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Antibiotics in severe acute pancreatitis

Review Article

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Abstract: Acute pancreatitis (AP) is a local inflammatory response with systemic effects and an adverse evolution in 20% of cases. Its mortality rate is 5-10% in sterile and 15-40% in infected pancreatic necrosis. Infection is widely accepted as the main reason of death in AP. The evidence to enable a recommendation about antibiotic prophylaxis against infection of pancreatic necrosis is conflicting and difficult to interpret. Up to date, there is no evidence that supports the routine use of antibiotic prophylaxis in patients with severe AP. Treatment on demand seems to be the better option, avoiding excessive treatment and selection of bacterial. In infected acute pancreatitis, antibiotics of choice are imipenem, meronem or tigecycline in patients allergic to beta-lactams. Also fluconazole must be given in determinate clinical situations..

Keywords: *Acute pancreatitis • Antibiotic prophylaxis • Antibiotic treatment*

Acute pancreatitis (AP) is a local inflammatory response with systemic effects and an adverse evolution in 20% of cases. Its mortality rate is 5-10% in sterile and 15-40% in infected pancreatic necrosis [1,2]. Incidence of AP seems to be rising in western countries. Gallstones or alcoholism causes about 75% of AP. The relative rate of these etiologies depends on the patient age and the area of enrollment. A thorough evaluation allows identification of the cause in another 10% of cases, leaving about 15-20% as idiopathic.

This name of AP is given to two different diseases, mild and severe AP. Most patients with the mild form recover after a few days without any specific treatment, including antibiotics. This edematous form of AP needs only to correct its etiological factor to avoid recurrence. By the opposite, severe AP presents a poor prognosis, with local and/or systemic complications, high morbidity and mortality [3].

A significant correlation exists between the development of pancreatic necrosis, the frequency of bacterial contamination of necrosis and the evolution of systemic complications. Pancreatic infection basically occurs in patients with pancreatic or peripancreatic necrosis and/or fluid collections. Pancreatic necrosis become infected in a percentage ranging from 20 to 70% and, as a rule, a time dependent increase of the infection rate with the duration of the disease is registered [4-7] (Figure 1). The late course of necrotizing pancreatitis is determined by bacterial infection of pancreatic and peripancreatic necrosis. Mortality is related to necrosis extent and associated to multiple organ failure and other infectious complications. Bacterial translocation is considered the most important trigger of septicemia in these patients [8].

Prevention and treatment of infection seems to be a profitable method to decrease hospital stay and mortality in necrotizing AP. Several controlled clinical trials proved a significant reduction in pancreatic infections or a significant reduction of hospital mortality with the use of prophylactic antibiotics. However, the results of these clinical trials are controversial and not convincing. The high number of papers related to this issue, most of them with different antibiotics regimens and some of them with important methodological defects, generates controversial results. More recent articles and meta-analysis on this subject tend to recommend the

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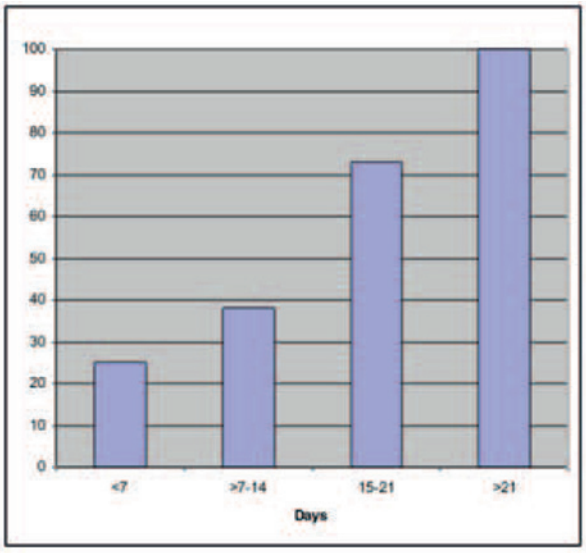

