The role of routine fine-needle aspiration in the diagnosis of infected necrotizing pancreatitis

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Background. *Diagnosing infected necrotizing pancreatitis (INP) may be challenging. The aim of this study was to determine the added value of routine fine-needle aspiration (FNA) in addition to clinical and imaging signs of infection in patients who underwent intervention for suspected INP.*

Methods. *We conducted a post hoc analysis of 208 consecutive patients from a prospective, multicenter database who underwent intervention because of suspected INP. In retrospect, 3 groups were constructed based on the patients preoperative characteristics: Clinical, imaging, and FNA. Patients in the clinical group had clinical signs of infection but no gas on preoperative computed tomography (CT) and no FNA performed before intervention. Patients in the imaging group had gas bubbles on the preoperative CT but no was FNA performed, whereas patients in the FNA group had a positive FNA before intervention. The reference standard for infection was the culture taken during the first intervention (either catheter drainage or necrosectomy).*

Results. *The initial intervention for INP was performed a median of 27 days (interquartile range, 20–39) after admission without difference between the 3 groups (*P *= .15). Infection was confirmed in 80% of 92 patients of the clinical group, in 94% of 88 patients of the imaging group, and in 86% of 28 patients of the FNA group (*P *= .07). Mortality was 19% and was not different between groups (*P *= .39).*

Conclusion. *INP can generally be diagnosed based on clinical or imaging signs of infection. FNA may be useful in patients with unclear clinical signs and no imaging signs of INP. (Surgery 2014;155:442-8.)*

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Acute pancreatitis is the most common gastrointestinal condition requiring acute hospitalization in the United States.[1] Twenty percent of these patients have necrotizing pancreatitis.[2] The 2012 revised Atlanta classification defines necrotizing pancreatitis by the presence of either pancreatic parenchymal or only peripancreatic necrosis.[3] In approximately 30% of these patients, infection of the necrosis occurs (infected necrotizing pancreatitis [INP]), which requires radiologic or operative intervention in the vast majority of patients.[2,4] Interventions in these often critically ill patients carry a morbidity of 50–100% and a mortality of 15–25%.[4-9] Therefore, many studies have focused on prevention of INP. Surprisingly, few studies have addressed the topic of diagnosing INP.

Suspicion of infected necrosis can be based on clinical signs only (eg, fever, organ failure), on imaging signs of gas bubbles in peripancreatic collections on computed tomography (CT), on positive microbiologic culture obtained by fine-needle aspiration (FNA), or on a combinations of all these factors.[10,11] Since the initial Atlanta

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classification[12] in 1993, only 1 retrospective study reported on the incidence of gas in peripancreatic collections (24% of 42 patients) in relation to patient outcome in patients with necrotizing pancreatitis.[10] In contrast, several studies reported on the use of FNA in diagnosing infected necrosis.[6,11,13-17] As a result of these studies, some authors propose routine FNA in patients with necrotizing pancreatitis, as reflected by the high use of FNA in the previous literature (40–100%).[5,17-19] The accuracy of FNA to diagnose infected necrosis may be high (range, 67–98%),[19-21] but, for several reasons, the added value of routine FNA may be limited.[7] First, with the current preferred approach of delayed intervention, even in case of infected necrosis, FNA seems to have limited therapeutic implications.[4,22] Second, false-negative and false-positive (contamination) rates have been reported up to be 25% and 15%, respectively.[7,18,23] Finally, although FNA is a considered to be a safe and minimally invasive procedure, it does carry a small risk of procedure-related complications (eg, bleeding, perforation, iatrogenic infection).[24]

The aim of this study was to determine the individual roles and (added) values of clinical and imaging signs and, especially, FNA in diagnosing INP.

PATIENTS AND METHODS

Patients. We performed a post hoc analysis in a prospective database of 639 patients with necrotizing pancreatitis, evaluated between March 2004 and November 2008 in all 8 Dutch university medical centers and 13 large teaching hospitals of the Dutch Pancreatitis Study Group. This cohort has been described previously.[4] During the study period, all patients admitted with acute pancreatitis were registered in a prospective database.[8,25] Patients were selected for the current study if they underwent intervention for suspected infection of peripancreatic or pancreatic necrosis. Patients were excluded if the intervention was performed for other indications than (suspected) infection (eg, abdominal compartment syndrome, bleeding, bowel ischemia, or perforation).

