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Review Article

Antibiotics in Acute Necrotizing Pancreatitis — Perspective of a Developing Country

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Abstract

Prophylactic antibiotics in acute necrotizing pancreatitis is controversial. The mortality of acute necrotizing pancreatitis is 8-25% in the western world. In view of the limited resources available for managing the complications of infected pancreatitis in developing countries, the use of prophylactic antibiotics may be recommended in selected cases.

Various antibiotics show good penetration into the pancreatic tissue; imipenem and quinolones have better penetration. Clinical trials on the use of prophylactic antibiotics in necrotizing pancreatitis have been reviewed.

Prophylactic antibiotics have been considered if greater than 30% pancreatic necrosis as documented by CT scan. Imipenem can be given for a duration of 10 to 14 days if no systemic complications are present. In a developing country where the cost of managing complications of pancreatitis can be a limiting factor for patients, the use of prophylactic antibiotics early on in the disease in selected cases can be beneficial.

Introduction

The indications for the use of prophylactic antibiotics in acute necrotizing pancreatitis (ANP) have been controversial. The use of prophylactic antibiotics should take into consideration the bacterial spectrum, concentration in pancreatic tissue, and emerging resistance patterns. In developing countries, availability and cost of the antibiotic are important issues, especially when comparing this to the cost of potential infectious complications in the setting of limited resources for the care of critically ill patients. Acute necrotizing pancreatitis has an 8 to 25% mortality reported in the developed world.[1,2] A mortality of 20% has been reported in a non-indexed journal from a center in Lahore, Pakistan.[3]

This review will attempt to answer certain critical questions regarding the use of prophylactic antibiotics for ANP, based on the literature available at this time.

Selection of trials for review:

An advanced search was performed in Pubmed with the phrase "pancreatitis antibiotics" with 'clinical trials' in limits. The search returned 74 articles. These were narrowed down by going through the title and abstracts and ten clinical trials were identified in which the use of antibiotics were assessed in acute pancreatitis (Figure-1).

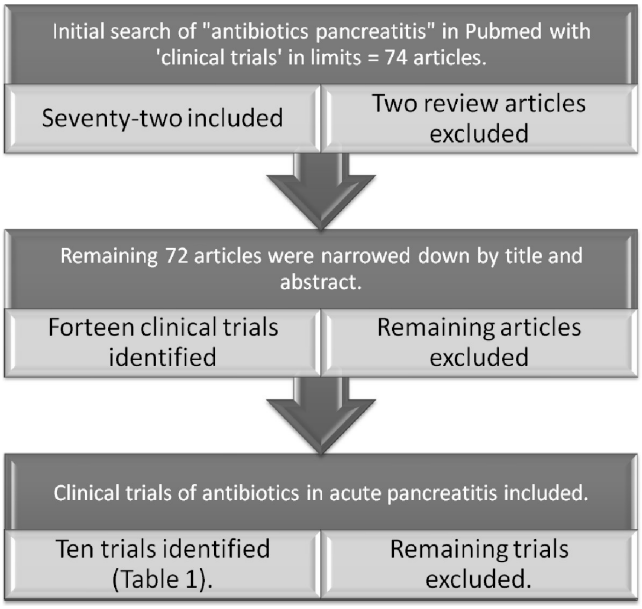

Figure 1: Figure showing the selection of clinical trials on antibiotics in acute necrotizing pancreatitis for review.

Impact of prophylactic antibiotics on outcome in ANP:

Several studies have been conducted to assess the benefit of prophylactic antibiotics in ANP. Various antibiotics have been used and have been compared with placebo or each other. Some of these studies have included patients with alcoholic pancreatitis only, while others have included patients with ANP regardless of the cause.

Pederzoli et al[4] recommend the use of prophylactic antibiotics based on the significantly decreased incidence of pancreatic sepsis in the antibiotic group of their randomized trial of 74 patients with CT proven pancreatic necrosis. Patients were randomized and were either started on imipenem within 72 hours or no antibiotic treatment. The incidence of infected pancreatic necrosis (IPN) in the imipenem group (5 out of 41, 12.2%) was less than half that of the group without antibiotics (10 out of 33, 30.3%) with a

p value of less than 0.01. However there was no difference in mortality between the two groups.

