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Analysis of Antibiotic Therapy in Acute Severe Pancreatitis

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Abstract

Background: Acute Pancreatitis is a common surgical entity that is increasing in incidence. Gallstones and alcohol consumption remain the major contributors of Acute pancreatitis. The disease usually follows a prolonged course with increased hospital stay, early and late complications contributing to increased patient morbidity and mortality. Traditionally the role of antibiotics is usually limited to severe necrotising pancreatitis. There is however increasing evidence to prove the role of antibiotic therapy in reducing mortality and long term morbidity in acute pancreatitis patients.

Objectives:

1. To retrospectively analyse antibiotic therapy in patients with Acute severe pancreatitis in the years 2014 - 2017 in the tertiary care hospital PSG IMSR located in Coimbatore, Tamilnadu, India
2. To analyse the role of antibiotics in patient prognosis and outcome

Type of study: Retrospective Observational study. *Duration of study*: January 2014-January 2017. *Methodology:* The present study was conducted in PSG Institute of Medical Sciences & Research, Coimbatore. We did a thorough retrospective analysis of case files of 900 patients with acute severe pancreatitis. Analysing the available data from case files. *Results*: Of 900 patients, 411satisfied the inclusion criteris, of these 63% (n=258) of patients were started antibiotics within 48 hrs of hospital admission. The first choice antibiotics were Piperacillin tazobactum and metronidazole in 45% of cases, Fluoroquinolones and metronidazole in 12% of cases and Cefaperazone sulbactum ± metronidazole in 14% of cases. In 26% of cases a combination of imipenem + Cilastatin was used. Antibiotic use did not improve survival, nor was there any observed survival benefit when the different antibiotic agents were compared (p = 0.7 and 0.4 respectively). The timing of antibiotic use also does not appear to confer a survival benefit (p = 0.5). All patients with proven pancreatic infection died, there was not a significant difference in survival in those with extra-pancreatic infections (p = 0.2).

Keywords: Acute Pancreatitis; Necrotising Pancreatitis; Severe Acute Pancreatitis; Antibiotic Prophylaxis; Retrospective Analysis.

Introduction

Acute pancreatitis is a common gastrointestinal emergency. Its incidence varies from 5 to 80 cases per 100,000 inhabitants per year, with an overall mortality rate of 10–15% [1]. More than two-thirds of patients will recover within 1 week, however the remaining one-third will experience multiple systemic and/or local complications, with a high mortality rate of 10–30%, 80% of deaths are due to infectious complications [2-3].

The use and efficacy of prophylactic antibiotic therapy in acute pancreatitis has long been debated. The role of prophylactic antibiotics to prevent infection and reduce mortality in pancreatitis was first evaluated in the 1970s, where several randomised controlled trials (RCTs) had been conducted and concluded that prophylactic antibiotics were effective in preventing secondary pancreatic infections and therefore in

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reducing the related mortality[4-6]. However, in recent studies, there have been multiple large controlled trials, with conflicting results [7-9], different consensuses reached and differing guidelines for the use of prophylactic antibiotics [10].

Acute Pancreatitis and its Management

Acute pancreatitis is complex disease. It ranges from a mild degree inflammation that lasts for few days to severe pancreatitis, which can lead to mortality, especially in the presence of multiple organ failure or severe pancreatic infections.

Severe pancreatitis progresses in two phases [11-12]. The early stage – the first 14 days from the onset of the disease – is characterised by a systemic inflammatory response syndrome (SIRS), which may be complicated by multiple organ dysfunction syndrome (MODS). In 15–20% of cases, this may be followed by a stage of secondary bacterial infection within the inflamed pancreas, typically 2–3 weeks from the onset of pancreatitis [13].

Pathogenesis of secondary bacterial pancreatic infection is still debated. Pathogens can reach the pancreas through the haematogenous pathway, the biliary system, ascending from the duodenum via the main pancreatic duct, or through transmural colonic migration via translocation of the colonic bacteria to the lymphatics. Most pathogens in pancreatic infection are gastrointestinal Gram-negative bacteria (Escherichia coli, Pseudomonas, Proteus, Klebsiella), which occur via disruption of the intestinal flora and damage to the bowel mucosa. Impaired body defences predispose to translocation of the gastrointestinal organisms and toxins with subsequent secondary pancreatic infection. But Gram-positive bacteria (Staphylococcus aureus, Streptococcus faecalis, Enterococcus), anaerobes and, occasionally, fungi have also been found [14-16]. Infection of sterile necrosis is attributed to bacteria of gut origin in up to 70% of cases [17].

