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ACUTE NECROTIZING PANCREATITIS: PATHOGENESIS ANTIBIOTIC PROPHYLAXIS AND MANAGEMENT

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ABSTRACT

Acute necrotizing pancreatitis (ANP) can have severe complications and high mortality despite treatment. The main causes of acute pancreatitis (AP) are gallstones, alcohol abuse, hypercalcemia, hypertriglyceridemia and various types of drugs. Of ANP infected necrosis and abscess involve enteric bacteria with *Escherichia coli* most common followed by *Staphylococci* and *enter ococci* included. Infecting micro flora can be monomicrobial or polymicrobial. Mortality in severe ANP up to 50% duringthe first weekis associated with multiple organ failure due to systemic infections. Prophylactic antibiotics in ANP are controversial. Some data prior to last negative trial of meropenem suggested the use of antibiotics if computed tomography (CT) scan showed more than 30% necrosis of pancreas. Recent data 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. More trials are needed to confirm whether prophylactic antibiotics are beneficial in ANP.

KEYWORDS: Acute Pancreatitis, Pancreatic Necrosis Mortality, Antibiotic Prophylaxis

INTRODUCTION

Acute pancreatitis (AP) or acute necrotizing pancreatitis (ANP) is a sudden inflammation of the pancreas. It can have severe complications and high mortality despite treatment. Most episodes of AP are associated with gallstones, or alcohol abuse. Other causes of AP are hyperkalemia, hypertriglyceridemia, anatomic abnormalities, familial syndromes, autoimmune disease, ischemia, pancreatic carcinoma, trauma, endoscopic retrograde cholangiopancreatography (ERCP) and drugs, among which are antimicrobial agents such as tetracycline, pentamidine, sulfonamides, didanosine, ertythromyc in, nitrofurantoin and metronidazole.[1,2]. Annual incidence of AP in USA is 18 per 100,000 population. In a European cross-sectional study, incidence of AP increased from 12.4 to 15.9 per 100,000 annually from 1985 to 1995, mortality remained stable as a result of better outcomes. Another study showed a lower incidence of 9.8 per 100,000 but a similar worsening trend increasing from 4.9 in 1963 to1974 [3,4]. Severe forms represent the 14 % only of all AP but mortality 20 % and morbidity 47 %. Data from other series coming from Europe and USA shows a percentage of severe forms little bit superior- 15- 25 % with related mortality up to 50 % [5]. Another study reported that acute necrotizing pancreatitis is associated with mortality rate of 30 % to 40 %. Twenty percent of deaths occur during the first week of illness, in the setting of this inflammatory milieu and associated with multiple organ failure due to systemic infectious complications [6] Infection of necrosis accounts for a major cause of death in the late phase of the disease, in general after second week when most deaths are the sequel of ongoing sepsis and septic multiple organ failure [7]. Approximately 40-75% of patients with ANP develop complications related to infection, 24% in the first week and 71% after third week of illness. These complications due to infection are responsible for up to 80 % of deaths in patients with AP [8,9]. The role of antibiotics in ANP is controversial. One recent expert opinion prior to last negative trial of meropenam suggested the use of antibiotics if

computed tomography (CT) scan showed more than 30 % necrosis of the pancreas [10]. Dellinger *et al* 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 [11]. This paper reviews, pathogenesis, antibiotic prophylaxis, and management of ANP.

ACUTE PANCREATITIS

Most common symptoms include: loss of appetite, diarrhea, fever, chills hemodynamic instability including shock, tachycardia, respiratory distress and peritonitis. Approximately 80 % of patients have mild disease; and most of these patients recover uneventfully. Pancreatic and peripancreatic necrosis are minimal. Approximately 20 % have severe pancreatitis with pancreatitis or peripancreatitic necrosis or pancreatitic fluid collections [12,13]. Classically the term *pancreatic pseudocyst* has been used to refer to all intrapancreatic and peripancreatic fluid collections, usually within a non-epithelialized capsule, arising in the setting of acute or chronic pancreatitis[14].

