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Acute Pancreatitis: Should We Use Antibiotics?

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Abstract Acute pancreatitis is a common cause of hospitalization and a major source of morbidity worldwide. When it is severe, and especially when it progresses to include necrosis of the pancreas, the risk of infection rises and mortality increases. Early reports suggested prophylactic antibiotics given in severe pancreatitis prevent infection and death. More recent clinical trials do not support this benefit, and meta-analyses on the topic offer conflicting recommendations. In this article, we evaluate the body of published literature examining the use of antibiotics as a preventive measure in acute pancreatitis. The highest quality, currently available data fail to support prophylactic use of antibiotics, which should be added to treatment regimens only where infection has been proven.

Keywords Acute pancreatitis · Acute necrotizing pancreatitis · Infected necrosis · Prophylactic antibiotics

Introduction

Acute pancreatitis leads to more than 220,000 hospitalizations annually in the United States, with additional cases remaining undiagnosed or mild enough to be managed in the outpatient setting [1]. It has been reported that pancreatitis is increasing globally, undoubtedly influenced by improved recognition by physicians and more widely available diagnostics [2, 3]. Given the prevalence of its most common causes (gallstone obstruction and alcohol use) pancreatitis will continue to be a major source of morbidity requiring acute care.

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Pancreatitis occurs when activated digestive enzymes directly inflame the pancreas. Gallstones, the most common cause, produce obstruction at the sphincter of Oddi, preventing activated enzymes from flow into the duodenum. Conversely, alcohol, the second most common cause, is thought to be a direct toxin, inappropriately activating trypsin within pancreatic acinar cells, which in turn activates the digestive enzymes that cause pancreatic inflammation [4, 5]. These two etiologies produce 70% to75% of all acute pancreatitis, with less common causes including other sources of biliary stasis; other toxins (scorpion bites, organophosphates); drugs (including those used to treat autoimmune disease and AIDS); endoscopic retrograde cholangiopancreatography (ERCP) procedures; hyperlipidemia; hypercalcemia; infections (including some bacterial, viral, and parasitic); autoimmune pancreatitis; ischemia; genetics; and trauma. Details of various etiologies, their putative mechanisms, and the proposed pathophysiology have been reviewed elsewhere [2, 5–8]. Idiopathic acute pancreatitis may account for as much as 20% of all cases.

Patients with pancreatitis typically present with abdominal pain, classically described as epigastric with a band-like distribution or radiation to the back. Sometimes pain is felt in the right or left upper quadrant, depending on the most inflamed segment of the pancreas. Patients often have nausea and vomiting, deny alleviating factors, and demonstrate guarding on abdominal exam [5]. Diagnosis is supported when lipase or amylase is three times normal and is confirmed when imaging, especially CT scan, reveals pancreatic inflammation [5, 9]. Other diagnostic tests are also used, such as serum liver enzyme elevations that generally support a gallstone etiology when present (associated liver inflammation is rare), and abdominal ultrasound to search for gallstones or dilated biliary ducts [2]. Further testing then distinguishes mild and severe

forms of pancreatitis in order for clinicians to plan monitoring and treatment.

Evolution of Acute Pancreatitis

Approximately 80% of patients with acute pancreatitis recover by 7 days while the other 20% have a more serious form described as severe acute pancreatitis (SAP) (Fig. 1). Among the group who do not resolve within 7 days, overall mortality is approximately 4% [2]. SAP is defined as the presence of systemic inflammatory response syndrome (SIRS) and/or evidence of organ failure, the most common three systemic complications being: renal, as demonstrated by a rising creatinine, respiratory, revealed by tachypnea or hypoxia, or cardiac/hemodynamic, observed as tachycardia or hypotension [10]. A few patients in the mild pancreatitis group meet SAP criteria initially but recover normal parameters quickly [9]. SAP criteria persisting longer than 48 h predicts patients who will fail to resolve within 7 days, and these patients have a prolonged, potentially rocky course of SAP, approximately 25% progressing to acute necrotizing pancreatitis (ANP). ANP, also referred to as interstitial edematous pancreatitis (IEP) by some authors [9], is defined by the presence of interstitial pancreatic necrosis on radiologic imaging [5]. The development of necrosis increases mortality risk to approximately 10%, with subsequent infection of necrotic pancreatic tissue increasing this risk further to about 25% (Fig. 1) [2, 8, 11].