Assessment of Severity and Prognosis

Tools have been developed to predict the severity of pancreatitis and the likelihood of complications and mortality. They have been shown to be superior to clinical judgment alone, and should be used in conjunction with typical clinical criteria, such as presence of comorbid conditions, age, and first episode of pancreatitis.

The Atlanta criteria use early prognostic signs, organ failure, and local complications to define disease severity [18-19] (Figure 1). Early prognostic signs include a Ranson score of 3 or greater, or an acute physiology and chronic health evaluation (APACHE II) score of 8 or greater. Organ failure is defined as shock, hypoxemia (partial arterial oxygen tension of 60 mm Hg or less), creatinine level greater than 2 mg per dL (177 μmol per L), or gastrointestinal bleeding (greater than 500 mL per 24 hours). Local complications include necrosis, abscess, or pseudocyst [20].

The Ranson score evaluates 11 factors within 48 hours of hospital admission to predict severity of pancreatitis and risk of mortality. However, the sensitivity for predicting poor outcome is only 70% [21]. The APACHE II scoring system uses 12 criteria to predict the severity of pancreatitis, with the risk of death increasing as the score increases. The CT severity index is based on CT findings at admission and evaluates for the presence of peripancreatic inflammation , phlegmon, and, if present, the amount of pancreatic necrosis. A total score of 5 or greater is associated with a statistically significant increase in morbidity and mortality.

Severity	*Criteria*
Mild	No organ failure
	No local complications (e.g., peripancreatic fluid collections, pancreatic necrosis, peripancreatic necrosis)
	No systemic complications
	Typically resolves in first week
Moderate	Transient organ failure (≤ 48 hours)
	or
	Local complications
	or
	Exacerbation of comorbid disease
Severe	Persistent organ failure (> 48 hours)

Fig. 1: Modified Atlanta Classification for acute pancreatitis (Column width)

Antibiotic Therapy in Acute Pancreatitis

The ideal drug to use should:

1. Have specific activity against the bacteria responsible for pancreatic infections
2. Be able to penetrate the pancreatic tissue, pancreatic exocrine secretions, and peri-pancreatic fluid/ exudates at therapeutic mean inhibitory concentrations
3. Be able to penetrate the pancreas during acute pancreatitis; and
4. Have a clear-cut clinical capacity to reduce the development of infected necrosis [22].

There is no evidence to support the previous criteria of ideal antibiotics, and physicians should realise that pancreatic infection normally starts in necrotic tissue. No antibiotics effectively penetrate necrotic tissue without blood supply, which makes pancreatic infections sometimes very resistant to antibiotics.

Imipenem, clindamycin, piperacillin, fluoroquinolones and metronidazole are known to have adequate tissue penetration and bactericidal properties in infected pancreatic necrosis, in contrast to penicillins, first-generation cephalosporins, aminoglycosides and tetracyclines, which are ineffective in acute pancreatitis [22]. Meropenem is shown to have as wide a spectrum as imipenem in preventing septic complications in acute pancreatitis [23]. The use of systemic antibiotics in pancreatic infections must be accompanied with drainage, either surgical or percutaneous.

One of the main problems of prolonged administration of antibiotics in severe acute pancreatitis is the development of multidrug resistance bacterial and fungal infection, which is associated with long hospital stay and poor outcome [24]. Hence, each case should be individually evaluated, weighing the benefits of antibiotics against the significant adverse events associated with their use, including increased bacterial resistance and fungal infections. Microbiologists with a specific interest in pancreatitis should be involved in such decisions, and blood culture is highly suggested as this might detect bloodstream infections associated with pancreatitis [25-26].

Objectives

1. To retrospectively analyse antibiotic therapy in patients with Acute severe pancreatitis in the years 2014 - 2017 in the tertiary care hospital PSG IMSR located in Coimbatore, Tamilnadu, India.
2. To analyse the role of antibiotics in patient prognosis and outcome.

Type of Study

Retrospective Observational study

Duration of Study

January 2014 - January 2017

Inclusion Criteria

1. Patient admitted in PSG hospitals coimbatore with the diagnosis of Acute pancreatitis (alcoholic and biliary) graded as Severe by Modified Atlanta classification.
2. Antibiotic therapy for the patients instituted within 48 hours

Exclusion Criteria

1. Post ERCP/Post operative pancreatitis
2. Non alcoholic non biliary pancreatitis
3. Mild and moderate pancreatitis

Methodology

The study was conducted in PSG IMS & R a tertiary care centre in southern India. There have been 900 patients admitted with the diagnosis of Acute Pancreatitis in the four year period considered for this study.

Among this the total number of cases that had Acute severe pancreatitis and had been given antibiotics wishing 48 hours were 411. These fit into the inclusion and exclusion criteria. Their data was analysed with their age , sex, alcoholic and gall stone pancreatitis, antibiotic instituted, duration if antibiotic and mortality.

