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Erstveröffentlichung in / First published in:

Viszeralmedizin. 2014, 30(5), S. 318 – 324 [Zugriff am: 29.04.2020]. Karger. ISSN 1662-6672.

DOI: https://doi.org/10.1159/000367948

Viszeralmedizin
Gastrointestinal Medicine and Surgery

Review Article · Übersichtsarbeit

Viszeralmedizin 2014;30:318–324
DOI: 10.1159/000367948

Published online: October 6, 2014

Antibiosis of Necrotizing Pancreatitis

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Keywords
Necrotizing pancreatitis · Antibiotics · Fungal infection · Microbiota

Schlüsselwörter
Nekrotisierende Pankreatitis · Antibotika · Pilzinfektion · Mikrobiota

Summary
Background: Necrotizing pancreatitis is a life-threatening presentation of acute pancreatitis. The mortality of 20–80% initially depends on the persistence of organ failure and systemic inflammatory response syndrome (SIRS) and, in the later course of the disease, on secondary infection of the necrosis. The questions whether prophylactic antibiotics aiming to prevent this infection should be administered and which antibiotic is the best to use, as well as the problem of fungal infection under antibiotic treatment are still intriguing and insufficiently solved. **Methods:** A search of the literature using PubMed was carried out, supplemented by a review of the programmes of the Digestive Disease Week (DDW) and the United European Gastroenterology Week (UEGW). **Results:** Despite the widely practised prophylactic antibiotic administration in severe pancreatitis, no evidence for the benefit of this strategy exists. One of the drawbacks might be a tendency for disastrous fungal infection under prophylactic antibiotics. Bacterial translocation from the gut in the second week after the onset of symptoms is the major source for infection of pancreatic necrosis and provides a clear indication for antibiotic treatment. However, routine fine-needle aspiration for a calculated antibiotic therapy cannot be recommended, and all other tests offer only indirect signs. Important factors such as enteral versus parenteral feeding and the method of necrosectomy are mostly neglected in the trials but seem to be essential for the outcome of the patient. **Conclusions:** Even though most meta-analyses including the newer double-blind, placebo-controlled trials on prophylactic antibiotics showed no beneficial effects in the prevention of infection of necrosis and/or outcome of the patients, this strategy is still widely used in clinical routine. Since nearly all trials published so far show systematic problems (i.e. inaccurate definition of the severity of the disease, poor statistical testing, and neglect of differences in the route of nutrition), there is a need for randomized controlled prospective trials with exact definitions of the disease.

Zusammenfassung
Hintergrund: Die nekrotisierende Pankreatitis weist eine Mortalität von 20–80% auf. Initial ist vor allem das Ausmaß des Organversagens entscheidend für die Prognose des Patienten. In der zweiten Krankheitswoche stellt dann die sekundäre Infektion der Nekrosen durch die Translokation von Darmkeimen das entscheidende Problem dar. Zur Vermeidung einer solchen Infektion werden klinisch sehr häufig Breitspektrumantibioktika prophylaktisch eingesetzt. Dies wird aber zunehmend kritisch diskutiert, und es existieren kontroverse Empfehlungen. **Methoden:** Eine Literaturrecherche unter Einbeziehung von PubMed und der Programme der Digestive Disease Week (DDW) und der United European Gastroenterology Week (UEGW) wurde durchgeführt. **Ergebnisse:** Die meisten Studien können den prophylaktischen Einsatz von Antibiotika bei der schweren Pankreatitis nicht rechtfertigen. Einige Studien belegen vielmehr eine Selektion resistenter Keime und vor allem auch eine erhöhte Rate von schwer therapierbaren Pilzinfektionen unter einer solchen Therapie. Daher sollte erst nach dem Nachweis einer Nekroseinfektion mit einer Antibiotikatherapie begonnen werden, wobei keine Routine-Feinnadelpunktion der Nekrose zum Keimnachweis durchgeführt werden sollte. Es stehen daher nur indirekte, meist bildgebende Verfahren für den Infektionsnachweis zur Verfügung. Entscheidende Faktoren wie die enterale Ernährung und die Methode der Nekrosektomie wurden bisher bei den meisten Studien vernachlässigt, scheinen aber essenziell für das Behandlungsergebnis des Patienten zu sein. **Schlussfolgerungen:** Die meisten publizierten Studien weisen eine sehr heterogene Definition der Erkrankung, uneinheitliche Behandlungsprotokolle und Ungenauigkeiten bei der statistischen Testung auf. Gerade entscheidende Faktoren wie die enterale Ernährung werden größtenteils komplett vernachlässigt. Es besteht daher ein Bedarf für randomisierte placebokontrollierte Studien, die diese Probleme berücksichtigen und suffiziente Schlussfolgerungen zur Antibiotikatherapie der schweren Pankreatitis zulassen.