Pathogenesis

Researchers suggest that infection increases mortality rates. In one series of 114 patients with pancreatic necrosis, intestinal microorganisms were cultured from necrotic tissues in 39.4% of cases. Mortality rate in patients with less than 50% gland necrosis rose from 12.9% to 38.9% if the necrotic tissue was infected, while mortality rates in patients with more than 50% necrosis rose from 14.3% to 66.7 % in the presence of infection. Of note, other studies have reported that mortality rates among patients with sterile necrosis are equal to those with infected necrosis.[15,16]. Definitions derived from the International Symposium on acute Pancreatitis,1992 [17] include: acute pancreatitis, severe pancreatitis, acute fluid collection, pancreatic necrosis, acute pseudo cyst, and pancreatic abscess. Several pathways of bacteria spread into pancreatic necrosis have been described: (a) hematogenous*via* the blood circulation;(b) ascending infection from the duodenum via the pancreatic duct;(c) from the portal vein and the liver *via* the biliary duct system; (d) trans colonic migration *via* lymphatic system [18]. The latter pathway is most important route with many *in vitro* and *in vivo* studies which clearly support this mechanism [17].

Infection and Infecting Micro Flora

In mild pancreatitis infection is rare, severe pancreatitis is associated with infection rate as high as 70 % [19]. Local infection may rise in necrotic pancreatic and peripancreatitic tissue without significant pus collection. The incidence of infection increases with the extent of necrosis and with time [20,21]. In one study, 49 % of infections in necrotizing pancreatitis developed within the first two weeks of illness, while 71 % of infections developed within the first three weeks of illness[16]. Another group reported the incidence of infection was highest among patients undergoing surgery 15 to 21 days into illness [15].

Pancreatic infection, including both infected necrosis and abscess usually involves gastrointestinal flora, including aerobes and anaerobes. Most commom gram negative (*Escherichia coli* and *Klebsiella* species, less commonly *Enterobacter, Pseudomonas, Proteus* and others) and less common gram positive (*enterococci, streptococci, and staphylococcal* species) bacteria participate and infection can be monomicrobial or polymicrobial. In a collected series of 45 articles, representing more than 1100 cases of secondary pancreatic infection the responsible organisms were *E.coli* (35 %), *Klebsiellapneuminiae* (24%), *Enterococci* (24%), *Staphylococcus* (14% and *Pseudomonas* (11%) [22]. Another study group reported that a great majority of patients infection is monomicrobial flora in 77.3 % and rest was 22.7%, polymicrobial of microbiological isolates from 22 patients, *E.coli* (25.9%), *Pseudomonas a eruginosa* (15.9%), *Staphylococcus aureus* (!5.3%,*Klebsiella*spp (10.1%) and with anaerobes bacteria accounting, for 15.8 %. All these

patients with infected necrosis and stressed the clinical relevance of occurrence of *Xantomonasmaltophilia* (3%) in pancreatic infection with mortality 100% [23]

One group has reported different microbiology of infected pancreatic necrosis in alcoholic and biliary pancreatitis among 70 patients with similar degrees of necrosis, who underwent surgery for pancreatitis These authors note a higher rate of infection overall and preponderance of gram- negative organisms in biliary disease patients [24]. Early exposure to broad spectrum antimicrobial therapy changes the flora that cause infections, and increasingly resistant infections and fungal infections have become more common [25]. One report includes prospective data on 57 patients (12%) developed either pure fungal infection or mixed fungal infection and bacterial infection; isolates were *Candida albicans* and *Torulopsis glabrata*, detected an average of 36 (range 18 to 80) days after onset of pancreatitis. Among these patients, four of seven had "primary "fungal infection" that developed in the absence of prior operative interventions. Fungal infection was associated with ERCP as the cause of AP (*P*=.02) and with exposure to parental nutrition and broad spectrum antibiotics [26]. Another group observed fungal infections in 17 of 46 patients (37%) with infected necrosis over 8 years period. There was no mortality difference attributable to fungal infection. A lower rate of fungal infection without mortality benefit was noted in a subset of 18 patients who received prophylactic antifungal treatment [27].