Sanio et al.[5] concluded that cefuroxime is beneficial if given early in ANP as it decreases both infective complications and mortality significantly. This conclusion was based on a randomized trial of 60 patients with alcohol induced ANP. Patients were divided into two groups. One received cefuroxime for 14 days prophylactically while the other did not receive any antibiotic unless evidence of infection was present. Less infectious complications were observed in the cefuroxime group (p=0.01). Mortality was also less in the cefuroxime group (1 out of 30, 3.3%) as compared to the non-antibiotic group (7 out of 30, 23.3%) with a p value of 0.03. This is the only study showing significant reduction in mortality with prophylactic antibiotics. It should be noted that patients included in this study had alcohol induced pancreatitis.

Delcenserie et al.[1] randomized patients with alcoholic ANP to receive prophylactic ceftazidime, amikacin and metronidazole for 10 days or no antibiotics. They found a significant reduction in the incidence of severe sepsis (caused by culture proven pancreatic infection) in the antibiotic group (0 out of 11, 0%) as compared to the non antibiotic group (7 out of 12, 58.3%). There was no significant difference in mortality between the two groups. Røkke et al. showed that antibiotic prophylaxis with imipenem in patients with severe pancreatitis (CRP>120 at 24hrs or CRP>200 at 48 hrs) reduced the complications and incidence of infections.[6] There was no significant difference in length of stay, need for intensive care, need for surgical intervention or 30 day mortality.

The clinical course of ANP as assessed by APACHE II score was compared in a randomized study by Schwarz et al.[7] that included 26 patients. They showed significant improvement in the clinical course of patients receiving prophylactic ofloxacin and metronidazole (APACHE II scores at day 1,5 and 10 were 15, 13 and 9.5) as compared to the control group(scores on day 1,5 and 10 of 11.5, 15, and 16) that did not receive prophylactic antibiotics. Due to the small number of patients, differences in mortality could not be assessed.

The impact of antibiotics on the need for surgical intervention was evaluated by Nordback et al.[4] They demonstrated a significant reduction in the need for surgery in patients receiving prophylactic imipenem (2/25, 8%) as compared to those patients who receive imipenem only when there is indication of necrosectomy.[8]

Isenmann et al.[9] conducted the first double blind study of antibiotic prophylaxis in ANP and found no significant difference in the in the incidence of infected necrosis, complications or mortality. They compared ciprofloxacin and metronidazole for 14 days (58 patients) versus placebo (56 patients). However, almost half (48%) of the placebo group had to be given open antibiotic treatment due to complications as opposed to 25% of the antibiotic group. The lack of significant difference in morbidity and mortality might be due to the fact that most bacteria from the antibiotic group were resistant to ciprofloxacin. Moreover, infections that developed in the placebo group were expeditiously treated due to which a reduction in mortality may not be evident. The authors suggest that in view of this, administering antibiotics promptly "on demand" can be effective in preventing infective complications.

Dellinger et al.[2] in a randomized double blind placebo controlled study found no significant difference between the outcome of two groups of patients with ANP, one receiving meropenem and the other placebo. However, there were some differences between the two groups, although these differences did not reach statistical significance. The placebo group had more patients who had greater than 30% necrosis, a greater proportion of patients with neither alcoholic nor biliary pancreatitis, and a higher infection rate.

A meta-analysis conducted by Dambrauskas et al[10] concluded that prophylactic antibiotics were superior to administering antibiotics when needed ("on demand") in ANP. Moreover, they found that carbepenems as prophylactic antibiotics significantly decreased the risk of developing pancreatic necrosis, sepsis, and decreased the need for surgery, although there was no significant change in mortality. Villatoro et al.[11] conducted a Cochrane review of five RCTs with 294 patients comparing antibiotics to placebo in acute pancreatitis with CT proven necrosis. They determined a significant reduction in mortality in the antibiotic group but no difference in the rates of infected pancreatic necrosis, operative treatment or non-pancreatic infections. This analysis was handicapped by the different antibiotics and duration of treatment in the different trials.