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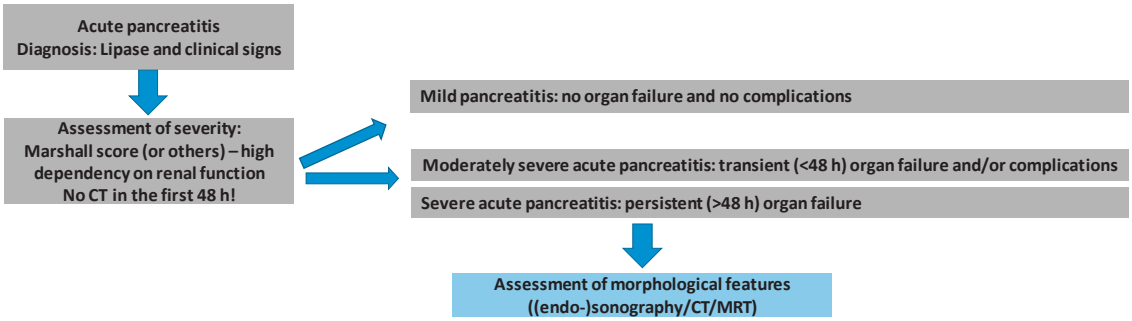
Introduction

Acute pancreatitis is one of the most common acute gastrointestinal diseases requiring hospitalization. The mortality rate of the disease is very heterogeneous, ranking from nearly 0% in case of a mild pancreatitis up to 80% in cases of a severe necrotizing pancreatitis [1]. The revision of the Atlanta classification (schematic presentation given in fig. 1) recently addressed this aspect of very diverse subgroups and defined three grades of severity for acute pancreatitis based on the presence and persistence of an organ failure and clearly described groups with regard to the presence/distribution of pancreatic necrosis [1]. Shortly after symptom onset, the presence of organ failure, e.g. renal dysfunction, determines the outcome of the patients [2] and can be used to stratify the patients in clinical treatment groups. In this initial phase of the disease, the presence of pancreatic necrosis is only of marginal importance for the treatment strategies even if the impact of the localization of the necrosis was highlighted in a recent manuscript, showing that patients with exclusive extrapancreatic fluid collections have a far better prognosis compared to those with parenchymal necrosis [3]. As mentioned above, the revised Atlanta classification defines necrotizing pancreatitis by the presence of either pancreatic parenchymal or only peripancreatic necrosis [1]. In approximately 30% of the patients an infection of the necrosis occurs [3], requiring intervention and resulting in a worse prognosis compared to the patients without infected necrosis. Prophylactic antibiotic administration is widely practised. However, there is a plethora of contradicting data for such an approach. First of all, there is no clear evidence that prophylactic antibiotics improve the patient outcome. Furthermore, the problem of fungal infection under prophylactic antibiotic administration is still a matter of concern. Infection of necrosis is mostly defined by clinical signs. The value of routine fine-needle aspiration and/or systemic blood sampling for the detection of infection is still ambiguous. Finally, in the last couple of years, growing evidence indicates that the enteral route of feeding is able to prevent or at least to reduce infection of necrosis and that minimally invasive necrosectomy significantly influences the patient's outcome. This review will give an overview of the existing data concerning antibiotic therapy of necrotizing pancreatitis. Since there are several meta-analyses of prophylactic antibiosis, we will build on these reports. Thereafter, we highlight important aspects of antibiosis in pancreatitis and illustrate why the existing data fail to sufficiently support prophylactic antibiotic treatment strategies.