Figure 1. Incidence rate of pancreatic necrosis in severe AP is time dependent

avoidance of antibiotic prophylaxis in this setting. The largest randomized placebo-controlled, double blind trial has been able to demonstrate that antibiotic prophylaxis with ciprofloxacin and metronidazole has no beneficial effects with regard to the reduction of pancreatic infection and the decrease of hospital mortality. This trial does not support antibiotic prophylaxis in all patients with necrotizing pancreatitis, but in specific subgroups of patients with pancreatic necrosis and a complicated course [2].

1. Mortality

Mild form of AP accounts for 80% of the cases; 95% of deceased patients for AP comes from the remaining 20%. Mortality rate has two peaks, early mortality (within the first six days of hospitalization) and late mortality (after the sixth day). The former is usually caused by a systemic inflammatory response syndrome (SIRS) through shock and multiple organ failure, effect of the circulating pancreatic enzymes and activated inflammatory mediators (cytokines, interleukins, prostaglandins, etc.). SIRS can evolve independently of the original injury and its management consists in the treatment of the damages caused by systemic inflammation. Late mortality is generally caused by local complications (necrosis infections or peripancreatic collections infections) or distant complications (pneumonia, septicemia). For some authors, late mortality has decreased because of better antibiotic treatment and nutritional support and learned surgical decisions [9], while others guess that mortality rate has not changed but moved from early to late peak [10,11].

Infection is widely accepted as the main reason for death in AP, mainly infected pancreatic necrosis, although older patients and those with comorbidities present high mortality attributed to others causes. The rate of infection correlates with the extent of necrosis and, therefore, with the severity of the disease [12]. This infection has an enormous impact in mortality, multiplying it by 4 to 15 times [13]. In general, infections are involved in 80% of deaths caused by AP [14]. Mortality in patients without necrosis is nearly 0%, with sterile necrosis is between 0 and 11% [15], and with infected necrosis reaches 40% [16].

2. Antibiotic prophylaxis

Antibiotic prophylaxis in the setting of pancreatic necrosis refers to the use of antibiotics to avoid infection in severe AP. This issue has remained controversial for the last four decades. The most important questions raised are about antibiotic indications, antibiotic selection and length of treatment. Inappropriately selected or distributed over time antibiotics may carry complications such as anaphylaxis and selection of resistant bacteria. The later affects not only the patient, but also the hospital bacterial flora and the population around the hospital. The same subjects may be applied to the treatment of fungal infections.

Available studies are not conclusive although some have shown benefit from antibiotic prophylaxis. These last studies used different antibiotic drugs, different selection criteria, and different length of treatment. Also, definitions of severe disease varied between trials although in each the aim was to deliver antimicrobial prophylaxis to patients with severe AP and evidence of pancreatic necrosis. Duration of prophylaxis was relatively long (up to 14 days). All of these studies were small and several did not have sufficient power to assess the effect of antibiotics on mortality rate. Combination of the numbers observed in these studies suggests that there may be a significant reduction in complications and deaths in patients with predicted severe AP treated with prophylactic antibiotics (Table 1), but this ignores the major inconsistencies within and between these trials [17-21]. The difficulties of interpretation were examined in detail in a Cochrane review [22]. There were variations in the findings between studies, which also had different end points. This heterogeneity makes meta-analysis less reliable and indicates the need for further double blind randomised controlled trials.

