Microbiologic analysis of peri-pancreatic fluid collected during EUS in patients with pancreatitis: impact on antibiotic therapy

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Background: Pancreatitis is a potentially life-threatening condition frequently accompanied by peri-pancreatic fluid collections (PPFC), such as pseudocysts or pancreatic necrosis. Aspiration of PPFCs during EUS interventions for microbiologic analysis is still rarely performed in clinical routine.

Objective: To evaluate the role of routine microbiologic analysis of PPFCs and its impact on antibiotic therapy in patients with pancreatitis.

Design: Prospective, observational, multicenter study.

Setting: Four treatment centers.

Patients: A total of 44 consecutive patients who presented for endoscopic treatment of PPFCs were included.

Intervention: Concomitantly, PPFC during intervention and concomitant blood cultures were obtained.

Main Outcome Measurements: Microbiologic examination of PPFCs and blood samples.

Results: Colonization of PPFCs was found in 59% of PPFC cultures, whereas all but 2 concomitant blood cultures showed no microbial growth. Risk factors for a colonization were the presence of necrosis ($P = .006$), acute pancreatitis ($P = .033$), leukocytosis ($P = .001$), elevated C-reactive protein levels ($P = .003$), fever ($P = .02$), turbid material ($P = .031$), and longer hospital stay ($P = .003$). In 23 patients with fluid colonization despite empiric antibiotic therapy, the treatment had to be adjusted in 18 patients (78%) according to the observed antibiotic susceptibility profile.

Limitations: Contamination cannot be totally excluded.

Conclusion: The microbiologic colonization of PPFCs in patients with pancreatitis is common. Only the direct microbiologic analysis of PPFCs, but not of blood cultures, is useful to optimize an effective antibiotic therapy in patients with pancreatitis. (Gastrointest Endosc 2013;78:303-11.)

Mortality dramatically increases if peri-pancreatic fluid collections (PPFC), such as pseudocysts or necrosis, become infected.[1,2] The secondary infection of PPFC remains the leading cause of mortality in patients with pancreatitis.[3] Prophylactic antibiotic therapy appears reasonable but remains controversial, and no larger investigation has shown a clear benefit up to now.[4,5] Furthermore, the differentiation between sterile and infected PPFCs in pancreatitis according to the clinical appearance and laboratory parameters remains difficult because both may present with fever, leukocytosis, and severe abdominal pain.[6] If an infection is suspected, empiric antibiotic

Abbreviations: EUS-FNA, EUS-guided FNA; PPFC, peri-pancreatic fluid collection.

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therapy with a broad-spectrum antibiotic like carbapenems has been suggested.[6,7] However, empiric non-targeted–based therapy carries the risk of selecting antibiotic-resistant strains and treatment failure. Samples from PPFCs for microbiologic analysis may be obtained percutaneously, during surgery, or by EUS-guided FNA (EUS-FNA).

EUS is now a standard technique for the diagnosis and management of PPFCs, including the chance to obtain samples for microbiologic analysis and transgastric or transduodenal drainage.[8] Although guidelines recommend microbiologic analysis of PPFCs, the importance of obtaining aspirates for microbiologic analysis during EUS in clinical routine has never been validated.

Therefore, our aim was to evaluate the value of the microbiologic analysis of aspirates from PPFCs in comparison with concomitant blood cultures and its impact on the antibiotic management in a multicenter study.

Take-home message

- Aspiration of peri-pancreatic fluid for microbiologic analysis during endoscopic intervention is a valuable diagnostic tool because it might lead to more adequate therapy and might help to establish a local antibiotic guideline for the management of peri-pancreatic fluid collection in patients with pancreatitis.

PATIENTS AND METHODS

Patients

This prospective study was conducted between April 2010 and October 2011 at the endoscopic unit of 2 university hospitals and 2 municipal hospitals. We included all patients with PPFCs who presented for endoscopic intervention. Informed written consent was obtained from all patients, and the trial was approved by the local ethics committee. The exclusion criteria were age under 18 years or absence of the written informed consent before intervention. Acute pancreatitis was defined as the presence of at least 2 of 3 of the following features: abdominal pain, serum lipase activity (3 times the upper limit of normal), and characteristic findings of contrast-enhanced CT.[6] Chronic pancreatitis was classified as the presence of pancreatic calcifications, dilatation of pancreatic ducts, and chronic abdominal pain.