Recommendations for/against Prophylactic Antibiosis

Since most patients with severe acute pancreatitis clinically present with symptoms like fever and very high levels of inflammatory markers such as C-reactive protein (CRP) and procalcitonin [4–6], there is a tendency to administer broad-spectrum antibiotics in the initial phase of the disease despite existing guidelines [7, 8]. Besides the inflammatory markers and the clinical status of the patients, the knowledge that, in addition to organ failure, infection of the necrosis is the critical determinant for the prognosis of the patient leads to the assumption that a prophylactic antibiotic treatment could be beneficial [9].



Type of pancreatitis	Collections <4 weeks	Collections >4 weeks
Interstitial (85%)	APFC (acute pancreatic fluid collection) - sterile - infected	Pseudocyst - sterile - infected - no solid material
Necrotizing (15%)	ANC (acute necrotic collection) - solid material - parenchymal and/or peripancreatic tissue - sterile/infected	WON (walled-off pancreatic necrosis) - mature, encapsulated necrotic collection with well defined wall - sterile/infected - parenchymal/peripancreatic/distant from pancreas

Fig. 1. Schematic presentation of the diagnostic algorithm of the revised Atlanta classification [1].

Table 1. Summary of the meta-analyses discussed in this review

Author	Year	Necrosis infection	Non-necrosis infection	Length of stay	Survival mortality	Comments
Golub et al. [33]	1998	n.a.	n.a.	n.a.	+	only if broad-spectrum AB were used
Gumaste [35]	2000	+	n.a.	n.a.	n.a.	imipenem was the most promising AB
Sharma and Howden [31]	2001	(+)	n.a.	n.a.	+	general recommendation for AB
Mazaki et al. [29]	2006	–	–	+	–	
Villatoro et al. [27]	2006	±	n.a.	n.a.	+	beta-lactams also reduce infection
Xiong et al.[a] [26]	2006	–	n.a.	n.a.	–	
Bai et al.[a] [40]	2008	–	n.a.	n.a.	–	
Hart et al. [24]	2008	–	+	+	–	
Wittau et al.[a] [23]	2008	–	n.a.	n.a.	–	discussed the shortcomings of trials supporting AB
Xu and Cai [22]	2008	+	+	+	–	carbapenems are superior
Jafri et al. [20]	2009	–	+	–	–	
Segarra-Newnham and Hough [19]	2009	±	±	±	±	heterogeneity of trials; on demand use of AB after confirmation of infection
Villatoro et al.[a] [17]	2010	–	–	–	–	none of the studies were sufficiently powered
Yao et al. [16]	2010	+	–	–	–	
Wittau et al.[a] [12]	2011	–	–	n.a.	–	
Jiang et al.[a] [10]	2012	n.a.	n.a.	n.a.	–	subgroups might benefit

[a]Meta-analysis showing no beneficial effects of prophylactic antibiotics at all.
+ = Positive influence of prophylactic antibiotics; – = no effect of prophylactic antibiotics; n.a. = not analyzed; AB = antibiotics.

However, the data for the outcome of the patients receiving prophylactic antibiosis are conflicting. In this review, we will summarize meta-analyses and reviews on this issue [10–34] (please also refer to table 1 for a short summary of the included meta-analyses) and will not discuss the original data in detail.