Several different scoring systems have been proposed to define morbidity, and to predict disease severity and risk of mortality in pancreatitis. These include Ranson's criteria; the Imrie scoring system; pancreatitis-specific use of Multiple Organ Dysfunction Score (MODS); Sequential Organ Failure Assessment (SOMA); and several iterations of the Acute Physiology and Chronic Health Evaluation (APACHE) [12]. In addition, inflammatory markers such as C-reactive protein (CRP) and other reported predictors of mortality, such as presence of obesity or hemoconcentration, are widely used for patients with pancreatitis [13–15], combined with severity of pancreatic inflammation on CT or other imaging [2, 12]. The overall goal of these prognostic efforts is to identify the 20% of acute pancreatitis patients with severe disease and target them for more aggressive treatment.

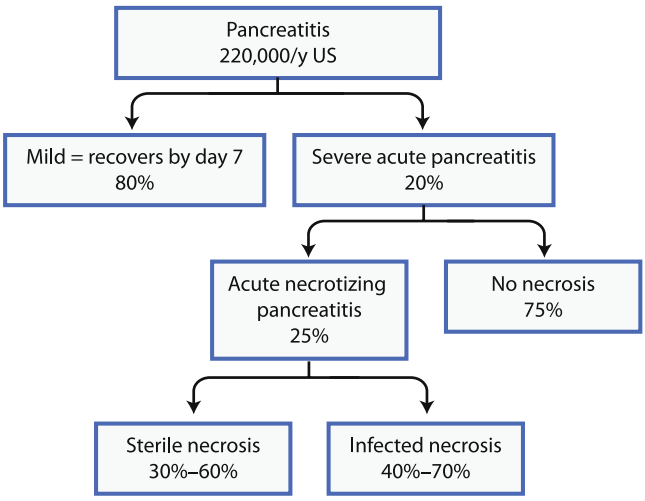

Fig. 1 Evolution of acute pancreatitis. Percentages show proportion of cases who recover early versus those who are severe, with subsets who develop necrosis or become infected [2, 4, 5]

Treatment of Acute Pancreatitis

Given that there is no specific therapy for a severely inflamed pancreas, what has been shown to be effective in the treatment of acute pancreatitis, particularly SAP? As with other illnesses associated with SIRS and organ dysfunction, the initial treatment strategy is volume resuscitation and support. In acute pancreatitis, the volume depletion typically begins with nausea and vomiting, and is thereafter compounded by local abdominal and systemic inflammatory reactions [10]. In rare, very severe cases, volume losses may include pancreatic hemorrhage or be exacerbated by myocardial depression. Pulmonary dysfunction is common in SAP and may be caused by atelectasis, pleural effusion, or acute respiratory distress syndrome (ARDS), the latter occurring in up to a third of SAP patients [10]. Support of hypoxia includes ventilation when necessary and recognizing the critical distinction between pulmonary congestion caused by ARDS, and that caused by cardiac failure, the latter a much less common consequence of pancreatitis and requiring a treatment strategy that undermines the volume resuscitation typically required. Acute renal injury in SAP is associated with higher mortality risk and is treated with adequate volume support and avoidance of renal insults such as intravenous contrast [10]. Early nutritional support is now known to prevent complications in SAP, with reduced progression to necrosis, fewer infections, and lower mortality using total enteral feeding compared to total parenteral feeding [16, 17].

The goal of aggressive care is to perfuse the inflamed pancreas and support any impaired organ systems during the period of systemic inflammatory response. Failure to do so increases the risk for ANP and for its dreaded potential sequela, infected pancreatic necrosis [2, 10] (Fig. 1). Hemoconcentration persisting 24 h after hospitalization, as a measure of inadequate volume resuscitation, is reported to be an accurate predictor of pancreatitic necrosis [2, 12]. Mortality risk increases as necrosis occurs, with death from SAP being bimodal in distribution (the first peak due to SIRS and associated organ failure within 2 weeks, and the

second peak from complications, typically infectious, occurring 2–6 weeks after diagnosis). Complications causing later mortality include infection within necrosed pancreatic tissue among patients who develop ANP, versus, much less commonly, walled-off pancreatic abscess, [18] or conditions of prolonged incapacitation, such as pneumonia or line sepsis [2, 10].

With these strategies now better understood for the support of patients with SAP, what can be done when ANP nonetheless occurs? Recognizing the increased mortality associated with infection of necrotic pancreatic tissue, anti-infective treatments have been applied, studied, and debated for over a decade. Some authors examined outcomes when antibiotics were given to all acute pancreatitis patients, while others looked specifically at populations where necrosis had occurred. Subsets undergoing ERCP procedures [19] or taking probiotic formulations [20] have also been studied. Below we discuss the literature evaluating the use of prophylactic antibiotic treatment to prevent infection, and its associated mortality, in ANP.