Conversely, a recent meta-analysis by Bai et al.[12] of seven trials involving 467 patients, showed that the incidence of infected pancreatic necrosis is not reduced by prophylactic antibiotics and there is no significant decrease in mortality either. They found that the mortality was significantly decreased in the antibiotic groups only in single centre trials and in single blind trials but not in multicentre or double blind trials. A recent meta-analysis of 502 patients from 8 studies showed no benefit of antibiotics in decreasing mortality or morbidity in severe acute pancreatitis.[13]

In summary, randomized double blind studies have not shown any significant difference in the outcome with prophylactic antibiotics. There have been multiple meta-analyses conducted in an attempt to define the role of prophylactic antibiotics. Unfortunately, due to the dearth of

homogenous RCTs, differing inclusion criteria, interventions, and end-points, the conclusions have been dramatically varied. The use of prophylactic antibiotics may prove to be cost-effective in settings where cost and availability of tertiary care facilities is a significant issue. For instance, 32.6%[14] of the population of Pakistan lives below the poverty line on the human poverty index. In such an environment, a strong case can be made for the administration of prophylactic antibiotics early in ANP to decrease the incidence of infectious complications and reduce the cost of patient care.

Bacteriology in ANP:

The organisms involved in infected ANP vary greatly and may be influenced by antibiotic usage. In patients with culture proven infected ANP, microorganisms responsible are usually of colonic origin[15] E. coli and Pseudomonas aeruginosa were the commonest organisms in acute pancreatitis in a study in India.[16] Howard et al concluded that prophylactic antibiotics altered the bacteriology of infected necrosis. They discovered that patients who receive prophylactic antibiotics for ANP and develop a secondary infection were predominantly infected by gram positive organisms. Conversely, gram negative pancreatic infection is more common in patients who do not receive prophylactic antibiotics.[17]

Penetration of antibiotics into pancreatic tissue:

The concentration of various antibiotics in necrotic pancreas has been evaluated in humans and experimental animal models. The penetration of imipenem in the pancreas in humans is adequate in terms of minimum inhibitory concentration (MIC) values for common organisms in infected pancreatic necrosis.[18] The concentration of cefoperazone in pancreatic juice of patients with acute pancreatitis was higher than the MICs of common pancreatic pathogens.[19] Cefotaxime and ceftizoxime have been found to have pancreatic tissue concentration for inhibiting some bacteria involved in pancreatic infections[20] while the concentration of cefoxitin in pancreatic juice was less than the MICs of commonly involved bacteria. Ciprofloxacin has higher concentration in both pancreatic juice and tissue than MICs of common pathogens involved.[20] Ofloxacin has good penetration into pancreatic tissue of rats with induced ANP[21] as well as in human pancreatic tissue in ANP.

Emerging resistance to antibiotics:

Although there are a variety of antibiotics that penetrate necrotic pancreas, their spectrum of coverage needs to be assessed. A study by Howard et al.[17] demonstrated that although prophylactic antibiotics change the bacteriology of infected ANP, there is no significant increase in resistant organisms. Conversely, the antibiotic group in the Isenmann et al. trial[9] had a significantly higher number of organisms resistant to ciprofloxacin ($p = 0.0001$).

The incidence of resistant organisms in infected pancreatic necrosis is variable. Infected pancreatic necrosis due to multi resistant organisms was found in only 3 patients out of 103 with ANP in a study in Switzerland[22]. Jan et al.[15] report 52% (24 out of 46) patients with antibiotic resistant organisms in an ICU setting. Most common resistant organisms in this study were Pseudomonas aeruginosa and methicillin resistant Staphylococcus epidermidis. Out of 11 organisms causing infection in ANP, Dellinger et al. found that 7 were resistant to meropenem (5 out of 6 in meropenem group and 2 out of 5 in placebo group).[2]

Choice of antibiotic:

The common bacteria in infected pancreatic necrosis should have the lowest incidence of resistance to the antibiotic chosen as prophylaxis in ANP. Although significant mortality benefit has been shown with cefuroxime as a prophylactic antibiotic, but imipenem has been used in more trials and is as effective as meropenem.[23] Ciprofloxacin has shown good penetration but the reported higher incidence of organisms resistant to it does not make it an attractive choice. The cephalosporins have not been used as much as the carbepenems in studies comparing antibiotics. It is important to review local antibiotic susceptibility data before choosing a prophylactic antibiotic. Imipenem has shown benefit in several studies as a prophylactic antibiotic. Based on the results of trials, meta-analysis, tissue penetration and bacteriology, it is an effective prophylactic antibiotic in ANP. Ciprofloxacin is not recommended as first choice because of high rates of bacterial resistance. Bassi et al.[24] conducted a multicentre study of 60 patients with at least 50% necrosis in ANP. Patients received either prophylactic imipenem or perfloxacin. Both antibiotics were given for 14 days. The incidence of pancreatic infections and sepsis was much less with prophylactic imipenem as compared to perfloxacin.

Currently, imipenem can be recommended as the prophylactic antibiotic of choice in ANP although the 27% resistance reported by Maravi-Poma et al.[25] is a cause for concern. A dosage of 500mg three times a day, as described by Pederzoli et al[4] and Røkke et al[6] is recommended.

Duration of antibiotic:

Antibiotics have been used for variable duration in several studies as shown in Table. Imipenem was given for 14 days in the majority of studies. In severe pancreatitis Røkke et al. showed benefit of imipenem even if given for 5 - 7 days.[6] Imipenem therapy for more than 14 days in patients without any systemic complications has not been shown to be superior to treatment for 14 days with the end point of prevention of pancreatic infections.[25] In addition, in patients with systemic

Table: Various clinical trials on prophylactic antibiotics in acute necrotizing pancreatitis with conclusions.

Study	Groups	Number of Patients	Infectious Pancreatic Necrosis	Sepsis	Need for Surgery	Mortality	Comments	Conclusion
Sanio et al[6] (1995)	--Cefuroxime 14 days	30	9 (30%)	4 (13.3%)	7(23.3%)	1(3.3%)	Comments	Conclusion
	--No antibiotics	30	12(40%)	8(26.6%)	14(46.6%)	7(23.3%)	Randomized study of alcohol induced Acute Necrotizing Pancreatitis (ANP) with CT proven necrosis and CRP > 120.	Prophylactic antibiotics are beneficial.
Delcenserie et al.[1] (1996)	--Ceftazidime+ Amikacin+ Metronidazole for 10 days.	11	0(0%)	0(0%)	-	1(9.1%)	All patients had acute alcoholic pancreatitis with CT proven pancreatic necrosis and 2 or more fluid collections.	Prophylactic antibiotics are beneficial in reducing the incidence of severe infection in ANP.
	--No antibiotics	12	2(25%)	7(58.3%)	-	3(25%)		
Schwarz et al.[7] (1997)	--Ofloxacin+ Metronidazole prophylactically	13	8(62%)	4(31%)	-	0(0%)	Clinical course as assessed by APACHE II score showed significant improvement in patients under prophylactic treatment. CT proven pancreatic necrosis.	Antibiotic prophylaxis improved the clinical course significantly.
	--Oflaxacin + Metronidazole if evidence of infection	13	7(54%)	6(46%)	-	2(15%)		
Pederzoli et al.[4] (1993)	--Imipenum for 14 days	30	5(12.2%)	11(26.8%)	12(29.3%)	3(7.3%)	Necrotizing pancreatitis proven by CT. Patients randomly assigned within 72 hrs of presentation.	Incidence of sepsis was significantly less in imipenum group. Prophylactic antibiotics are recommended in ANP.
	-- No antibiotics.	30	10(30.3%)	26(78.8%)	11(33.3%)	4(12%)		
Manes et al.[23] (2003)	-- Meropenem for 14 days.	88	10(11.4%)	19(21.6%)	15(17%)	12(13.6%)	CT proven necrosis. No control group without prophylactic treatment. Both groups received antibiotics.	Meropenem is as effective as imipenem in preventing septic complications.
	-- Imipenem for 14 days.	88	12(13.6%)	21(23.9%)	16(18.2%)	10(11.4%)		
Nordback et al.[8] (2001)	--Early prophylactic imipenem	25	2(8%)	-	2(8%)	2(8%)	CT proven necrosis. Early vs. on demand imipenem treatment is compared. Endpoint of study was necrosectomy due to infection.	Early imipenem significantly decreased the need for surgery and major organ complications.
	--Delayed imipenem	33	14(42%)	-	14(42%)	5(15%)		
Isenmann et al.[9] (2004)	--Ciprofloxacin + Metronidazole for 14 days -- Placebo	58	12%	-	-	5%	Placebo controlled double blind study. CT proven necrosis. CRP > 150. Protocol had to be opened in 48% of placebo group for treatment of infectious complications vs. 25% of antibiotics group.	No difference in infectious complications or mortality. No benefit of prophylactic antibiotics in ANP.
		56	9%	-	-	7%		
Dellinger et al.[2] (2007)	--Meropenem for 7-21 days	50	9(18%)	16(32%)	13(26%)	10(20%)	Multicenter Randomized, Double-Blind, Placebo-Controlled Study. Primary endpoint was development of pancreatic or peri-pancreatic infection within 42 days of randomization.	No statistically significant difference between the two groups in outcome. Does not early prophylactic antibiotic use in patients with ANP.
	-- Placebo	50	6(12%)	24(48%)	10(20%)	9(18%)		
Maravi-Poma et al.[25] (2003)	--Imipenem for 14 days.	46	13 (28%)	5(11%)	-	9(19.6%)	The second group received antibiotics for as long as systemic complications of the disease persisted.	Antibiotics for a longer duration do not decrease septic complications but in patients with systemic complications till day 14 of treatment, prolonged administration on antibiotics tends to reduce mortality.
	--Imipenem for more than 14 days.	46	14(30.4%)	7(15%)	-	8(17.4%)		
Bassi et al.[24] (1998)	--Perfloxacin 14 days	30	10(34%)	13(44%)	-	7(24%)	Multicentre study. At least 50% necrosis.	Pefloxacin is inferior to imipenem in the prevention of infections in ANP.
	--Imipenem 14 days	30	3(10%)	6(20%)	-	3(10%)		