Definitions and groups. A definitive diagnosis of INP was established by a positive microbiologic culture obtained at the first intervention (either via percutaneous drainage or surgical necrosectomy). For this post hoc analysis, the intervention culture was considered to be the reference standard for infection, regardless of other subsequent cultures obtained by drainage or re-interventions. A positive FNA culture before intervention or the presence of gas in peripancreatic collections on CT was not considered definite proof for infection, being the diagnostic variables under study. In clinical practice, however, a positive FNA culture was indicative of infected necrosis. Patients without intervention for suspected infected necrosis were excluded from further analysis because the reference standard was lacking in these patients. All included patients were divided in 3 groups: (1) Clinical signs of infection (clinical group); (2) gas in peripancreatic collections on CT and clinical signs (imaging group); and (3) FNA and clinical signs (FNA group).

To facilitate the analysis between the study groups, patients who had both gas in peripancreatic collections on CT and in whom FNA cultures were performed ($n = 16$) were included in the imaging group, because FNA requires an additional intervention, whereas information on the presence of gas in peripancreatic collections can be derived from the CT that has already been performed routinely. In the clinical situation, however, this positive FNA was not ignored and used in the diagnostic workup to establish the diagnosis of infected necrosis; therefore, an additional sensitivity analysis was performed to determine the impact of including these 16 patients in the FNA group.

Treatment protocol. The treatment protocol has been described in detail previously.[4] In short, patients received broad-spectrum antibiotics in case of (suspected) INP initially. In case of clinical improvement, the antibiotic treatment regimen was narrowed based on culture results (if available). The majority of patients received broad-spectrum antibiotics for several weeks. Owing to the multicenter character of this study, it was not possible to record the exact use of antibiotics in all patients. Intervention was postponed if possible for ≥4 weeks after onset of symptoms to allow for demarcation and encapsulation of the infected collection, so-called walled-off necrosis. The minority of the present cohort ($n = 88$) was included in the PANTER trial and was randomized to open necrosectomy ($n = 45$) or to the step-up approach ($n = 43$).[8] Since 2006, a multidisciplinary expert panel, consisting of 8 gastrointestinal surgeons, 1 gastroenterologist, and 3 radiologists guided decisions on intervention. Patients with (suspected) INP were evaluated by the expert panel, and the treating physician was informed about the individual recommendations of the members of the panel. Notably, in every case, the ultimate decision for treatment and intervention was made by the treating physician.

Clinical group. Patients who had no gas in peripancreatic collections on CT and in whom no FNA was performed were classified as patients in whom the suspicion of INP was based on clinical signs. Unfortunately, no algorithm exists for establishing the diagnosis of infected necrosis only based on clinical signs; therefore, it is not possible to provide clear cutoff points of sign and biochemical and mechanical outcome parameters to define infection. Usually, clinical deterioration was an important observation in patients with (suspected) infected necrosis. Examples of clinical signs were persisting sepsis, (new or prolonged) organ failure, increased need for cardiovascular and/or respiratory and/or renal support, leukocytosis, increased levels of C-reactive protein, and fever. Moreover, no other infectious focus must be found or held responsible for the clinical deterioration. Because experienced clinical judgment is needed in these complex and usually critically ill patients, in the majority of patients the decision to intervene was advised by the expert panel.

Imaging group. Patients with gas bubbles on CT were included in this group. CTs were performed at the discretion of the treating physician. One dedicated abdominal radiologist (T.L.B.) reviewed all CTs, and was blinded for the clinical background and treatment.

FNA group. With the policy of postponing intervention regardless the presence of (suspected) infection, routine FNA was not used routinely. The indication for performing FNA was left to the treating physician; therefore, FNA was only performed in case of unclear clinical and radiologic signs of infection. FNA was performed with ultrasound or CT guidance.

Data collection. The following data were extracted from the prospective database: Patient demographics, past medical history, American Society of Anesthesiologists class, etiology, day of hospital admission, duration of hospital stay, laboratory findings, CT findings from the initial hospitalization and second review by an experienced abdominal radiologist, presence of infectious complications, presence of (multiple) organ failure, clinical course, type of intervention(s), cultures from FNA and first intervention, and mortality.