Endoscopic procedure

Indications for endoscopic intervention were either drainage of large or symptomatic pseudocysts or diagnostic puncture of symptomatic PPFCs (abdominal pain and/or fever). All EUS procedures were performed by using Olympus endoscopes (Olympus, Hamburg, Germany), which were disinfected according to the guidelines of the Robert Koch Institute, and contamination was excluded by a regular smear test.[9] Peri-pancreatic fluid collections were aspirated through a puncture set or the biopsy needle. Approximately 0.5 to 10 mL of fluid (mean 2 mL) was collected and transferred into a sterile tube. Concomitantly, blood cultures were obtained directly or within 12 hours after intervention. At least 1 single dose of antibiotic was documented as an antibiotic treatment before intervention.

Microbiologic analysis

Aspirate samples were cultured under aerobic conditions on 5% Columbia sheep blood agar (Becton Dickinson GmbH, Heidelberg, Germany), MacConkey agar (Oxoid GmbH, Wesel, Germany), and yeast extract agar for 48 hours, with the first reading after 24 hours. Anaerobic growth was observed by the use of Schaedler agar (Becton Dickinson GmbH) for up to 96 hours. Incubation of blood cultures (BD BACTEC standard aerobic and anaerobic media; Becton Dickinson GmbH, Heidelberg, Germany) was terminated after 7 days if no microbial growth had be registered. Species differentiation was then performed according to German laboratory practice guideline DIN EN ISO 15189. Species identification and antibiotic susceptibility testing were performed by using the VITEK-2-XL (bioMérieux, Nuertingen, Germany) system and Merlin MICRONAUT Sprint Dispenser automated broth micro-titer system (Genzyme Viro-Tec, Russelsheim, Germany). Micro-titer plates of 384 wells (No. EG-009) were used as recommended by the German Network for the Antimicrobial Resistance Surveillance.[10] Microorganisms present in concentrations $>10{,}000$/mL were considered as infection; lower concentrations were judged as contamination only.

Management of data and statistical analysis

Data collection and storage were performed by using a specially designed data bank (Microsoft Access 2003, Unterschleißheim, Germany). Data were expressed as number/percent or mean $\pm$ standard deviation. All collected parameters of patients with positive aspirate cultures were compared with those of sterile culture results. Noncontinuous parameters were analyzed by χ^2 test or Fisher exact test as appropriate, and continuous parameters were analyzed by using the Mann-Whitney U test. P values $< .05$ were considered statistically significant. Parameters with significant statistical difference as well as parameters with differences $< .100$ were further included in a multivariate analysis (logistic regression by using stepwise backward elimination) to detect independent risk factors. All calculations were done by using the SPSS Statistical Package (version 19.0, SPSS Inc, Chicago, Ill). All authors had access to the study data and had reviewed and approved the final manuscript.

RESULTS

Patients and clinical characteristics

During the study period, 44 consecutive patients were prospectively recruited from 2 university hospitals and 2 peripheral hospitals. Reasons for PPFCs were mainly acute

TABLE 1. Demographic, clinical, and laboratory test characteristics of study patients (n = 51)

Parameter	Patients (n = 44) No. or mean ± SD	% or range
Demographic data		
Male	30/44	68%
Female	14/44	32%
Age, y	52 ± 13.7	32-90
Clinical presentation		
Hospital stay before intervention, d	35 ± 35	2-154
Patients in ICU	10/44	23%
Fever	19/44	43%
Abdominal pain	31/44	70%
Background of peri-pancreatic fluid collection		
Acute pancreatitis	32/44	73%
Chronic pancreatitis	12/44	27%
Cause of pancreatitis (n = 44)		
Biliary	15/44	34%
Alcoholic	7/44	16%
Post ERCP	4/44	9%
Postoperative	3/44	7%
Other*	4/44	9%
Unknown	11/44	25%
Endosonographic characteristic		
Pure PPFC without necrosis	22/44	50%
PPFC with necrosis	22/44	50%
Size, cm	7.7 ± 3.5	2-17
Turbid aspirate	32/44	73%
First intervention	24/44	55%
EUS-guided drainage	27/44	61%
Diagnostic puncture	17/44	39%
Laboratory parameters before intervention		
Leukocyte count (normal 4.4-11.3 × 10^3/μL)	12.9 ± 8.5	3.4-43.4
CRP (up to 8 mg/L)	151 ± 117	1-375
Amylase (up to 100 U/L)	126 ± 179	12-594
Lipase (13-60 U/L)	180 ± 312	5-1612

SD, Standard deviation; *ICU,* intensive care unit; *PPFC,* peri-pancreatic fluid collection; *CRP,* C-reactive protein.
*Hyperlipidemia (n = 1), autoimmune pancreatitis (n = 1), traumatic (n = 1), and drug related (n = 1).