Table 1. Antibiotic treatment, duration and results [14, 17-21]

Reference	Agent	Duration (days)	Pancreatic infection (%)		Deaths (%)	
			Treat	Control	Treat	Control
Pederzoli	Imipenem	14	12.2	30.3	7.3	12.1
Sainio	Cefuroxime	14	30	40	3.3	23.3
Delcenserie	Ceftazidime, amikacin, metronidazole	10	0	25	9	25
Schwarz	Ofloxacin, metronidazole	>10	61.5	53.8	0	23.1
Nordback	Imipenem/ cilastatin	Non	8	42.4	8	15.2
Isenmann	Ciprofloxacin, metronidazole	14	12.1	8.9	5.2	7.1
All			17.4	28.8	5.6	14.7

Early studies on antibiotic prophylaxis did not show benefit, probably because the selected antibiotic, ampicilin, has not good pancreatic tissue diffusion (Table 2), [23-25] although the trial of Finch et al was a well designed, randomized, double blind study (unrepeated for the following 30 years). More recently, several others prospective trials, using broad-spectrum antibiotics with good pancreatic diffusion, have shown a significant decrease in the infection rate of pancreatic necrosis [18], sepsis incidence [16] and mortality rate compared with patients not receiving antibiotic prophylaxis (Table 3) [20]. A meta-analysis including eight trials showed a significant reduction in mortality for patients with severe pancreatitis receiving antibiotics with adequate spectrum and diffusion, although not all of the assays achieve the same conclusion because of inadequate sample size [28]. The authors, supporting this meta-analysis as an alternative to a difficult, expensive, multicentric prospective randomized trial, concluded that it is recommended that all patients with severe AP be treated with broad-spectrum antibiotics that achieve therapeutic levels in pancreatic tissue (Figure 2). Since there is not evidence of benefit in patients with mild, edematous AP, the use of antibiotics is not recommended in these cases.

Notwithstanding this recommendation, drug choice and length of treatment for prophylaxis are not clearly determined [29]. Main mechanism of pancreatic infection is early bacterial translocation from bowel [30] even though other sources are possible such as biliary tract, venous catheters, etc. accounting for the presence of Staph. aureus, enterococcus and fungi. The frequency of fungi may be increased by the use of broad-spectrum antibiotics [31]. The more frequent infectious agents are shown in Table 4 [32]. Monobacterial infection occurs in 55-60% of cases of infected necrosis, the rest being multibacterial. In pancreatic abscess multibacterial infection is more frequent.

Fungal infections are increasingly being recognized. Candida is the most common agent. Fungal infection increases incidence of systemic complications and mortality. Important risk factors for fungal infection include broad-spectrum antibiotics, prolonged hospitalization and surgical/endoscopic interventions, use of total parenteral nutrition and mechanical ventilation. The pathogenesis of fungal infection in patients with AP is multifactorial: translocation of microorganisms across the gut epithelium, lymphocyte dysfunction and virulence of the invading microorganisms. The gold standard for diagnosis of fungal infection is histological

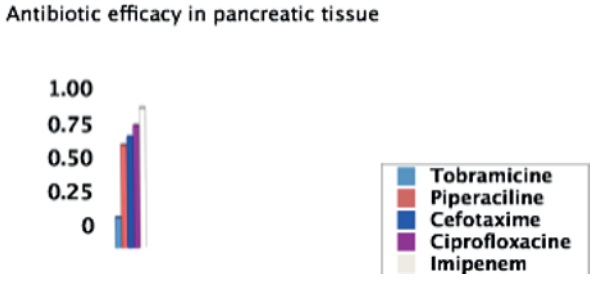

Figure 2. Antibiotic efficacy in pancreatic tissue

Table 2. First studies in prophylactic antibiotics

First Period (1970)	Study	Antibiotic	Results
Howes R et al. J Surg Res 1975 [23]	Random	Ampicilin vs. control	= infect = mortal
Craig RM et al. Ann Intern Med 1975 [24]	Random	Ampicilin vs. control	= infect = mortal
Finch WT et al. Ann Surg 1976 [25]	Random Double blind	Ampicilin vs. control	= infect = mortal