Statistical analysis. All patients were analyzed in the 3 predefined groups. Per group, all data were pooled and baseline characteristics were listed. Percentages were calculated for baseline characteristics and all intervention cultures were compared. Continuous data were presented as mean values ± standard deviation (SD), whereas and non-normally distributed data were presented as median (interquartile range [IQR]). Differences were compared with the Chi-square or Mann-Whitney U tests, as appropriate. All statistical analyses were performed using SPSS for Windows version 16.0.2 (SPSS, Chicago, IL).

RESULTS

Baseline characteristics. Of 639 consecutive patients with necrotizing pancreatitis, 208 (32%) underwent either percutaneous drainage or operative necrosectomy for suspected INP, and could be evaluated for the reference standard of infected necrosis. Median age was 60 years (IQR, 48–69) with a male:female ratio of 2:1. The clinical group consisted of 92 of 208 patients (44%); these patients had neither gas bubbles on CT nor was FNA performed. Gas in peripancreatic collections on CT was seen in 88 of 208 patients (42%; imaging group) and FNA was performed in 28 of 208 patients (13%; FNA group). Baseline characteristics are shown in Table I.

Timing of intervention. There was no difference in timing of the first intervention between the 3 groups. In the clinical group ($n = 92$), intervention was performed at a median of 27 days (IQR, 21–38) after hospital admission, versus 31 days (IQR, 22–46) in the imaging group and 31 days (IQR, 18–38) in the FNA group ($P = .15$).

Gas in collections with necrosis ($n = 88$) was seen after a median of 22 days (IQR, 13–37) after hospital admission and the first intervention was performed a median of 10 days later. The first FNA ($n = 28$) was performed a median of 17 days (IQR, 10–28) after hospital admission and the first intervention was performed a median of 14 days later.

Diagnostic accuracy. Infected necrosis was documented by a positive culture of material obtained during the first intervention (ie, the reference standard) in 74 of 92 patients (80%) in the clinical group, in 83 of 88 patients (94%) in the imaging group, and in 24 of 28 patients (86%) of the FNA group ($P = .07$).

In 19 of the 28 patients (68%) in the FNA group, the FNA cultures matched with the intervention cultures. In 8 of 28 patients (29%), other (new) micro-organisms were found during intervention; in these patients, the FNA culture was considered to be false negative. In 1 patient (4%), a false-positive culture was found. When all 44 patients who underwent FNA before intervention were analyzed (including all 16 patients with both gas bubbles and FNA), 27% of FNA cultures (12/44 patients) did not match with cultures taken from the intervention, regardless of the presence

Table I. Baseline characteristics

Characteristic	*All patients (n = 208)*	*Clinical group (n = 92)*	*Imaging group (n = 88)*	*FNA group (n = 28)*
Age (y)	60 (48–69)	58 (45–69)	61 (51–72)	57 (43–64)
Male gender	142 (68)	60 (64)	60 (68)	22 (79)
Etiology				
Biliary	101 (49)	36 (39)	49 (56)	16 (57)
Alcohol abuse	44 (21)	30 (33)	10 (11)	4 (14)
Other	18 (9)	6 (8)	7 (8)	5 (18)
Unknown	45 (21)	20 (21)	22 (25)	3 (11)
ASA class on admission				
I (healthy status)	57 (27)	21 (23)	22 (25)	14 (50)
II (mild systemic disease)	113 (54)	53 (59)	50 (57)	10 (36)
III (severe systemic disease)	38 (18)	18 (18)	16 (18)	4 (14)
Predicted severity of pancreatitis				
APACHE-II score on admission	8 (5–11)	9 (5–11)	8 (5–11)	6 (4–10)
APACHE-II score >8 on admission	95 (46)	47 (50)	42 (48)	6 (21)
Imrie-score on admission	4 (3–5)	4 (2–5)	3 (3–5)	4 (2–5)
Imrie-score ≥3 on admission	158 (76)	69 (75)	67 (76)	22 (79)
Highest CRP level in first 48 h of admission (mg/L)	295 (212–380)	289 (210–372)	289 (205–381)	335 (245–438)
CRP >150 (mg/L)	179 (86)	77 (78)	77 (88)	25 (89)
CT severity index	8 (6–10)	8 (4–10)	6 (6–10)	7 (6–8)
Pancreatic necrosis	156 (75)	66 (72)	70 (80)	20 (71)
Peripancreatic necrosis alone	52 (25)	26 (28)	18 (20)	8 (29)
Extent of pancreatic necrosis (%)				
<30	102 (49)	40 (45)	46 (52)	16 (57)
30–50	53 (25)	28 (30)	17 (19)	8 (29)
>50	53 (25)	24 (25)	25 (28)	4 (14)

