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Original article

Probiotic treatment with Probioflora in patients with predicted severe acute pancreatitis without organ failure☆

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ABSTRACT

Background: We previously demonstrated that probiotic prophylaxis, in patients with predicted severe pancreatitis, did not prevent infectious complications but unexpectedly increased the risk of bowel ischemia and mortality. The suggestion that these negative findings are only observed in the presence of organ failure at the start of probiotic treatment has not been confirmed.
Methods: In a retrospective analysis, all patients with predicted severe acute pancreatitis without initial organ failure admitted to a medium care facility of a teaching hospital in Prague from January 2003 to December 2010 were included. All patients routinely received probiotic treatment with Probioflora. Total parenteral nutrition (TPN) was routinely started and shifted toward total enteral nutrition. Infectious complications, mortality and the incidence of bowel ischemia were recorded.
Results: 99 consecutive patients, mean age 56 years, were included. Infectious complications occurred in 42 patients (42%), consisting of bacteremia ($n = 40$), pneumonia ($n = 11$) and infected necrosis ($n = 11$). Bowel ischemia was detected in two patients (2%). Overall mortality was 8%.
Conclusion: In this retrospective study no apparent positive or negative impact of probiotic treatment with Probioflora was demonstrated when administered to patients with predicted severe acute pancreatitis without initial organ failure.

1. Introduction

In 80% of patients, acute pancreatitis runs a mild course, but 20% of patients develop necrotizing pancreatitis [1]. If pancreatic or peripancreatic necrosis becomes infected, intervention is generally required. This is associated with high morbidity and mortality [1]. Next to infected necrotizing pancreatitis, other infectious complications, such as bacteremia and pneumonia, are risk factors for mortality in acute pancreatitis [2]. Therefore, any treatment regimen capable of lowering the infection rate in acute pancreatitis could potentially reduce both morbidity and mortality.

Some authors propose that bacterial translocation from the small bowel is the main route of infection but others do not agree [3–6]. Prophylactic measures using antibiotics or probiotics and early start of enteral feeding have been hypothesized to reduce the infection rate, each by different mechanisms. Several recent meta-analyses have found no beneficial effect of systemic antibiotic prophylaxis in terms of reducing infectious complications and mortality [7,8]. In patients with acute pancreatitis, routine enteral nutrition, when compared to routine parenteral nutrition, are associated with a lower mortality [9,10]. However, it is suggested that this difference is a reflection of the fact that patients with parenteral nutrition may suffer from gut failure [11].

Several clinical studies have assessed the effect of probiotics prophylaxis with contradictory results. Some suggested that probiotics prophylaxis reduces the infection rate and the need for surgical intervention in patients with necrotizing pancreatitis [12]. The unexpected outcome of the Dutch PROPATRIA study [13] resulted in a premature termination of several randomized trials

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in which probiotics were administrated to patients with acute pancreatitis [14,15], including a termination of a prospective study with the same probiotics used as in the PROPATRIA study in the Faculty Thomayer's Hospital, Prague, Czech Republic.

Although the use of probiotics in acute pancreatitis is still a delicate issue, the negative outcome of the PROPATRIA study requires elucidation of the mechanism responsible for the negative outcomes observed [16]. Since the PROPATRIA publication, no new studies have been performed on probiotics in patients with severe pancreatitis. In 2010, we became aware of the fact that in the Faculty Thomayer's Hospital, the use of probiotic treatment in patients with predicted severe pancreatitis had continued, but only in patients without initial organ failure. As a part of our mutual interest in the impact of probiotics on these patients we retrospectively analyzed these patient data with the aim to unravel the mechanism of probiotic-induced bowel ischemia.

2. Methods

2.1. Patient selection

A retrospective analysis was performed including all consecutive patients with acute pancreatitis who were admitted to the Faculty Thomayer's Hospital, between January 1st, 2003 and December 31st, 2010. All patients with predicted severe pancreatitis without initial organ failure were admitted to the medium care unit where they routinely received probiotic treatment. Patients with organ failure on hospital admission were admitted to the intensive care unit (ICU) where they did not receive probiotic treatment. These patients were excluded from analysis. The database of the medium care was searched for patients with the ICD-10 code for acute pancreatitis (K85, 0).