Over the last decade, there was a change in the recommendation of prophylactic usage of antibiotics. Nearly all studies, meta-analyses, and reviews before 2004 showed the superiority of prophylactic antibiosis [31–33, 35]. Due to an improvement of the quality of the studies (e.g. more exact definition of severe pancreatitis and greater patient numbers enrolled) there was a shift to a more restrictive administration only after confirmation of infection of the necrosis. One of the landmark studies leading to this shift was one of the first placebo-controlled, double-blinded trials by Isenmann et al. [36]. This work showed no differences in the rate of infected pancreatic necrosis, systemic complications, or mortality between the placebo and the ciprofloxacin/metronidazole arm. However, as discussed later, the choice of antibiotics in this study could be questioned, and there are still meta-analyses and reviews that support a prophylactic antibiotic strategy [16–18, 22, 24, 27, 28, 31, 32]. Mostly depending on publication date, these studies either recommend prophylactic antibiosis because of a general outcome benefit (meta-analyses of studies before 2004) or they outline advantages for subgroups or specific problems without advantages regarding mortality. In 2001, Bassi et al. [32] concluded that prophylactic antibiotics reduce the incidence of infected necrosis and pancreatic abscesses during severe pancreatitis and that this approach was the only one tested at the time in several randomized studies. However, the authors suggested that a combination of broad-spectrum antibiotics, selective digestive decontamination, and enteral nutrition might be beneficial in severe pancreatitis [32]. For selective intestinal decontamination, there is a controlled clinical trial reporting a reduced mortality [37].

The route of nutrition might have influenced the patients' outcome in these trials on prophylactic antibiotic use, as discussed later. In the same year, another meta-analysis concluded that prophylactic administration of antibiotics with proven efficiency in necrotic pancreatic tissue should be given to every patient with severe pancreatitis because of a general reduction of sepsis and mortality in all patients [31]. The choice of the antibiotics might explain some of the controversy in the field as well as in meta-analyses. In 2006, a Cochrane review concluded that antibiotic prophylaxis significantly reduces mortality and infection of pancreatic necrosis when beta-lactams were used [27]. Quinolone plus imidazole regimens were not effective, and the authors clearly criticized the quality of the existing studies and recommended better designed studies that directly compare different antibiotics

[27]. However, the same group of authors revisited this issue in 2010 and found no beneficial effects of the antibiotics on infection of necrosis or death [29]. Even after the publication of the first double-blind, placebo-controlled trials in 2004 and 2007 [36, 38], showing nearly no effects of the prophylactic antibiotics, two meta-analyses concluded that prophylactic antibiotic treatment is associated with a significant reduction of pancreatic or peripancreatic infection, non-pancreatic infection, and length of hospital stay [22, 24]. However, neither a reduced mortality nor a lower frequency of surgical intervention was observed in these analyses. In contrast, a recent meta-analysis showed a general reduction of infection of intrapancreatic necrosis and, in a subgroup analysis, a beneficial effect of prophylactic antibiotics on infection of necrosis in general and also on mortality in single-blinded randomized controlled trials (RCTs) [16].

As already mentioned, in the beginning of this century there was a shift in the results of the trials on prophylactic antibiotics. In 2012, a meta-analysis of 11 RCTs showed by means of a subgroup analysis that there was a significant reduction of the mortality rate in the period before 2000, while no significant reduction occurred in the period from 2000 onwards [10]. The authors further reasoned that there might have been an apparent publication bias in the period before 2000 but that certain patients with severe pancreatitis could still benefit from antibiotic prophylaxis. In line with this meta-analysis, nearly all new but also some older reviews and meta-analyses [10, 12, 17, 19–21, 23, 25, 29, 30, 39, 40] conclude that a general recommendation for prophylactic antibiotics cannot be given. Most of these authors also see a need for better trials since some subgroups might benefit from antibiotics. One interesting point was addressed by a group of authors from Pakistan [18]. They stated that in developing countries the cost needed for managing complications of pancreatitis might be a limiting factor, and since prophylactic antibiotics could be beneficial in selected cases, they should be applied early in the course of the disease [18].