Antibiotic Prophylaxis in Acute Necrotizing Pancreatitis

Randomized trials examining the effect of antibiotics on morbidity and mortality in acute pancreatitis began to appear in the 1970s [21–23]. These early trials included patients with mild pancreatitis and used ampicillin as the treatment arm, showing no significant effect on mortality. In 1998, Golub et al. [24] published a meta-analysis of the first eight clinical trials to study this topic, including the three early trials mentioned above, and reported a mortality benefit not with ampicillin, but with the use of broad spectrum antibiotics expected to penetrate pancreatic tissue [21–29]. Their meta-analysis included 514 total patients, and they noted that only one of the eight individual trials was able to show benefit with antibiotic therapy [27]. Since this early effort, many systematic reviews have been written on this topic in an attempt to answer the important quandary of whether antibiotics can prevent infection and death in ANP.

Table 1 lists the published meta-analyses along with the clinical trials included in each, and whether benefit was discovered for the two outcomes, infected necrosis, and mortality. Note that despite inclusion of many of the same individual clinical trials, the meta-analyses draw differing conclusions regarding whether prophylactic antibiotics significantly reduce infection of necrotic pancreatic tissue or overall mortality among patients with ANP. Critical to understanding potential sources of these discrepancies are the important bias-reducing methods used for conducting therapeutic trials, and for later combining them into meta-analyses. Table 2 provides methodology checklists for both the therapy trial (referred to as the randomized, controlled trial [RCT] when randomization and a control group are present), and the meta-analysis. These checklists are derived from Jadad scoring [30] and the Users' Guides [31, 32, 33•], each intended to measure authors' attempts to reduce bias and thereby provide highly valid study results that can be appropriately applied to patient care. We refer the reader to the guides in Table 2 as we attempt to draw a clinical recommendation from the meta-analyses and their contained clinical trials in Table 1.

All meta-analyses covered here are strengthened by their requirement for randomization among included trials, and their ability to combine individual data rather than aggregate data from individual studies. Following initial efforts of Golub et al., Sharma et al. [34] published a 2001 meta-analysis rejecting for inclusion most of the earlier clinical trials. As with all later meta-analysis authors, they rejected trials using ampicillin for reasons of poor pancreatic penetrance and emerging bacterial resistance. In addition, they followed an important rule of meta-analysis in formulating a focused clinical question: whether prophylactic antibiotics improve outcomes in acute *necrotic* pancreatitis rather than in all acute pancreatitis. Including only trials that verified necrosis in their subjects, they further rejected Luiten et al. [26] and Delcenserie et al. [28]. This left 160 patients from three trials, and provided an overall conclusion that antibiotics significantly reduce mortality with a nonsignificant trend toward reduction in infection of necrotic pancreatic tissue.

2006 produced an explosion of meta-analysis effort with four publications reaching contradictory results [35–38]. Heinrich et al. [35] and Villatoro et al. [36] both report mortality benefit but no reduction in infection of pancreatic necrosis with prophylactic antibiotics. Mazaki et al. [37] and Xiong et al. [38] report no significant benefit in either outcome. All four reviews agree on inclusion of trials by Nordback et al. [39] and Isenmann et al. [40], the latter marking the first double-blinded study to examine this issue. Mazaki et al. and Xiong et al. sacrificed focus of their clinical question by including Spicak et al. [41] and, in Xiong's case, Delcenserie et al. [28], studies that did not establish necrosis of the pancreas for inclusion. In addition, Xiong et al. should likely be rejected outright due to their failure to report any assessment of validity of the included trials.

In 2007, Dambrauskas et al. [42] included multiple trials that had been rejected by others for the following reasons: Takeda et al. [43] used continuous infusion of antibiotic with a protease inhibitor as their treatment arm; Bassi et al. [44] and Manes et al. [45] compared two antibiotic arms without controls; and Maravi-Poma et al. [46] compared imipenem for 14 days with more prolonged imipenem in patients with ANP. Dambrauskas et al. additionally failed to report on individual validity of their included trials. Also in 2007, de Vries et al. [47•] was published late enough to include the second double-blinded study on this topic, a multicenter trial

Table 1 Meta-analyses examining the effect of prophylactic antibiotics on the outcomes of infected necrosis and mortality in patients with acute necrotizing pancreatitis