2.2. Definitions

Acute pancreatitis was defined as acute upper abdominal pain with a serum amylase level at least three times higher than the upper limit of normal. Predicted severity of the pancreatitis was assessed by the Imrie score [17] and the serum C-reactive protein level [18]. Patients with an Imrie score of 3 or more, or with C-reactive protein over 150 mg/L, both within 48 h after hospital admission, were classified as 'predicted severe acute pancreatitis'. In case of clinical deterioration a contrast-enhanced CT scan (CECT) was performed to detect pancreatic or peripancreatic necrosis.

2.3. Nutrition

Immediately after hospital admission, all patients (regardless of organ failure) received total parenteral nutrition (TPN). Within the first days after admission, a nasojejunal tube was inserted to administer probiotics and eventually enteral feeding as well. Total parenteral nutrition was provided for at least ten days, with, if tolerated, a gradual shift toward total enteral nutrition. Depending on the calculated dietary needs of the patient, enteral nutrition consisted of Nutrison standard, Nutrison Multi Fibre or Nutrison Protein Plus (all Nutricia, Prague, Czech Republic). Patients received enteral nutrition until all signs of pancreatitis (e.g., fluid collections) were resolved on CECT. Consequently, patients could be discharged from hospital while on total enteral nutrition. These patients were followed clinically and radiologically in the outpatient department for weeks to months.

2.4. Probiotics

Probiotics were administered upon admission to the medium care through a nasojejunal tube and continued until the last day of hospital admission. The probiotic mixture, containing 3.0×10^9 bacteria per gift, was administered twice daily and consisted of seven different probiotic strains (i.e., *Lactobacillus acidophilus*, *L. bulgaricus*, *L. casei*, *Bifidobacterium bifidum*, *B. longum*, *B. lactis*, and *Streptococcus termophilus*; Probioflora, Goldim, Prague, Czech Republic). When patients developed organ failure and needed ICU treatment, they were transferred to the ICU and treatment with Probioflora was continued. As these patients did not have organ failure at the time the probiotics were started, they were included in the analysis, according to the intention-to-treat principle. After hospital discharge, patients were advised to continue the use of these probiotics, which in the Czech Republic are available over the counter. Since Probioflora was administered as part of a routine daily clinical practice in patients with abdominal diseases, including acute pancreatitis, no ethical approval for this retrospective study was required.

2.5. Procedures and definitions

On admission, standard laboratory tests and abdominal ultrasound were performed to establish the cause of the pancreatitis. In case of cholangitis and/or choledocholithiasis, endoscopic retrograde cholangiography (ERC) with endoscopic sphincterotomy (ES) was performed.

Infection of (peri-)pancreatic necrosis was defined as a positive bacterial culture of necrotic tissue obtained during intervention (i.e., percutaneous catheter drainage (PCD) or open necrosectomy), gas in the fluid collection on CECT, or a positive bacterial culture obtained with fine-needle aspiration (FNA). In case of (suspected) infection, patients were treated with intravenous antibiotics. Intervention was performed if patients deteriorated in spite of maximum conservative treatment.

Single organ failure was defined as pulmonary failure (PaO2 $<$ 60 mmHg, despite FiO2 of 0.30, or need for mechanical ventilation), circulatory failure (circulatory systolic blood pressure $<$ 90 mmHg, despite adequate fluid resuscitation, or need for inotropic support) or renal failure (creatinine level $>$ 177 μmol/L after rehydration or need for hemofiltration or hemodialysis). Multiple organ failure was defined as failure of two or three organ systems at the same time. Disseminated intravascular coagulation (platelet count $<$ 100×10^9/L), severe metabolic disturbance (calcium level $<$ 1.87 mmol/L) and gastrointestinal bleeding ($>$500 ml of blood/24 h) were reported as systemic complications [19]. For reasons of comparability of the data from this study with those of the PROPATRIA study [13], infectious complications were defined as infected (peri-)pancreatic necrosis, bacteremia, pneumonia, urosepsis and infected ascites.