Table 3. Second period in prophylactic antibiotics

Second Period (1990)	n	Antibiotic	Study	Inclusion	Comments (Weakness)	Results
Pederzoli P et al. Surg Gynecol Obstet 1993 [18]	74	Imipenem	RCT A vs. control	Biliary, alcoholic, idiopathic Necrosis > 30%	No blind Random bias Delayed Prophylaxis	- **infect** = mortal
Luiten EJ et al. Ann Surg 1995 [27]	102	Ampicillin	RCT Descontaminac vs. control	Grave concerning CT o Imrie score	No blind No atb IV	= infect = mortal
Sainio V et al. Lancet 1995 [20]	60	Cefuroxime	RCT A vs. control	Alcoholic Necrosis PCR > 120		= infect - **mortal**
Delcenserie R et al. Pancreas 1996 [14]	23	Ceftazidime+ Amikacine + Metronidazole	RCT A vs. control	Alcoholic Severe concerning CT	No blind Alcoholic **N**	- **infect** = mortal
Schwarz M et al. Dtsh Med Wochenschr 1997 [21]	26	Ofloxacin + Metronidazole	RCT A vs. control	Biliary, alcoholic, idiopathic	No blind **N**	= infect = mortal
Bassi C et al. Gastroenterology 1998 [22]	60	Imipenem vs. Pefloxacin	RCT A vs. A		No blind Pefloxacin	- **infect** = mortal
Nordback I et al. J Gastrointest Surg 2001 [17]	58	Imipenem (immediate vs. delayed)	RCT Imp vs. Imp		No blind Timing started	- **surgery** = mortal

Table 4. Etiologic agents in infected acute pancreatitis

Etiologic agents		Percentage
Gram-negative bacilli	Escherichia coli	25-35%
	Klebbsiella spp	10-25%
	Enterobacter spp	3-7%
	Proteus spp	8-10%
Other gram-negative bacilli	Pseudomonas spp	11-16%
Gram-positive cocci	Staphylococcus aureus	14-15%
	Enterococcus spp	4-7%
Anaerobius		6-16%
Yeast		36%*

exam, but a positive biopsy is rare. Therefore, therapy must begin when diagnosis is suspected. The number of fungal infections was not significantly different (4% with therapy versus 4.9% in controls) in the aforementioned Cochrane review [22]. In a recent report including 50 patients, 18 of them with fungal infection experienced more frequent respiratory failure and hypotension, longer hospital stay and longer ventilatory assistance than the others. Independent risk factors were antibiotic treatment for longer than four weeks and hypotension [33]. Other authors reported a similar fungal infection rate (37%) and did not find risk factors nor increased mortality for patients with fungal infection. Eighteen patients out of 46 were treated and only 3 of them developed fungal infection [34].

In trials, prophylaxis has usually been administered for a defined period (Table 1). If antibiotic prophylaxis is used, it seems sensible to limit the duration of prophylaxis to 7–14 days. Treatment should not be continued beyond that time without evidence of infection provided by bacterial growth on culture. When such evidence exists, appropriate antibiotic therapy should be guided by the results of sensitivity testing in accordance with critical care medicine guidelines [36]. Limited use of broad-spectrum antibiotics, early introduction of enteral nutrition, and timely change of vascular catheters are important preventive strategies.

Even among proponents of prophylaxis there is little agreement on either the choice of agent or the duration

Table 5. Adequate antibiotic pancreatic tissue and fluid penetration

References	Antibiotic
Brattström, 1989 [38] Büchler, 1992 [39] Bassi,1994 [4] Minelli, 1996 [40]	Imipenem
Wittau, 2006 [41]	Ertapenem
Brattström, 1987 [42] Büchler, 1992 [39] Pederzoli, 1987 [43] Isemann, 1994 [44] Adam, 2001 [45]	Ciprofloxacin
Brattström, 1987 [42] Büchler, 1992 [39] Pederzoli, 1987 [43]	Ofloxacin
Bassi, 1994 [4] Malmborg, 1990 [46] Bertazzoni, 1996 [47]	Pefloxacin
Wacke, 2006 [48]	Moxifloxacin
Büchler, 1992 [39] Bassi, 1994 [4] Wallace, 1986 [49] Büchler 1989 [50]	Metronidazole
Brattström, 1988 [51]	Clindamycin
Martin, 1997 [52]	Ceftriaxone
Drewelow, 1993 [53]	Ceftazidime
Delcenserie, 2001 [54]	Cefepime
Wallace, 1984 [55]	Chloramphenicol
Wallace, 1986 [49]	Trimethoprim sulfometoxazole
Shrikhande, 2000 [56]	Fluconazole