AP is diagnosed clinically, with positive imaging, and blood tests, blood tests are mainly amylase, lipase, levels, serum calcium and glycosuria. If the lipase level is about 2.5 to 3 times that of amylase, with decreased serum calcium and glycosuria, it is indication of pancreatitis due to alcohol [28].

AP Classification by Severity

Multiple criteria have been suggested as predictors of survival. Two such scoring systems are the Ranson and APACHE 11(Acute physiology and chronic health evaluation) indices. Most, studies but not all studies report that Apache score may be more accurate. In the negative study of Apache, the Apache 24 hr. score used rather 48 hours score. The Apache 11 can be fully calculated upon admission. As the Apache 11 is more cumbersome to calculate, presumably patients whose only laboratory abnormality is an elevated lipase do not need prognostication with Apache 11; however the approach is not studied.; The Apache 11 score can be calculated at

www.sfar.org (http://www.sfar.org/scores2/apache22html) [29,30].

Ranson Criteria

Ranson criteria are a clinical prediction tool for predicting the severity of acute pancreatitis. It was introduced in 1974. The criteria for point assignment is that a certain breakpoint be met at any time during 48 hour period, so that in some situations it can be calculated shortly after admission. It is applicable to both gallstone and alcoholic pancreatitis.

Ranson's score of ≥8 sgnifies substantial pancreatitic necrosis at least 30 % glandular necrosis according to contrast-enhanced CT, and predicts organ failure.

Interpretation If Score ≥3, severe. If score < severe pancreatitis unlikely or

Score 0-2: 2% mortality Score 3 to 4: 15% mortality Score 5 to 6:40% mortality Score 7-8:100% mortality [2,31]

APACHE 11

"Acute Physiology And Chronic Health Evaluation" (APACHE 11) score > 8 points predicts 11% mortality to 18% mortality. [3].

Balthazar Score

Developed in the early 1990s by Emi J. Balthazar *et al*, the computed Tomography Severity Index (CTSI) is a grading system used to determine the severity of acute pancreatitis. The numerical CTSI has a maximum of ten points, and is the sum of the Balthazar grade points and pancreatitis necrosis grade points [33].

Balthazar Grade

Grade A: Normal CT, 0 points, Grade B; Focal or diffuse enlargement of the pancreas points.

Grade C; Focal gland abnormalities and test pancreatitic inflammation 2 points.

Grade D; Fluid collection in a single location 3 points.

Grade E; Two or more fluid collections and /or gas bubbles in or adjacent to pancreas 4points.

Necrosis Percentage

0 points –No necrosis, 2 points- 0-30% necrosis, 4 points-30 –to 50% necrosis, diagnostic points-> 50% necrosis

CTSI staging of acute pancreatitis severity has been shown by a number of studies to provide more accurate assessment than APACHE 11, Ranson and C-reactive protein (CRP) level [34-36].However, a few studies indicate that CTSI is not significantly associated with the prognosis of hospitalization in patients with pancreatic necrosis, nor is it and accurate predictor of AP severity [37].

PROPHYLACTIC ANTIBIOTICS

Recent studies suggested benefit of antibiotic prophylaxis to prevent infectious complication but the topic is complex [38]. Earlier studies did not indicate favorable effects on outcome of AP[39].

The reasons for these negative results: (a) studies were conducted before CECT era; (b) many of the included patients had edematous pancreatitis; (c) use of ampicillin that subsequent studies showed to be unable to reach pancreatic necrosis [17].

