russotto V, Maggiore A, Attanasio M, Naro AR, Raineri SM, et al. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. Cochrane Database Syst Rev 2016;16:CD004920.