2.6. Data collection

The following data were extracted from the patient records: comorbidity, length and body weight, American Society of Anesthesiologists classification (ASA classification), etiology, day of onset of symptoms, day of hospital admission, length of hospital stay, need for ICU admission, relevant laboratory findings (i.e., amylase, lipase, C-reactive protein, white blood cell count, blood glucose, liver enzymes, calcium, hematocrit, arterial oxygen pressure, base deficit, urea, serum albumin), bacterial cultures, outcome of fine-needle aspiration (FNA), findings on CECT scan, presence of cholangitis or cholecystitis, presence of (multiple) organ failure and systemic complications, performance of ERCP and ES, length of administration of enteral nutrition and probiotics, type of intervention, presence of infectious complications, presence of bowel ischemia and mortality.

2.7. Statistical analysis

Absolute frequency and percentages were calculated for infectious complications, mortality and bowel ischemia. Normally distributed data are presented as means (±SD). Non-normally distributed data are presented as median with interquartile range (IQR: P25–P75). Statistical analyses were performed using SPSS® for Windows® version 16.0.2 (SPSS, Chicago, Illinois, USA).

3. Results

3.1. Baseline characteristics

From January 1st, 2003 to December 31st 2010, 99 consecutive patients with predicted severe pancreatitis without organ failure were admitted to the medium care unit. All these patients received enteral nutrition and Probioflora as described. Baseline characteristics are shown in Table 1. Male:female ratio was 1:1, with a median age of 56 years (IQR 44–68 years). Median time between onset of symptoms and hospital admission was 0 days (IQR 0–0 days), and since patients were immediately admitted to the medium care unit, the time between hospital admission and admission to the medium care was also 0 days (IQR 0–2 days). The twice daily, single dose of Probioflora and enteral nutrition was initiated after a median of 4 days (IQR 2–8 days). CECT was performed after a median of 6 days (IQR 4–7 days) in hospital.

3.2. Outcomes

Table 2 shows the patient outcomes. Sixty patients (60%) developed necrotizing pancreatitis, with a median CT severity index of 5 (IQR 3–6). Infectious complications were diagnosed in 42 patients (42%): bacteremia in 40 patients (40%), pneumonia in 11 patients (11%) and infected necrosis in 11 patients (11%). No patients developed urosepsis or infected ascites. Severe systemic complications occurred in 48 patients (48%): severe metabolic disturbance in 47 patients (47%), disseminated intravascular coagulation in 11 patients (11%) and severe gastrointestinal bleeding in 2 patients (2%). New onset organ failure during hospital admission, but *after* administration of Probioflora, was reported in 27 patients: seven patients (7%) developed single organ failure and 20 patients (20%) developed multiple organ failure.

Infected necrosis was proven in 11/99 patients (11%) by a positive culture obtained during the first intervention. In two patients (2%) decompression laparotomy was performed because of an abdominal compartment syndrome.

16/99 Patients (16%) who were admitted to the medium care unit needed transfer to the ICU because of development of organ failure. Overall median length of hospital admission was 19 days (IQR 13–30 days).

Eight patients (8%) died. Except for one patient, all eight patients had new onset multiple organ failure during hospitalization and in 3/8 patients (38%) infected necrosis was diagnosed. In 6/8 patients (75%) autopsy was performed and no signs of bowel ischemia were detected.

3.3. Infectious complications

The pathogens isolated from the patients with infectious complications were mainly Staphylococcus spp. and Enterococcus spp. (Table 3). The overall median time between hospital admission

Table 1
Baseline characteristics of 99 patients with predicted severe pancreatitis receiving probiotic treatment with Probioflora.