pancreatitis (73%) and chronic pancreatitis (37%). Pancreatitis was mainly related to biliary obstruction (34%), alcohol abuse (16%), or after ERCP (9%). In 25% of patients, the cause of pancreatitis remained unknown. Detailed clinical and laboratory characteristics are given in Table 1. Main indications for intervention of PPFCs were pain (n = 31; 70%) and/or fever (n = 19; 43%). Criteria of transgastric or transduodenal drainage of the pseudocyst were dependent mainly on size (mean cyst size of 7.7 cm) and on the clinical symptoms of patients with abdominal pain and/or fever. Another factor that supported our decision was the EUS appearance of the fluid collection (turbid fluid on EUS in 73% of cases). Clear aspirates were found in 12 of 44 PPFCs. Fifty percent of patients presented with PPFCs without signs of necrosis.

The patients were hospitalized for an average of 1 month before intervention; from these patients, 23% were treated in the intensive care unit. The mean delay of onset of symptoms for acute pancreatitis was 25 days (5-91 days). The endosonographic puncture of PPFCs was performed on therapeutic interventions (eg, transgastric drainage) in 27 cases (61%) or for diagnostic reasons in 17 cases (39%). Twenty patients (45%) had already received at least 1 EUS intervention at the pancreas before the index intervention; in 6 patients, transgastric drainage was placed before the index intervention. Three patients developed fever after EUS intervention despite receiving antibiotic prophylaxis, whereas only 1 patient without preinterventional antibiotics developed postprocedural fever. Otherwise, no adverse events were observed during or after EUS intervention, especially no signs of bleeding or perforation.

General microbiological characteristics

Aspiration of peri-pancreatic fluid collections was successful in all examinations. Twenty-six of the aspirates cultures (59%) showed microbial growth. Only 2 concomitant blood cultures (13%) of those positive aspirate cultures showed microbial growth of the same organisms as found in the aspirate culture. On the other hand, whenever aspirate culture showed microorganisms present in concentrations <10,000/mL (in 18 aspirate cultures), the