Year	1st Author	Included trials	Antibiotic in treatment arm	[a]Total subjects	Validity of trials assessed	Benefit shown for:	
						Infected necrosis	Mortality
1998	Golub	Craig '75 Howes '75	Ampicillin Ampicillin	514	Yes	Not tested	Yes
		Finch '76	Ampicillin				
		Perderzoli '93	Imipenem				
		Luiten '95	Cefotaxime IV or norfloxacin PO/PR				
		Sainio '95	Cefuroxime				
		Delcenserie '96	Ceftazidime, amikacin, metronidazole				
		Schwarz '97	Ofloxacin and metronidazole				
2001	Sharma	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	160	Yes	No	Yes
		Schwarz '97	Ofloxacin and metronidazole				
2006	Heinrich	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	288	Yes	No	Yes
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
2006	[b]Villatoro	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	294	Yes	No	Yes
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
2006	Mazaki	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	329	Yes	No	No
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		Spicak '04	Ciprofloxacin/metronidazole				
2006	Xiong	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	338	No	No	No
		Delcenserie '96	Ceftazidime, amikacin, metronidazole				
		Schwarz '97	Ofloxacin and metronidazole				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		Spicak '04	Ciprofloxacin/metronidazole				
2007	Dambrauskas	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	1,279	No	Yes	Yes
		Delcenserie '96	Ceftazidime, amikacin, metronidazole				
		Schwarz '97	Ofloxacin and metronidazole				
		[d]Bassi '98	Pefloxacin versus imipenem				
		[d]Takeda '00	Nafamostat CRAI with imipenem				
		Nordback '01	Imipenem				
		[d]Manes '03	Meropenem versus imipenem				
		[d]Maravi '03	Imipenem 14 days versus longer				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
2007	de Vries	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	397	Yes	No	No
		Delcenserie '96	Ceftazidime, amikacin, metronidazole				
		Schwarz '97	Ofloxacin and metronidazole				
		[c]Isenman '04	Ciprofloxacin and metronidazole				
		[c]Dellinger '07	Meropenem				
2008	Hart	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	429	Yes	No	No

Table 1 (continued)

Year	1st Author	Included trials	Antibiotic in treatment arm	[a]Total subjects	Validity of trials assessed	Benefit shown for:	
						Infected necrosis	Mortality
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		Spicak '04	Ciprofloxacin/metronidazole				
		[c]Dellinger '07	Meropenem				
2008	Xu	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	540	Yes	Yes	No
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		Spicak '04	Ciprofloxacin/metronidazole				
		[c]Dellinger '07	Meropenem				
		Rokke '07	Imipenem				
2008	Bai	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	467	Yes	No	No
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		Spicak '04	Ciprofloxacin/metronidazole				
		[c]Dellinger '07	Meropenem				
		Rokke '07	Imipenem				
2009	Jafri	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	502	Yes	No	No
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		Spicak '04	Ciprofloxacin/metronidazole or meropenem				
		[c]Dellinger '07	Meropenem				
		Rokke '07	Imipenem				
2010	[b]Villatoro	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	404	Yes	No	No
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		[c]Dellinger '07	Meropenem				
		Rokke '07	Imipenem				
2010	Bai	Perderzoli '93 Sainio '95	Imipenem Cefuroxime	519	Yes	No	No
		Schwarz '97	Ofloxacin and metronidazole				
		Nordback '01	Imipenem				
		[c]Isenmann '04	Ciprofloxacin and metronidazole				
		[c]Dellinger '07	Meropenem				
		Rokke '07	Imipenem				
		[c]Garcia-Barrasa '09	Ciprofloxacin				
		Xue '09	Imipenem				

CRAI, continuous regional arterial infusion

[a] Number of subjects in meta-analyses varies despite inclusion of same trials when authors use subsets of original data

[b] Cochrane Reviews (only the two most recent Cochrane Reviews are included for this article)

[c] RCT included blinding

[d] RCT contained no control arm

Table 2 Checklist for assessing validity by publication type [30–32, 33•]

Clinical trial comparing treatments	Meta-analysis
• Randomization?	• Addresses focused clinical question?
–Concealment of randomization?	• Criteria for trial inclusion appropriate?
• Double-blinding?	• Unlikely important data were missed?
• Follow up of subjects?	• Validity of included trials assessed?
• Intention to treat?	• Combines individual data (rather than aggregate data)?
• Groups similar at start?	• Results similar from study to study?
• Groups treated equally?	

by Dellinger et al. [48•] comparing meropenem with placebo and finding no difference in infected necrosis or mortality. De Vries, who rejected Nordback's trial [39] for giving antibiotics to control patients if inflammatory markers were increasing, goes on to show an inverse-linear relationship between the methodologic quality score of included trials and the mortality benefit reported. In other words, the more rigorous an RCT's methods in terms of concealment of randomization, blinding, similarity of groups, etc., the less likely it was to show mortality benefit for prophylactic antibiotics.