The data was analyzed using Microsoft Excel

Results

Of 900 patients surveyed, 500 fit the inclusion and exclusion criteria. Of which 411 received antibiotics. 63% (n = 259) of patients were started antibiotics within 48 hrs of hospital admission. 37% (n=152) did not receive any antibiotics (Figure 2).

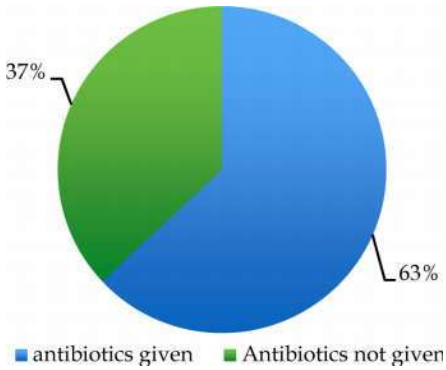

Fig. 2: Chart showing percentage of patients started on antibiotics vs Patients who did not receive antibiotics (Column width)

The first choice antibiotics were Piperacillin tazobactum and metronidazole in 45% of cases, Fluoroquinolones and metronidazole in 12% of cases and Cefaperazone sulbactum ± metronidazole in 14% of cases. In 26% of cases a combination of imipenem + Cilastatin was used (Figure 3).

Total mortality was 11 due to various complications negative bacilli as a causative organism.Antibiotic use did not improve survival, nor was there any observed survival benefit when the different antibiotic agents were compared (p = 0.7 and 0.4 respectively). The timing of antibiotic use also does not appear to confer a survival benefit (p = 0.5). It was, however, associated with a statistically significant reduction in hospital stay (p = 0.040). All patients with proven pancreatic infection died, there was not a significant difference in survival in those with extra-pancreatic infections (p = 0.2).

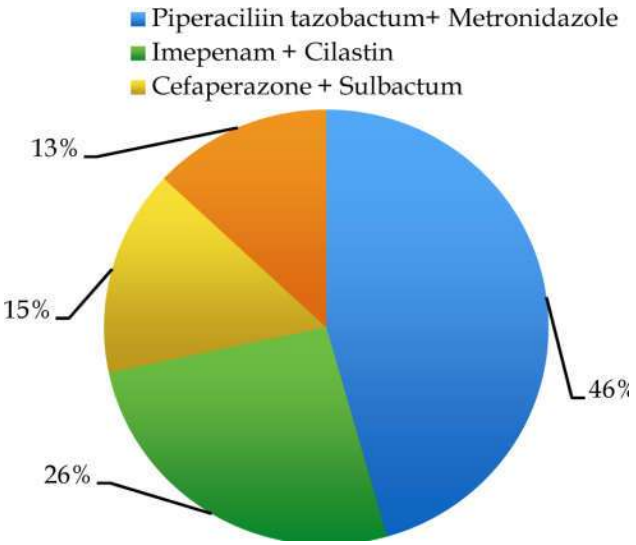

Fig. 3: Chart showing percentage of antibiotics used

Discussion

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 raise dare 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 [27-28]. The latter 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 [29-31].

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) [25-30].

The studies do not specify an appropriate antibiotic or duration protocol common to all. In our study we have found that while antibiotic use did not alter the mortality or survival benefit, it did alter the length of hospital stay and ICU admissions.

Conclusion

Evidence is accumulating to suggest that prophylactic antibiotics in patients with acute pancreatitis is not associated with a significant decrease in secondary pancreatic infection and mortality. We do not therefore recommend routine prophylactic antibiotic therapy for all patients with acute pancreatitis.

Table 1: Table showing patients surveyed in the year 2014 – 2017

Year	Total cases analysed (n=411)	Antibiotics given (n=259)	Antibiotics not given	Mortality
2014	126	80	46	3
2015	129	97	32	2
2016	130	71	59	4
2017	26	11	15	0

Table 2: Table showing sex, mean duration of antibiotics and mean duration of hospital stay in both groups and mortality in both groups

Patients surveyed (n=411)	Male (n=266)	Female (n=145)	Mean duration of antibiotics	Mortality
Patients who received antibiotics (n=259)	172	87	10	11
Patients who did not receive antibiotics (n=152)	94	58	Not applicable	0

Conversely, the prompt use of prophylactic antibiotics once a physician detects early markers associated with high risk of pancreatic infection is mandatory. These subset of patients with proven evidence of infection may benefit from easy antibiotic prophylaxis. Being able to identify biomarkers indicating pancreatic infection and whether they predict responsiveness to antibiotics would significantly enhance the clinical management of acute pancreatitis.

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