complications at day 14 of treatment, prolonging imipenem administration decreases mortality. No other studies are available comparing the duration of antibiotic treatment.

As mentioned, the penetration of imipenem into necrotic pancreatic tissue is best in the initial stages of the disease. A Cochrane review concluded that antibiotic treatment for 10 to 14 days decreases mortality and the risk of developing infected pancreatic necrosis.[26] Antibiotics should be stopped on day 14 if no systemic complications of ANP or evidence of infection is present as prolonged administration has not shown any additional benefit. Moreover, prolonged administration provides favourable conditions for the selection of resistant organisms.

Fungal infections:

The incidence of pancreatic fungal infections might be

related to the frequent use of prophylactic antibiotics in patients with ANP. These infections are mostly secondarily acquired during hospital admission. Candida infection of pancreatic necrosis is associated with a significantly higher mortality rate (p 0.0001) and fungal infection is an independent predictor of mortality.[27] A meta analysis by Villatoro et al.[11] found no significant difference between the incidence of fungal infections between patients treated with prophylactic antibiotics and those who were not. There is an ongoing debate on the use of antifungal agents along with prophylactic antibiotics.

Evidence supporting the use of prophylactic antifungal agents in acute necrotizing pancreatitis is lacking and more research is needed in this area. Furthermore, the routine use of antifungal agents can increase the incidence of resistant fungal infections. Until more data is available, we do not recommend the routine use of prophylactic antifungals along with prophylactic antibiotics.