From this point on, through the 2008–2010 meta-analyses, quality of the included trials and the summarizing meta-analyses increased, and the benefit of prophylactic antibiotics disappeared. Referring to Table 1, Hart et al. [49], Bai et al. [50•], and Jafri et al. [51], in addition to 2010 updates by Villatoro et al. [52] and Bai et al. [53•], reported no significant decrease in rates of pancreatic tissue infection or rates of mortality with the use of prophylactic antibiotics given to patients with acute necrotic pancreatitis. Xu et al. in 2008 [54] were the exception, reporting significant protection from infection of necrotic pancreas tissue, but have been criticized by others for including subsets of patients not proven to have necrosis, and for using a fixed effects model for their meta-analysis where a random effects model is more appropriate to the natural heterogeneity of included populations [50•]. Over time, more individual trials allowed larger meta-analyses, and a third higher quality, double-blind trial showed no significant difference with prophylactic antibiotics [55•].

Beyond Contradictory Meta-Analyses

Epidemiologists and statisticians have argued that large randomized controlled trials are superior to meta-analyses for distinguishing between the null hypothesis and a true benefit or harm of a treatment intervention [56]. Combining small trials with few outcomes, particularly if validity is low or results are dissimilar, can produce large confidence intervals around a summary relative risk, and therefore little certainty about a drug's effect. The distortion or bias caused by heterogeneity of included trials means some meta-analyses are more appropriate for hypothesis expansion than for application to patient care [57]. Referring to Table 1 and applying the standards in Table 2, meta-analyses did not provide us with confident conclusions when the question was not sufficiently focused on patients with necrosis or on antibiotics with adequate penetration, when scope of included trials allowed those without controls, or when validity of individual trials was not tested. Newer, generally larger, higher quality meta-analyses published on this topic since 2008 agree that prophylactic antibiotics given to patients with ANP do not reduce incidence of infected necrosed tissue or mortality.

Luckily, we now have three RCTs that are of higher quality, including a placebo group and keeping the patients with ANP and their clinicians blind to group allocation [40, 48•, 55•]. Blinding reduces bias in outcome reporting, particularly for inadvertent partiality regarding which patients are sent for cultures of necrosed pancreatic tissue. Two of these trials are also stronger because they are multicenter studies [40, 48•]. All three of these trials reported no difference in rates of pancreas infection or mortality, providing the clearest answer that prophylactic antibiotics should not be part of clinical protocols for treatment of ANP.

Conclusions

Acute pancreatitis that progresses to pancreatic necrosis has a considerable fatality rate, largely from infectious complications. It stands to reason that prophylactic antibiotics were considered a potential way to reduce mortality, and they have been part of many treatment regimens since early reports claimed effectiveness. Conflicting reports lead to considerable debate, and a large number of meta-analyses attempted to clarify the issue, but also produced opposing recommendations. Applying standards of well done RCTs and meta-analyses, the higher quality data now clearly point to no beneficial role for prophylactic antibiotics.

While the lack of effect for preventing infection of the pancreas or for decreasing mortality appears established,

some reports claimed benefit of prophylactic antibiotics on other outcomes, such as length of hospital stay, the need for surgery or intensive care, or the incidence of nonpancreatic infections. These reports have been inconsistent and are not supported by the newer, double-blinded trials. In addition, given that extrapancreatic infections in ANP are largely the result of prolonged hospitalization and disability (such as catheter infections or pneumonia), one would have to argue that any patient with extended infirmity be given prophylactic antibiotics, a suggestion clearly without merit given the expansion of resistant bacteria and the rise in *Clostridium difficile* infections. On a related note, some authors report a transition in the causative agents of infected necrosis, from predominately gram-negative gut flora to gram-positive, possibly hospital acquired organisms, with the advent of antibiotic prophylaxis [58•]. In addition, some note that fungal infections increase in relation to the duration of prophylaxis given [46].

It is difficult to imagine a topic that investigators have tried harder to solve than one which has generated 14 meta-analyses in just under as many years. The cumulative data now conclude that prophylactic antibiotics are not beneficial, and might be harmful, in patients whose acute pancreatitis has evolved to necrosis of the pancreas. Only a large, multicenter study including hundreds of patients with CT-proven necrosis, properly randomized to produce similar groups, controlled with a placebo arm, double-blinded, adequately followed up, and with statistical analysis according to group allocation will produce a more credible and accurate result. For now, the only appropriate use of antibiotics in acute pancreatitis is when infection has been established, and prophylactic use should be removed from treatment paradigms.

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