	$n = 99$
Age (years)	56 (44–68)
Sex (male)	58 (59%)
BMI (kg/m^2)[a]	30.7 (5.9)
Cause of pancreatitis	
Biliary	51 (52%)
Alcohol	25 (25%)
Other	23 (23%)
American society of anesthesiologists classification	
I (healthy status)	25 (25%)
II (mild systemic disease)	43 (43%)
III (severe systemic disease)	31 (31%)
Severity of pancreatitis	
Imrie score (first 48 h)	3.1 (1.4)
Ranson score (first 48 h)[b]	3.8 (1.9)
C-reactive protein (mg/L) (highest first 48 h)[b]	221 (81)
Time from first symptoms to admission (days)	0 (0–0)
Time from admission to first dose (days)	4 (2–8)
Time from admission to enteral nutrition (days)	4 (2–8)

Data are *n* (%), mean (SD), or median (IQR). Unless noted, data were available in all 99 patients.
[a] Data available in 35/99 patients.
[b] Data available in 98/99 patients.

Table 2
Clinical outcome.

	$n = 99$
Contrast-enhanced CT	
Necrotizing pancreatitis	60 (60%)
<30% necrosis	36 (36%)
>30% necrosis	24 (24%)
No contrast-enhanced CT performed	3 (3%)
CT severity index	5 (0–10)
Any infectious complication	42 (42%)
Infected necrosis	11 (11%)
Bacteremia	40 (40%)
Pneumonia	11 (11%)
Percutaneous drainage	8 (8%)
Surgical intervention, any indication	9 (9%)
Necrosectomy	7 (7%)
Intensive care admission	16 (16%)
Intensive care stay (days)	25 (12–36)
Hospital stay (days)	19 (13–30)
OF during admission, any onset[a]	27 (27%)
MOF during admission, any onset[a]	20 (20%)
Bowel ischemia	2 (2%)
Mortality	8 (8%)

Data are *n* (%), mean (SD), or median (IQR). OF: organ failure. MOF: multiple organ failure.
[a] New onset (multiple) organ failure during hospital admission, but after administration of probiotics was started.

Table 3
Pathogens isolated from 42/99 patients with an infectious complication.

Gram-positive bacteria	
Staphylococcus spp.	26
Staphylococcus epidermidis	9
Staphylococcus hominis	6
Staphylococcus aureus	6
Enterococcus spp.	5
Corinebacterium spp.	4
Streptococcus spp.	3
Gram-negative bacteria	
Enterobacter spp.	17
Klebsiella spp.	10
Escherichia coli	5
Pseudomonas spp.	4
Other gram-negative microorganisms[a]	6
Fungi	0

When different organisms were cultured from different sites of a single patient, all microorganisms are listed. If a single organism was cultured from different sites of a single patient, this organism was listed only once.
[a] Acinobacter spp. (1), and Sphingobacter spp. (1).

and diagnosis of any infectious complication was 11 days (IQR 8–19 days). Median time between admission and diagnosis of bacteremia was 9 days (IQR 6–15 days), pneumonia 7 days (IQR 3–13 days) and infected necrosis 19 days (IQR 13–31). In patients with infected necrosis, infection was diagnosed in 1/11 patients (9%) in the first week after admission, in 2/11 patients (18%) in the second week after admission, in 4/11 patients (36%) in the third week after admission and in 4/11 patients (36%) after three weeks of admission.

3.4. Bowel ischemia

Bowel ischemia was diagnosed in two patients who received Probioflora and enteral nutrition. As no data were available on histopathological examination, no specific cause for the bowel ischemia could be reported.

The first patient was a 51-year old male with an alcoholic pancreatitis without comorbidity. Open necrosectomy due to infected necrosis was performed in six separate procedures on day 34, 44, 52, 62, 90 and 109. During necrosectomy on day 62, multiple necrotic perforations of the descending colon were found. Ultimately, this patient recovered.

The second patient who developed bowel ischemia was a 62-year old male with a history of gastro-esophageal reflux disease and axonal neuropathy, who was admitted with biliary pancreatitis. On day 38, a laparotomy was performed and a small part of the duodenum and the proximal jejunum were resected because of ischemic alterations at the site of the tip of the nasojejunal feeding tube. On day 42, an ischemic colitis was found during the second open procedure. The patient died on day 62 and no autopsy was performed.