Cost of management:

In Pakistan, a country where 32.6% of the people live below the poverty line,[14] and other low income and developing countries, the cost of management of any disease should always be taken into account. There is an enormous difference in the cost of providing prophylactic antibiotic in the setting of acute necrotizing pancreatitis vs. the cost of managing serious complications later in an intensive care unit (ICU) when prophylactic antibiotics are not given initially. In a Canadian study the ICU costs per day were 6 to 7 times more than non-ICU stay per day and there was an approximate reduction of $ 1200 for one day in the general ward instead of the ICU.[28] In UK the cost per day for ICU stay has been estimated to be $1357.[29] Ten times more resources are required for the treatment of acute necrotizing pancreatitis after necrosectomy in ICU than the management of other conditions in the ICU.[30] The cost of an ICU bed per day in a private tertiary care hospital in Pakistan is Rupees 6310 (US$ 87) excluding the charges for medicines etc. compared to Rupees 1570 (US$ 21) per day for a bed in a regular surgical ward. The cost of 10 days of prophylactic imipenem is Rupees 27000 (US$365). Patients in ICU requiring a ventilator need to pay an additional Rupees 35000 (US$ 455) per day although this ventilator cost varies a lot depending on the hospital as charges can be as low as Rupees 4000 (US$53) per day; still a major burden on the majority of the patients. In case surgical intervention is needed, the cost of a scheduled laparotomy is approximately Rupees 150,000 (US$ 1950) in a tertiary care setting and approximately Rupees 50000 (US$ 660) at a private hospital. Keeping in view the serious infective complications of acute necrotizing pancreatitis, the enormous cost of surgery and intensive care needed for managing these complications and the universal non-availability of tertiary care in a developing country, prophylactic use of imipenem in acute necrotizing pancreatitis will be favourable for the patient.

Indications of prophylactic antibiotic in ANP:

The severity of ANP is dependent on the degree of pancreatic necrosis. The degree of pancreatic necrosis is best established by contrast enhanced CT which is fast and reliable.[31] Pancreatic necrosis develops 24 to 48 hours of onset of symptoms.[32] CT scan done within 12 hours of onset of symptoms may fail to reveal necrosis. The optimum time for a CT scan is approximately 48 hours after the onset of symptoms. There is a low risk of infected necrosis if the necrosis is less than 30%.[33] Thus prophylactic antibiotics can be avoided in such patients if there is no organ failure or local complication. The UK guidelines for the management of acute pancreatitis[33] suggest that antibiotics should only be considered for patients with more than 30% necrosis.

In severe acute pancreatitis, fluid collections are common but most resolve spontaneously. Patients with peri-pancreatic fluid collections without evidence of necrosis still have a 22% incidence of local complications.[34] In such cases, as most of these collections resolve spontaneously, antibiotics should not be given if there is no evidence of sepsis or organ failure. If needed, material should be obtained for culture and sensitivity by FNA and should guide antibiotic therapy.

If the facility of CT scan is not available or if there is a delay, C- reactive protein levels can be used to predict the development of pancreatic necrosis. According to the Sartorini consensus,[35] CRP levels start to rise above 150 mg/l within 48 hours and differentiate between mild and severe disease. Hence, prophylactic antibiotics can be useful if the CRP is above 150mg/l (the value agreed upon at the Sartorini consensus), within 48 hours of onset of symptoms until the patient can be transferred to a higher level facility for a CT scan.

In summary, prophylactic antibiotics in ANP have been recommended in patients with CT evidence of more than 30% pancreatic necrosis or in patients with significant elevation of C-reactive protein.

Conclusion

The current data available on the use of prophylactic antibiotics in acute necrotizing pancreatitis is not in agreement on its effect on patient outcome. Conclusions of various meta-analyses are different. Until more randomized trials are available that clearly show no change in outcome with the use of antibiotics, the use of imipenem as a prophylactic antibiotic for 10 to 14 days is recommended in ANP with more than 30% necrosis, especially in settings of developing countries where tertiary care is not readily available, majority of patients are unable to bear the financial burden of management of

complications after ANP, and where health care insurance is the exception rather than the rule. Thus in settings of developing countries the use of imipenem as prophylaxis in ANP can be cost effective and prevent severe and potentially fatal infective complications. Prophylactic antibiotics for patients with fluid collections are not recommended if there are no signs of sepsis or organ failure. Routine use of prophylactic antifungals is not recommended in acute necrotizing pancreatitis but the decision should be individualized for each patient.

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