Several groups had evaluated antimicrobial penetration into pancreatic tissue. In human studies, antibiotic levels in pancreatic tissue and fluid tend to correlate with degree of inflammation; thus higher levels occur in patients with pancreatitis than in members of control groups [40]

In general antibiotics can be assigned to the following categories: (1) poor pancreatic penetration (aminoglycosides, first-generation cehalosporins, cefotoxin, and ampicillin; (2) variable pancreatic penetration, reaching minimum inhibitory concentration (MIC) for some but not all relevant organisms, (mezlocillin, not available in the United States), pipercillin and cefotaxime); and (3) pancreatic penetration reaching MIC for most relevant organisms fluoroquinolones, imipinem, ceftazidime, cefepine, metronidazole, clindamycin, chloramphenicol, doxycycline and fluconazole[41]

One group developed an **efficiency factor** incorporating each drug's pancreatic penetration, with a factor 1.0 considered optimal. The efficiency factors were 0.98 for imipenem, 0.86 to 0.87 for fluroquinolones, and 0.71 to 0.78 for pipercillin and third generation cephalosporin [42].

Dellinger *at al*, recently presented the results of a randomized, double blind, placebo-controlled, multicenter trial with meropenem prophylaxis in 100 patients with severe acute pancreatitis, including 57 patients with 30 % pancreatic

necrosis. This trial failed to demonstrate a beneficial effect of meropenem prophylaxis on infection of pancreatic necrosis and mortality [10].

An international group of renowned pancreatologist in 2004 recommended against the routine use of prophylactic systemic antibacterial or antifungal agents in patients with necrotizing pancreatitis. The main reason for this was the inconclusive evidence and divided expert opinion [43]

Schwarz *et al*, published only in German, which favored antibiotic prophylaxis. In contrast, the authors did not include 2 randomized controlled Czech trials of Spicak*et al*, both of which failed to show an effect of antibiotic prophylaxis [44-46].

Rokke et al,[47] showed that antibiotic prophylaxis with imipenem in patients with severe pancreatitis (CRP >120 at 24hrs or CRP >200 at 48hrs) reduced the complications and incidence of infections. There was no significant difference in length of stay, need for intensive care, need for surgical intervention or 30 day mortality.

Another group demonstrated that a role for prophylactic antibiotics in ANP. Until we are able to demonstrate an advantage of antibiotic prophylaxis in a high-risk human population, the absence of proven benefit and potential side effects of this strategy should be acknowledged and the use of antibiotics should be limited to the treatment of documented infection

Isenmann *et al* [48], conducted the first double blind trial of antibiotic prophylaxis in ANP and found no significant difference 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 placebo 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 antibiotic group were resistant to ciprofloxacin. Moreover, infections that developed in the placebo group were expeditiously treated, thus due to which a reduction in mortality by another antibiotic prophylaxis may not be evident.

In a recent meta-analysis 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 center trials in single blind trials but not in multicenter or double blind trials [49]. In another meta-analysis of 502 patients from 8 studies showed no benefit of antibiotics in decreasing mortality or morbidity in severe acute pancreatitis [50].

MANAGEMENT AND TREATMENT

Infection of pancreatic necrosis in severe AP indicates a surgical approach as soon as possible[51]. Although some groups have reported successful medical management of infected necrosis, most believe that thorough surgical debridement of infected necrosis and removal of all associated collections are necessary[52]

No studies have evaluated the optimal timing of surgery for infected necrosis in particular, but one randomized clinical trial studying patients with severe necrotizing pancreatitis found a trend toward higher mortality (58% vs. 27 %) associated with early surgery [53].

The role of surgery in the management of sterile necrosis is more controversial. Some believe that a subset of patients with severe sterile necrosis that has organized over the course of a prolonged illness (4 to 6 weeks or more) may benefit from surgical debridement [54]

Nordback *et al,* report a very interesting trial on the utilization of antibiotics (imipenem 3g/day) for the prophylaxis of pancreatic infection. They found a significant reduction of the pancreatic infection rate in the treated group (8% vs 42 % of the control group) but, more interesting 9 out of 14 patients without prophylaxis who develop an infection were cured with imipenem without surgical debridement [55].

CONCLUSIONS

Antibiotic prophylaxis in ANP is an unending debate. Some studies recommend the use of prophylactic antibiotics in ANP. Recent data available from a double blind placebo controlled study found no significant difference between the outcome of two groups of patients with ANP, another receiving meropenem and other placebo. Meta-analysis also failed to show benefit.

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