Microbiology of Infection in Acute Severe Pancreatitis

In general, acute pancreatitis is a disease which is not mediated by microbiota, and the initial high values for inflammatory markers like CRP and procalcitonin are signs of a systemic inflammatory response syndrome (SIRS) and might predict the outcome of the patients; however, they are not markers for an infection [4–6]. Translocation of bacteria from the small bowel 7–14 days after the onset of pancreatitis is thought to be the major source for infection of necrosis [41], highlighting the importance to maintain the barrier function of the gut [42] through early enteral feeding [43, 44]. A recent single-centre study of 51 consecutive patients in India showed that there might be differences in the bacteriology of pancreatic and peripancreatic infections [45]. Pancreatic infections were more often monomicrobial with a shift from Gram-negative to Gram-positive microbes as the pancreatitis progressed. Extrapancreatic infections were more often polymicrobial. Most commonly, the blood stream was invaded by Gram-positive bacteria, and another study showed a correlation between the bacteria isolated from the blood and the severity of the disease [46].

Which Is the 'Right' Compound for Antibiotic Therapy of Pancreatitis

Some meta-analyses and reviews suggested a possibility that the lack of clinical benefit of prophylactic antibiotics in some RCTs could be attributed to the usage of a non-effective compound [27, 35]. Several preclinical and clinical studies analysed the penetration of antibiotics in the pancreatic tissue and/or pancreatic juice to predict their effectiveness in the treatment of necrosis infection [47–56]. However, such a prediction has clear limitations, as demonstrated by the example of imipenem versus pefloxacin [48, 49]. In a study trying to predict the effectiveness of antibiotics in pancreatitis, pefloxacin or metronidazole was superior to imipenem with regard to antimicrobial activity, penetration rate, persistence, and therapeutic concentration in the necrotic pancreatic area [49]. In contrast, in the follow-up controlled clinical trial pefloxacin was inferior to imipenem in the prevention of infections [48]. Since such RCTs comparing different antibiotics against each other and against placebo are nearly completely lacking, the rather aged recommendation for imipenem as the antibiotic of choice is still widely practiced in clinical routine [17, 18, 35, 57].

Fungal Problematic

The usage of antifungal prophylaxis has been debated without any clear tendencies for the last 15 years [58–63]. The fact that fungal infection, most often caused by *Candida* species, is a predictor for a worse outcome in necrotizing pancreatitis is widely established [59, 60, 63]. Especially antibiotic treatment promotes the overgrowth of unaffected microorganism and is thought to be a major risk factor for fungal infection [59, 60, 64]. Thus, there is an ongoing debate whether an antifungal prophylaxis should be generally combined with prophylactic antibiotics [14, 58–60, 62]. Up to now, no randomized trial on prophylactic fungal therapy in pancreatitis exists. As in the case of prophylactic antibiotics, several other factors such as the route of feeding and drainage of necrosis might be crucial for the outcome of the patient and could spare the need for an antimicrobial treatment in general as well as an antifungal prophylaxis, which could additionally select multiresistant subspecies [60, 62].

Diagnosis of Infection

Based on the existing double-blind randomized trials, antimicrobial therapy can only be recommended after confirmation of infection of necrosis [7, 8]. One of the existing gold standards, i.e. fine-needle aspiration, was recently challenged by van Baal et al. [65].