of therapy. Although concerns have been expressed about the risk of encouraging selective growth of resistant organisms, the results of bacterial culture of fine needle aspirates from areas of pancreatic necrosis in the randomised trials reported to date have not addressed this issue. As the risk of infected necrosis and infection in the peripancreatic tissue is very small when there is less than 30% of pancreatic necrosis, prophylactic antibiotic therapy should be considered only for patients with CT evidence of more than 30% pancreatic tissue necrosis.

Starting of treatment is also controversial. It is accepted to initiate it after surgical necrosectomy, even without a microbiological diagnosis [36].

A more recent trial that compared ciprofloxacin/metronidazole and placebo did not support the use of prophylactic antibiotics [19]. This study was stopped after interim analysis of 76 patients with necrosis (of a total of 114 patients randomised) showed no differences in the primary outcomes of infected necrosis, systemic complications, and mortality rates. However, infectious complications, multiple organ failure, sepsis, or SIRS occurred in only 28% of patients who received antibiotics compared with 46% of the placebo group. All patients with these features received treatment with antibiotics. Other multicentric, double blind, randomized trial comparing meronem and placebo showed no statistically significant difference between the treatment groups for pancreatic or peripancreatic infection, mortality or requirement for surgical intervention, and did not support early prophylactic antimicrobial use in patients with severe acute necrotizing pancreatitis [37] (Table 5) [4,18,32,38-56].

Last Cochrane review analysed 7 trials recruiting 404 patients randomized to receive antibiotics or placebo. Although death occurred less frequently after antibiotics (8.4%) than placebo (14.4%), as did infected pancreatic necrosis (19.7% vs. 24.4%) and other infections (23.7% vs. 36%), differences were not statistically significant and thus genuine benefit could not be confirmed. There were no major problems with antibiotic resistance and fungal infections were similar (3.9% versus 5%). Many different regimens were used, and of the two main types of antibiotics used, beta-lactam appeared to work better than quinolone plus imidazole. Only one type of antibiotic (imipenem) showed a significant decrease in infection of pancreatic necrosis [57].

Among the existing meta-analyses, only one showed a significant reduction in the mortality rate with antibiotic prophylaxis. Most of them concluded that administration of antibiotic prophylaxis is not recommended (Table 6) [57-65]. In the paper by Wittau et al, 14 trials were included with a total of 841 patients [66]. The use of antibiotic prophylaxis was not associated with a statistically significant reduction in mortality, incidence of infected pancreatic necrosis, incidence of nonpancreatic infections, and surgical interventions.

There remains no consensus view on the value of antibiotic prophylaxis and current academic opinion tends to be unfavourable for antibiotic prophylaxis for severe AP. In summary, to date there is no evidence that supports the routine use of antibiotic prophylaxis in patients with severe AP.