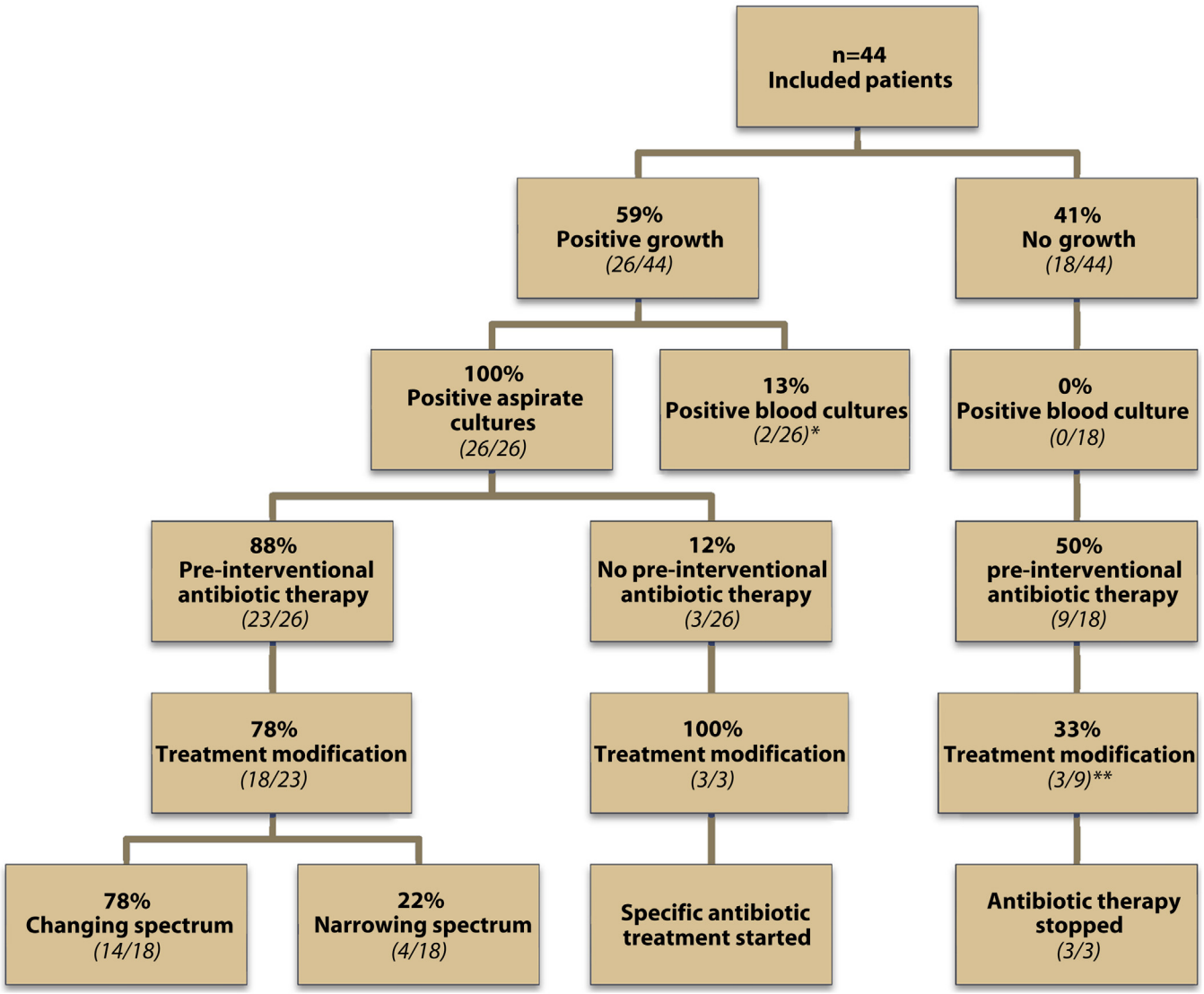

Figure 1. Results of microbiologic analysis of peri-pancreatic fluid collection aspirates versus blood cultures and its effect on modification of antibiotic treatment. *Same organisms found in aspirate and blood culture. **Patients continued antibiotics despite negative growth because of high fever (n = 2) or C-reactive protein levels (n = 6).

concomitant blood culture also remained sterile (Fig. 1). Polymicrobial growth (Table 2) was more common (n = 17/26; 65%) in comparison to monomicrobial cultures (n = 9/26; 35%). Gram-positive bacteria were more prevalent than gram-negative bacteria and *Candida* species (61%, 18%, and 20%, respectively). Only 1 bacterial species (2%) showed multiple-drug resistance to antibiotics (methicillin-resistant *Staphylococcus aureus*). A total of 51 organisms were isolated, comprising 17 different species. The most frequently encountered organisms were *Enterococcus* species (37%), *Candida* species (20%), and *Streptococcus* species (16%).

Risk factors for colonization of PPFC

A comparison between the group of patients in whom the aspirate cultures showed a positive growth (n = 26) and the group with sterile aspirate cultures (n = 18) was performed in all collected preinterventional parameters. The univariate analysis revealed that fever before intervention, acute pancreatitis, the presence of pancreatic necrosis, turbid material aspirated during intervention, and elevated leukocyte or C-reactive protein levels are risk factors for bacterial growth in peri-pancreatic fluid (Table 3). In contrast, patient sex, age, intensive care unit admission, the cause of pancreatitis, the presence of echogenic material on EUS, previous interventions before the index intervention, or stenting before the index intervention were not significantly associated with microbial growth of PPFCs later on. Even when we stratified the patients according to previous interventions in relation to the presence of microbial growth there were no significant differences (P = .946).

TABLE 2. Type and frequency of grown organisms in positive aspirate cultures

	No.	%
Positive culture	26	100
Polymicrobial infection	17	65
Monomicrobial infection	9	35
Total no. organisms	51	100
Gram-positive bacteria	31/51	61
Enterococcus species	19/31	61
Streptococcus species	8/31	26
Lactobacillus species	3/31	10
Staphylococcus species	1/31	3
Gram-negative bacteria	9/51	18
Enterobacter cloacae	3/9	33
Klebsiella species	2/9	22
Escherichia coli	1/9	11
Citrobacter brakkii	1/9	11
Species not identified	2/9	22
Fungi	10/51	20
Candida species	10/10	100
Resistant organisms	1/51	2
Methicillin-resistant *Staphylococcus aureus*	1/1	100

Antibiotic susceptibility testing and resistance profile

Thirty-two patients were pretreated with empirical antibiotics before intervention (at least a single dose), mainly with meropenem and metronidazole, mostly in combination with other antibiotics. Despite preinterventional antibiotic treatment, 23 patients (72%) showed positive aspirate cultures. For the 51 organisms cultured in the study, antibiotic susceptibility was tested for at least 15 types of antimicrobial substances. We observed a limited covering spectrum or high resistance to meropenem and metronidazole. The most common bacteria growing outside the covering antibiotic spectrum or with a high resistance profile were *Enterococcus* species and *Candida* species.