Continuous variables are presented as median values (interquartile range); percentages are in parenthesis.
APACHE, Acute Physiology And Chronic Health Evaluation; *ASA*, American Society of Anesthesiologists; *CRP*, C-reactive protein.

of gas in peripancreatic collections on CT. In 11 of 44 patients (25%), other (new) micro-organisms were found during intervention compared with the FNA culture (median time between FNA and intervention 9 days; IQR, 5–20), and in 1 of 44 patients (2%), a positive FNA culture was found with subsequently a negative intervention culture. In this patient, the time interval between FNA and intervention was five days. These data are shown in detail in Table II.

Mortality. Overall mortality was 19% (40/208 patients) without differences between the groups: 18% (17/92 patients) in the clinical group, 17% (15/88 patients) in the imaging group, and 28% (8/28 patients) in the FNA group ($P = .39$). Mortality in all 44 patients who underwent FNA before intervention was 27% (12/44 patients).

Microbiology. In 184 of 208 patients (88%), infected necrosis was confirmed by culture taken at the first intervention. In 114 of these 184 patients (62%), the infection was monomicrobial, whereas in 70 patients (38%), ≥2 bacteria/fungi were cultured. The mortality between these groups did not differ (18%; 21/114 patients) with monomicrobial culture versus 21% (15/70 patients) with polymicrobial culture ($P = .62$). *Escherichia coli* was cultured most frequently (40%), followed by *Staphylococcus spp.* (28%) and *Enterococcus spp.* (25%). Yeasts were cultured in 9% of patients, predominantly *Candida spp.* No data were available about the resistance pattern of micro-organisms cultured from the necrosis.

DISCUSSION

This study suggests that the diagnosis of INP can be based on clinical and imaging signs in the majority of patients. FNA can be used selectively in patients in whom the clinical signs are unclear and have no imaging signs of infection.

Routine use of FNA has been advocated previously in patients suspected of having INP.[26,27] This recommendation dates from a time period where the diagnosis of infected necrosis was believed to require immediate operative treatment or interventional drainage. In current series, however, intervention was usually postponed if clinically

Table II. Data from 12 patients with discrepancy between FNA culture and intervention culture

Patient	*FNA culture*	*Sensitivity profile*	*Antibiotics started after culture*	*Intervention culture*	*Sensitivity profile*	*Antibiotics started after culture*	*Time between FNA and intervention (d)*
1	*Moraxella spp.*	PENI	IMIP, FLUCO	No growth	n.a.	IMIP, FLUCO	5
2	*C albicans* *E faecium*	VANCO, FLUCO	VANCO, FLUCO	*C albicans*, *E faecium*, *P aeruginosa*,	MERO, FLUCO	VANCO MERO, FLUCO	1
3	*H influenza*	Missing	Missing	*S salivarius*, *Prefotella* spp.	AUGM, PENI, COTRIM	Missing	1
4	No growth	n.a.	Missing	*Klebsiëlla* spp.	AUGM, CIPRO	MERO, CIPRO	5
5	*P mirabilis*	PENI, AUGM	IMIP	*C albicans*, *E faecalis*	AUGM, VANCO	IMIP	7
6	No growth	n.a.	None	*Enterococcus* spp.	VANCO	VACO	8
7	*E cloacae*	Missing	MERO	*E cloacae*, *E faecium*	Missing	VANCO, COTRIM	9
8	*Streptococcus* spp. *Enterococcus* spp.	Missing	VANCO, FLUCO, CEFTA	*B fragilis*, *E faecium*	Missing	VANCO	11
9	No growth	n.a.	None	*Citrobacter* spp., *E faecalis*	AUGM, IMIP	IMIP, TEICO, FLUCO	15
10	No growth	n.a.	TAZO	*Stenotrophomonas* spp.	TAZO, COTRIM	CLINDA, COTRIM	20
11	*E coli*	Missing	Missing	*E coli*, *E. cloacae*, *Streptococcus* spp.	Missing	Missing	36
12	No growth	n.a.	None	*S aureus*	FLUCLOX	FLUCLOX	44