Table 6. Meta-analyses of RCT in 2nd and 3rd period.[53, 56-62]

RCT in 2nd and 3rd period	N studies (patients)	Criteria	Infection	Surgery	Mortality
Heinrich S et al. Ann Surg, 2006 [58]	5*	RCT Ab vs. control	**ns**		Yes
Villatoro E et al. Cochrane Database, 2006 [57]	5* (294)	RCT Ab vs. control	**ns**	**ns**	Yes
Mazaki T et al. Br J Surg, 2006 [59]	6* (329)	RCT Ab vs. control	**ns**	**ns**	**ns**
Xiong GS et al. Med Princ Pract, 2006 [60]	6* (338)	RCT Ab vs. placebo	**ns**	**ns**	**ns**
Hart Pa et al. South Med J, 2008 [61]	7** (429)	RCT Ab vs. placebo	**ns**	**ns**	**ns**
Bai Y et al. Am J Gastroenterol, 2008 [62]	7** (467)	RCT Ab vs. placebo	**ns**		**ns**
Xu T et al. Scand J Gastroenterol, 2008 [63]	8** (540)	RCT Ab vs. placebo	**ns**	**ns**	**ns**
Jafri NS et al. Am J Surg, 2009 [64]	8** (502)	RCT Ab vs. placebo	**ns**	**ns**	**ns**
Jiang K et al. World J Gastroenterol, 2012 [65]	7** (439)				

3. Antibiotic selection in infected acute pancreatitis

Ideal antibiotic, for treatment or prophylaxis, should get a good penetrance into pancreatic tissue and fluids (Table 5) and cover bacterial flora most frequently contaminating them. After the paper by Wallace et al in the 80's on antibiotic diffusion into pancreatic juice, [55] Büchler studied some of these drugs concentration in blood and pancreatic tissue and found high concentrations for ciprofloxacin, ofloxacin and imipenem; also pefloxacin and metronidazole achieved inhibitory concentrations for most of the sensitive bacteria [26].

Three questions arise when we have to select an empirical treatment: Which one is more adequate for bacterial flora and bacterial resistance in our hospital? When we must begin the treatment? For how long we keep the drug without clinical or microbiological demonstration?

Selected antibiotic should be a broad-spectrum one, being carbapenems those of choice [65,66]. They should be initiated "on demand" (Table 7) and kept no more than 14 days without microbiological demonstration of infection. When comparing prophylaxis and on demand use of ciprofloxacin and metronidazole, Iganatavicius et al concluded that the use of prophylactic antibiotics does not affect mortality rate, but may decrease the need for interventional and surgical management and lower the number of reoperations, [67] while other authors only recommend on demand use of antibiotics [68].

In summary, antibiotic treatment using carbapenems and quinolones is indicated on demand in patients with severe AP and multiorgan failure at admission and in those with hemodynamic shock. Antibiotics are also useful in patients with biliary AP, clinically acute cholecystitis and/or cholangitis, bacteremia, positive bronchoalveolar lavage, and urinary tract infection [69]. Antibiotics of choice are imipenem, meronem or tigecycline in patients allergic to beta-lactams. Fluconazole must be given if surgery is performed, if fungal isolation

Table 7. Treatment "on demand"

Indications for antibiotic treatment "on demand" in patients with necrotizing pancreatitis
Newly developed sepsis /SIRS
Newly developed multiple organ failure, ESAP
Extrapancreatic infection: pneumonia, UTI, intraabdominal infection, sepsis without known focus
After surgery for pancreatic infection to prevent persistence of systemic sepsis

** Isenmann et al. 2004 is included ** Insemann et al. 2004 and Dellinger et al. 2006 are included*
Ns: no significance. RCT: randomized control trial. Ab: antibiotic
SIRS: Systemic Inflammatory Response Syndrome; ESAP: Early Severe Acute Pancreatitis; UTI: Urinary Tract Infection

in blood, drainaged fluids or tissue is obtained or when clinical improvement is followed by the complications described in the treatment on demand.

4. Conclusion

The evidence to enable a recommendation about antibiotic prophylaxis against infection of pancreatic necrosis is conflicting and difficult to interpret. Although there is no consensus on this issue, the routine use of antibiotics as prophylaxis against infection in severe AP is not recommended. Treatment on demand seems to be the better option, avoiding excessive treatment and selection of bacterial.

Conflict of interest statement

Authors state no conflict of interest.

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