Impact of the PPFC culture results on antibiotic management

In 44 patients undergoing EUS interventions, a positive aspirate culture result was found in 26 of patients despite the fact that 23 of these patients (88%) were pretreated with antibiotics. Because of the microbiologic results of the aspirate cultures, the antibiotic therapy had to be changed in 18 of 23 patients (78%), either by changing or narrowing the spectrum of the given substance. Fever resolved in febrile patients, and all patients clinically improved after antibiotic modification. The 4 patients who were not pretreated with antibiotics were given guided antibiotic therapy according to the susceptibility and resistance profile (Fig. 1).

From the clinical point of view, 19 patients had preprocedural fever, and a positive aspirate culture result was detected in 15 (79%) of those 19, although they all received preinterventional antibiotics. In most of those patients (11/15), culture results of PPFCs revealed organisms that were either resistant to empirical antibiotic treatment or were not covered by the initially chosen empiric antibiotics. The antibiotic treatment subsequently had to be modified in 73% of cases according to the results obtained by the pancreatic aspirate cultures. In the absence of fever (n = 25; 57% of all patients) a positive aspirate culture was still found in 11 of 25 patients (44%). Eight patients received antibiotics in the absence of fever because of elevated C-reactive protein levels and sonographic signs of necrosis (n = 7) or because of prior microbiologic analysis of PPFCs before the index intervention (n = 1). Seven of these 8 patients (88%) benefitted from the PPFC culture results by the antibiotic modification (Fig. 2).

We further analyzed patients with acute pancreatitis (n = 32/44; 73%) (Fig. 3). In 23 of 32 patients (72%), colonization of PPFCs was observed; 20 of these patients were under antibiotic treatment before EUS examination. In those patients, the antibiotic treatment had to be modified in 15 of 20 patients (75%), according to aspirate culture results.

DISCUSSION

The therapy of symptomatic or infected PPFCs in patients with pancreatitis is mainly interventional drainage and antibiotic treatment. However, despite therapy, the mortality of pancreatitis remains intolerably high, indicating the need for further diagnostic and therapeutic strategies. The role of antibiotics in preventing infection of PPFCs or reducing the severity of a clinical course of pancreatitis is still controversial and was not the object of this study.[11-14] Some authors recommend broad-spectrum antibiotic treatment in patients with pancreatitis and infected PPFCs. However, non-targeted antibiotic therapy carries the risk of bacterial resistance, secondary problems (eg, *Clostridium difficile*), and failure of treatment if the applied antibiotic therapy does not cover the actual microbial spectrum.

At first sight, blood cultures appear to be attractive, especially in patients with fever, because they are easy to obtain. However, in our study, blood cultures remained sterile in almost all patients with PPFCs. Transcutaneous

TABLE 3. Risk factors of positive culture growth in peri-pancreatic aspirates

	No growth (n = 18)		Growth (n = 26)		
Parameter	**No. or mean ± SD**	**% or range**	**No. or mean ± SD**	**% or range**	***P* value**
Male	11	61%	19	73%	.402
Female	7	39%	7	27%	
Age, y	56 ± 14.6	40-90	54 ± 13.3	32-83	.756
Hospital stay, d	21.5 ± 29.9	2-127	44.4 ± 34.9	7-154	.003
ICU admission	3	17%	7	27%	.425
Acute pancreatitis	10	56%	22	85%	.033
First intervention	10	56%	14	54%	.911
Previous intervention	8	44%	12	46%	.946
Stent before intervention	1	6%	5	19	.194
Fever	4	22%	15	58%	.020
CRP (mg/L)	93.4 ± 106 (normal, <8)	1-311	189.3 ± 109	2-375	.003
Leukocyte count ($\times 10^3/\mu L$)	8.9 ± 4.1 (normal, 4.4-11.3)	3.4-20.2	15.6 ± 9.7	4.9-43.4	.001
Lipase (U/L)	192.7 ± 277 (normal, 60)	5-895	172.3 ± 338	8-1612	.611
Turbid aspirate	9	50%	23	88%	.031
PPFC with necrosis	6	33%	16	62%	.066

SD, Standard deviation; *ICU,* intensive care unit; *CRP,* C-reactive protein; *PPFC,* peri-pancreatic fluid collection.

puncture of PPFCs represents another option but is difficult to perform, especially when PPFCs are difficult to reach. Obtaining samples for microbiologic analysis during surgery has been described in different studies and is performed routinely once surgery is necessary in patients with pancreatitis.[15]

Since the last decade, EUS plays an important role of diagnosis and treatment of PPFCs. EUS-guided transgastric drainage has proven to be efficient in the treatment of pseudocysts and pancreatic necrosis.[8] During EUS intervention, aspiration of fluids from PPFCs can be obtained easily for microbiologic analysis. Main indications for intervention of PPFCs were pain and/or fever. This study did not focus on asymptomatic PPFCs, which often resolve spontaneously with resolution of the pancreatitis. EUS-FNA outside the clinical setting of this study has not been studied and is not being advocated. However, the role of microbiologic analysis of fluids from PPFCs, and especially the impact on antibiotic management, have never been studied.