CEFTA, Ceftazidim; *CIPRO*, ciproxin; *CLINDA*, clindamycin; *COTRIM*, cotrimoxazol; *FLUCO*, fluconazole; *FLUCLOX*, flucloxacilline; *IMIP*, imipenem; *MERO*, meroponem; *n.a.*, not applicable; *PENI*, penicillin; *TAZO*, tazocin; *TEICO*, teicoplanine; *UGM*, augmentin; *VANCO*, vancomycin.

possible until the necrosis had become walled off.[4,6,22,28] Thus, even after confirmation of the diagnosis of infected necrosis, intervention was postponed whenever possible. This attempt to put off the intervention for about 4 weeks is reflected by our data showing that the median timing of intervention was 29 (IQR, 22–41), without difference between the groups. Apparently, FNA did not necessarily prompt earlier intervention, whereas mortality was comparable between groups. Notably, no mortality was observed in the 11 patients with gas bubbles and/or positive FNA in whom intervention was postponed and ultimately waived because of successful conservative treatment.[4] These findings support the concept that the diagnosis of INP does not mandate an emergency intervention and are in line with previous studies.[4,7,29] Future studies should determine whether earlier intervention after positive FNA without the current 10- to 14-day delay can decrease morbidity or mortality.

The presence of gas in peripancreatic collections is considered by many as pathognomonic for INP.[11] Only 3 studies reported the incidence of gas in peripancreatic collections.[10,11,20] Two studies published before 1993 included only a small number of patients (<30).[11,20] The third study, describing 42 patients with pancreatic necrosis on CT, found gas bubbles in 20 patients (48%).[10] But, because no consecutive series was described, the actual incidence of gas bubbles in patients with necrotizing pancreatitis remained unclear. In the current study, only patients in whom an intervention was performed for suspected INP were included (208/639 patients). Even though this was a selected subgroup of patients, it enabled us to compare the CT (and FNA) findings with the reference standard.

Infection of necrosis can occur at any time after onset of symptoms, but has a peak incidence between weeks 3 and 4.[30] Therefore, FNA performed early in the disease course often yields negative results. Moreover, negative FNA cultures are obviously only reliable for a short period of time. Cutoff points varying from 1 to 27 days have been reported,[19,21,31] but most studies do

not actually report on the time between FNA culture and intervention.[6,11,13-17]

The role of antibiotics in patients with suspected INP remains a topic of debate. In the current study, almost all patients with suspicion of infected necrosis received broad-spectrum antibiotics as part of the conservative treatment strategy. Consequently, outcome of FNA cultures may be influenced and false-negative FNA cultures could occur. This possibility may be partly the reason for the high false-negative rate of 29%. Conversely, prolonged antibiotic treatment before intervention could result in a negative intervention culture and thus, false-positive FNA cultures and false-positive gas bubbles in peripancreatic collections. Whether antibiotics substantially influenced the intervention cultures remains unclear, although this possibility may explain in part the false-positive outcomes of both FNA and CT findings.

Our results show that in almost 40% of patients with INP, multiple micro-organisms were found at cultures taken from the first intervention and that in 27% of patients, these findings did not (fully) correspond with the micro-organisms found with FNA culture. This finding may indicate that translocation of other intestinal micro-organisms occurred in the time period between FNA and intervention. These findings do not support the routine narrowing of antibiotic treatment based on FNA cultures.

Our study has some limitations. First, because not all patients with necrotizing pancreatitis underwent a routine FNA and a subsequent intervention, this study cannot be seen as a purely diagnostic study; however, it seems rather unlikely that such a study will be ever performed given the clear ethical problems with such an approach. Second, both FNA and CT were performed at the discretion of the treating physician. We cannot exclude the possibility that only patients without obvious clinical signs and no gas bubbles on CT underwent FNA. This approach to treatment could lead to selection bias, but has no further implications for the management of the individual patient. The main strength of our report, however, lies in the use of a multicenter, prospective database focused specifically on intervention in necrotizing pancreatitis in a consecutive series of patients.

In conclusion, this study showed that in the majority of INP patients can be diagnosed based on clinical and imaging signs, and that FNA may be reserved for patients with unclear clinical signs without imaging signs of infection. Although FNA may lead to an earlier diagnosis of INP, it is unclear whether this is of additional value.

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