The authors demonstrated that based on clinical and imaging signs (gas bubbles in computed tomography) the diagnostic accuracy for infection of the necrosis and most importantly the outcome of the patients did not differ from the group receiving a fine-needle aspiration. However, especially the clinical signs are not well defined and include persisting sepsis, (new or prolonged) organ failure, increased need for cardiovascular and/or respiratory and/or renal support, leukocytosis, increased levels of CRP, and fever. Moreover, no other infectious focus must be found or held responsible for the clinical deterioration. Radiological signs such as the inclusion of air in the diagnosis of infection of necrosis were already established in other studies [1]. New 16S-based techniques might offer the required sensitivity and specificity for early detection of general bacteraemia [46] and might also be a tool for prediction of necrosis infection. The content of liquid in the necrosis might predict the need for intervention in general but might also define a subgroup that benefits from antimicrobial therapy [66].

Enteral Feeding and Therapy of the Infected Necrosis

In acute pancreatitis, the infection of necrosis is the major determinant for the outcome of the patient after the initial phase. Not only prevention of necrosis infection but also improved treatment of infected necrosis significantly influence any prophylactic antimicrobial strategy and must be included in the design of RCTs. Early enteral feeding, which is known to prevent bacterial translocation through stabilization of the gut barrier and motility, has been shown to be effective in the prevention of infection and to be beneficial for the overall outcome in acute pancreatitis [44, 67]. Since the aspect of nutrition was poorly addressed in the RCT on prophylactic antibiotics, studies comparing antibiotics with placebo in a fixed setting of early enteral nutrition are needed. In addition, the outstanding work of the Dutch Pancreatitis Study Group clearly showed that a minimally invasive step-up approach in the treatment of infected necrosis is superior to open surgery, resulting in lower morbidity and mortality [43, 68]. Upcoming trials of this and other groups might further disclose if minimally invasive laparoscopy or endoscopy should be preferred in the treatment of the necrosis [69].

Conclusions

Based on the placebo-controlled trials and the recent meta-analyses on prophylactic antibiosis in necrotizing pancreatitis, antibiotic therapy with a broad-spectrum antibiotic like imipenem should be started only after confirmation of infection of the necrosis. However, nearly all authors concluded that the existing trials have several shortcomings and clearly voiced the need for better placebo-controlled trials. Such trials have to address several points:

Exact Definition of the Necrosis and Infection

Since the localization of the necrosis (i.e. peripancreatic vs. mixed) is influencing the outcome of the patient independently, this information must be considered in the inclusion/exclusion criteria. In addition, incidence of infection of necrosis is one of the central questions of these trials and, as discussed above, only poorly defined by non-invasive techniques.

Early Enteral Nutrition

As early enteral nutrition has been shown to significantly reduce the rate of infection of necrosis and to improve the outcome of the patients, the route of nutrition must be included in the study protocol.

Choice of Antibiosis

Currently, imipenem seems to be the most potent antibiotic but nearly no data comparing antibiotics directly are available. Based on empirical clinical knowledge, however, we would suggest that any conducted trial should include an imipenem group besides the placebo group.

Prophylactic Antifungal Therapy

One argument against prophylactic antibiotics in necrotizing pancreatitis is the selection of resistant microbiota, especially *Candida* spp. Therefore, trials on antibiotics should also include groups receiving a prophylactic antifungal therapeutic like caspofungin or amphotericin B besides the antibiotic agent.

Therapy of Infected Necrosis

If the overall outcome of the patient is included in the study protocol, the method of draining the infected necrosis must be included since the minimally invasive approach has been shown to be superior to open surgical procedures.

Although several other important points could be listed, these five aspects already highlight the need for multicentre, placebo-controlled studies including high numbers of patients. In the recent past, the Dutch Pancreatitis Study Group showed how such studies could change the therapeutic approach to severely ill patients suffering from necrotizing pancreatitis and dramatically improve their outcome. Therefore, we hope that at least some of the points raised in this review will be addressed by appropriately designed trials in the near future.

Acknowledgement

Funding to AA by the Sander Foundation (2010.076.1), the DFG (Deutsche Forschungsgemeinschaft), and the German Cluster of Excellence 'Inflammation at Interfaces' is acknowledged.

Disclosure Statement

The authors have nothing to declare.

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