Our data showed that polymicrobial growth was frequently found with a relatively high percentage of *Candida* species, which is consistent with other studies that examined samples obtained during surgery.[15] In this study, we mainly detected *Enterococcus* species, *Candida* species, and *Streptococcus* species, whereas other studies found *Staphylococcus* species more often.[15] The presence of *Candida* species must be taken into account if drug therapy of PPFCs is an option.[16,17]

Risk factors for colonization of PPFCs included fever, acute pancreatitis, pancreatic necrosis, duration of hospital stay, turbid material aspirated during intervention, and elevated leukocyte and C-reactive protein levels. Our data indicated that obtaining samples in patients with those risk factors is required. Interestingly, with the exception of pancreatic necrosis, we did not identify a specific endosonographic sign as a risk factor for microbial infection. In fact, previous EUS intervention and even manipulation before the index intervention such as stenting was not significantly associated with the observed presence of microbial growth in this study. These results are different from those regarding other infectious diseases, such as cholangitis, where multiple interventions in the biliary system are a risk factor for bacteriobilia.[18] However, prior manipulation by endoscopic procedures may predispose to colonization. In addition, our patients were in general hospitalized longer and were potentially at risk for secondary infection. However, the hospital stay was not independently associated with microbial growth of PPFCs in this cohort. Further studies have to be performed to clarify these findings.

Available blood cultures drawn during episodes of fever showed only a very low sensitivity. These results are consistent with previous data showing a low sensitivity of blood