4. Discussion

This cohort of patients with predicted severe pancreatitis without initial organ failure was analyzed retrospectively in order to obtain clues for the yet unknown mechanism behind probiotic-induced bowel ischemia, as shown in the PROPATRIA study. Although in the current study treatment of the patients was not state-of-the-art (e.g. initial total parenteral nutrition in every patient), we focused on potential negative effects of probiotic treatment with Probioflora and did not find an increased incidence of bowel ischemia and mortality.

This conclusion is based on comparison with the literature [13,20]. Unfortunately, a direct comparison with the patients included in the PROPATRIA trial [13] is not realistic given the major differences between both cohorts: 1) PROPATRIA included patients with initial organ failure whereas this study did not, 2) the mixture of probiotics used was different and 3) parenteral nutrition was administered routinely in the current study, whereas in PROPATRIA enteral nutrition was used.

In the current study, probiotics were administered after a median of four days of hospital admission. Administration of probiotics starting four days after admission is outside the time interval considered “the window for prophylaxis”, suggested to be as small as 48 h. In a mouse model for acute pancreatitis, Rychter et al. showed that the effectiveness of probiotics strongly depends on the timing of administration; administration of probiotics before induction of pancreatitis prevents intestinal barrier dysfunction to occur, while administration started after induction of disease was ineffective in this respect [21].

The percentage of infectious complications reported in this study (42%) is higher than reported in two large randomized controlled trials (30% and 31%) [13,22]. The high rate of infections may be related to the prolonged use of TPN as this has been documented to increase the incidence of positive blood cultures [9].

In the current study, ultimately 27 patients developed (late) organ failure, while receiving Probioflora and ultimately 16 of these patients were admitted to the ICU. In none of these patients with organ failure was bowel ischemia diagnosed. However, one has to bear in mind that there was no formal strategy to detect bowel ischemia in these patients. The overall incidence of bowel ischemia was 2% and mortality 8%. Both these frequencies are within the expected range as described in the literature in patients with predicted severe acute pancreatitis [20]. The bowel ischemia, however, was diagnosed after several weeks after hospital admission (i.e. day 38 and day 62), whereas in the PROPATRIA study bowel ischemia was diagnosed within the first 2 weeks of admission. Furthermore, in PROPATRIA in all but one of the 9 patients who developed bowel ischemia already suffered from organ failure on the first or second day of admission. These findings might suggest that the patients in the current study may have suffered from another type of bowel ischemia and not specifically probiotic-related.

In 2009, Besselink et al. discussed whether the negative outcome of the PROPATRIA study may be related to the presence of organ failure at the time the probiotics were administered [6]. The post-hoc sub-group analysis of the PROPATRIA cohort showed that a higher degree of enterocyte damage occurred in patients who received probiotics when they already had organ failure. These findings may suggest that probiotics do not increase the incidence of bowel ischemia when administered to patients without early organ failure. Although the current study supports this hypothesis there is no clear mechanism available to explain these findings.

In conclusion, this study describes the first analysis of a cohort of patients with predicted severe pancreatitis without initial organ failure treated with probiotic treatment with Probioflora after the unexpected outcome of the PROPATRIA study in 2008. Although we acknowledge that patient care was not conform current guidelines and comparison with the PROPATRIA study is not realistic, we could not find a clear positive or negative impact of probiotic treatment with Probioflora on the incidence of bowel ischemia and mortality in patients with predicted severe pancreatitis without organ failure.

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Author involvement

Study concept and design: all authors.
Acquisition of data: MCvB, PK.
Analysis and interpretation of data: MCvB, MGB, HCvS, HGG.
Drafting of the manuscript: MCvB.
Critical revision of the manuscript for important intellectual content: all authors.
Statistical analysis: MCvB, MGB.
Technical or material support: all authors.
Study supervision: HGG.

Conflict of interest

No conflicts of interest exist for each author.

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