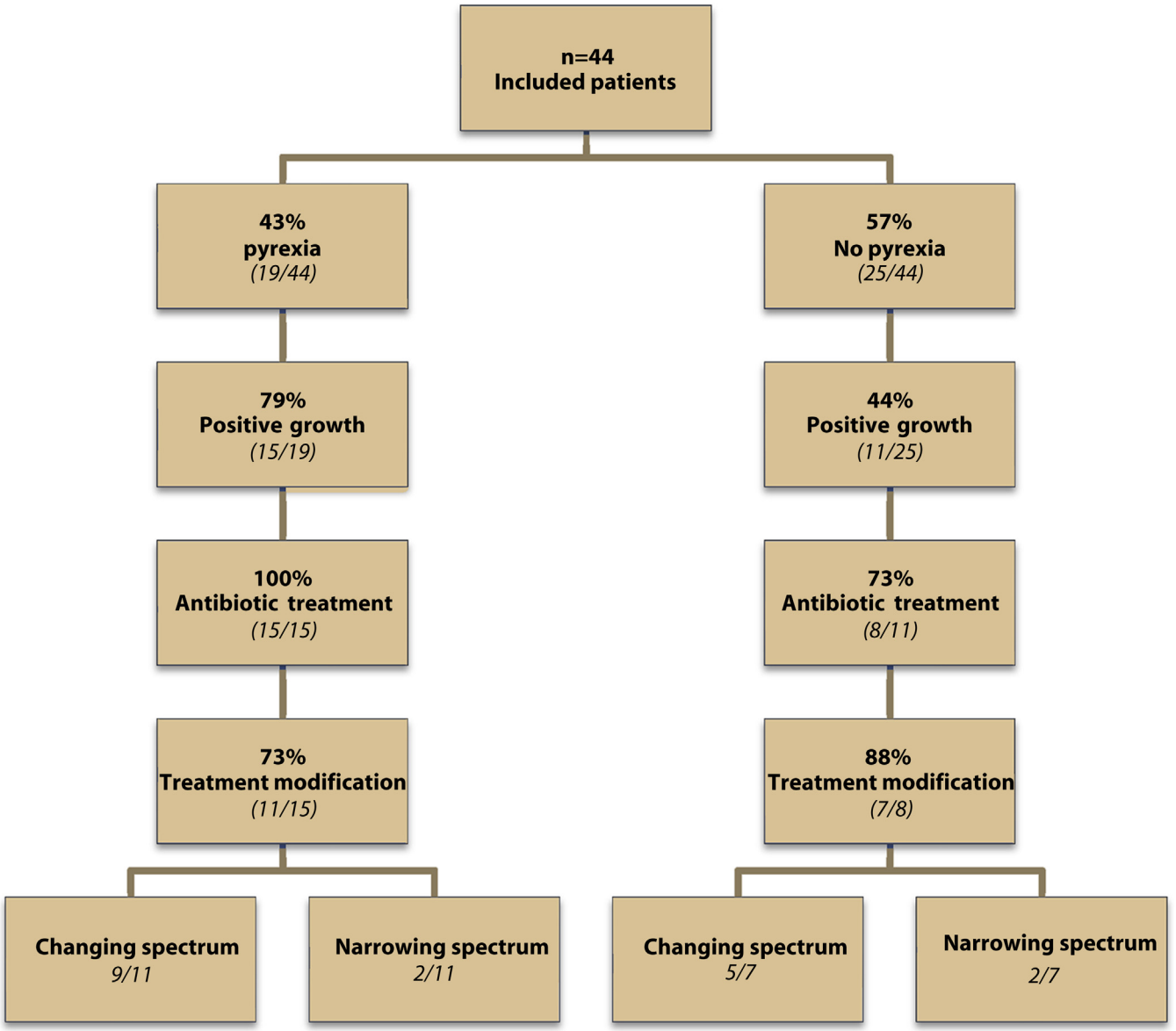

Figure 2. Prevalence of positive aspirate culture and its effect on modification of antibiotic treatment in patients with fever versus without fever before the intervention.

cultures in patients with infection.[19] The high sensitivity of cultures from PPFCs is physiologically plausible because the material for microbiologic analysis is obtained directly from the place where the inflammation occurs. It is noteworthy that microorganisms found in blood cultures also were found in PPFC samples, indicating that cultures from PPFC results are as effective as positive blood cultures. These data strongly support the need for fluid aspiration in patients with PPFCs presenting for EUS. However, this evaluation of the effect of antibiotic adjustment will be the subject of a future case-control study. The clinical improvement of patients in which the antibiotic regimen was modified may be due to a combination of antibiotic modification and endoscopic procedure (eg, transgastric drainage). We believe that it would have been unethical not to adjust antibiotic treatment according to microbiologic results in patients with pancreatitis and PPFCs. Randomized controlled trials are needed to investigate the independent role of guided antibiotic management of PPFCs in an improvement of outcome.

We cannot totally exclude contamination of the endoscope while passing the oral cavity, oropharynx, and esophagus before reaching the stomach and duodenum. For example, the presence of *Staphylococcus aureus* in a single patient may be from contamination. However, at the present time there is no known procedure to totally avoid contamination during the passage. To avoid contamination via cross-transmission between different patients, the duodenoscopes were vigilantly disinfected according to the guidelines of the Robert Koch Institute, the national institute

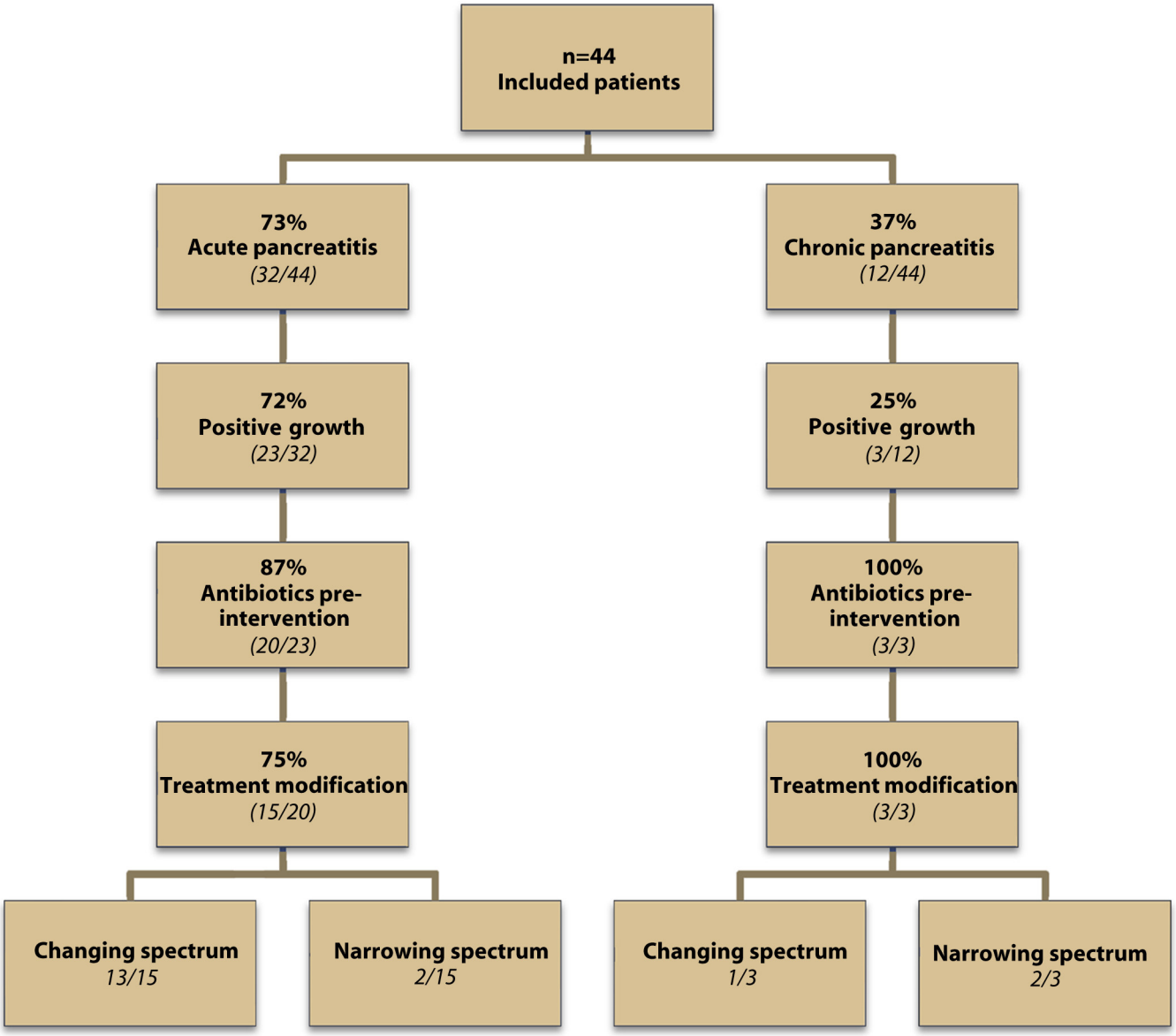

Figure 3. Prevalence of positive aspirate culture and its effect on modification of antibiotic treatment in patients with acute pancreatitis versus other pancreatic disorders.

for prevention of infections in Germany.[9] The recommendations of this institute are binding on German scientists. The detection of microorganisms in concentrations >10,000/mL of PPFC was considered as infection; lower concentrations were judged as contamination or colonization only. A potential accidental contamination of samples may have occurred during the procedure. Finally, the clinical success after changes in the antibiotic regimen was able to distinguish between contaminants and true infectious agents.

In this study, we found a colonization of PPFCs despite the use of meropenem, ampicillin with sulbactam, levofloxacin, or piperacillin. In contrast, tazobactam showed the lowest resistance and best covering spectrum. Tazobactam may be the drug of choice in our patient cohort because the resistance profile is rather low, and this antibiotic reaches a high concentration in PPFCs, a necessary feature that should always be considered for the choice of antimicrobial drug.[12]

We are well aware that antibiotic susceptibility profiles depend on local antibiotic usage policy and the prior antibiotic treatment as well as the underlying diseases of patients. Our results indicate that a general guideline for management of PPFCs cannot be applied to all centers. However, microbiologic analysis of PPFCs should be performed to determine local guidelines to suit different populations and variations in clinical practices. This study suggests the use of tazobactam as an empiric, first-line treatment of our patients with pancreatitis and PPFCs, if antibiotic treatment is necessary.

Recent guidelines recommend the routine use of antibiotic prophylaxis when pancreatic cystic lesions are punctured.[20] However, in a retrospective study by Guarner-Argente et al,[21] no statistically significant differences were detected in postinterventional infection after EUS-FNA of pancreatic cystic lesions with or without empiric antibiotic prophylaxis. Their findings are consistent with ours, because 3 patients with antibiotic prophylaxis developed postprocedural fever, whereas only 1 patient without preinterventional antibiotics developed fever after intervention. However, a larger prospective study is needed to clarify the role of antibiotic prophylaxis prior EUS intervention.

In conclusion, our results indicate that cultures of PPFCs seem to be more valuable than blood cultures in identifying microorganisms in patients with pancreatitis. A sample of PPFCs for microbiologic analysis will be a valuable diagnostic tool because it leads to a more adequate therapy and helps to establish a local antibiotic guideline for the management of PPFCs in patients with pancreatitis.

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