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Overuse and Misuse of Antibiotics and the Clinical Consequence in Necrotizing Pancreatitis

An Observational Multicenter Study

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Objective: The use and impact of antibiotics and the impact of causative pathogens on clinical outcomes in a large real-world cohort covering the entire clinical spectrum of necrotizing pancreatitis remain unknown.

Summary Background Data: International guidelines recommend broad-spectrum antibiotics in patients with suspected infected necrotizing pancreatitis. This recommendation is not based on high-level evidence and clinical effects are unknown.

Materials and Methods: This study is a post-hoc analysis of a nationwide prospective cohort of 401 patients with necrotizing pancreatitis in 15 Dutch centers (2010-2019). Across the patient population from the time of admission to 6 months postadmission, multivariable regression analyses were used to analyze (1) microbiological cultures and (2) antibiotic use.

Results: Antibiotics were started in 321/401 patients (80%) administered at a median of 5 days (P25-P75: 1-13) after admission. The median duration of antibiotics was 27 days (P25-P75: 15-48). In 221/321 patients (69%) infection was not proven by cultures at the time of initiation of antibiotics. Empirical antibiotics for infected necrosis provided insufficient coverage in 64/128 patients (50%) with a pancreatic culture. Prolonged antibiotic therapy was associated with *Enterococcus* infection (OR 1.08 [95% CI 1.03-1.16], $P = 0.01$). *Enterococcus* infection was associated with new/persistent organ failure (OR 3.08 [95% CI 1.35-7.29], $P < 0.01$) and mortality (OR 5.78 [95% CI 1.46-38.73], $P = 0.03$). Yeast was found in 30/147 cultures (20%).

Discussion: In this nationwide study of patients with necrotizing pancreatitis, the vast majority received antibiotics, typically administered

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This study is investigator-initiated (St. Antonius Hospital) and is supported by the Antonius Research Fund. The funder had no role in any part of the study design, conduct and analysis.

H.C.T., P.C.N. and Y.A.M. collected and entered all data, F.v.d.B. and S.M.v.D. verified all entered data. T.L.B. reviewed abdominal radiologic images. H.C.T. performed the statistical analysis. H.C.T. drafted the manuscript. F.v.d.B., P.C.N., S.M.v.D., J.v.B., C.S.W., D.S.U., Y.A.M., W.L.C., S.B., M.H., A.I., Y.I., J.M.J., P.J.F.d.J., R.Q., M.P.S., M.S., A.C.I.T.L.T., N.G.V., M.G.B., M.J.B., E.S., R.C.V., R.P.V., H.C.v.S. co-authored the writing of the manuscript. All authors critically assessed the study design, included patients in the study, edited the manuscript, and read and approved the final manuscript.

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The authors declare no conflicts of interest.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

ISSN: 0003-4932/23/27804-e812
DOI: 10.1097/SLA.0000000000005790

early in the disease course and without a proven infection. Empirical antibiotics were inappropriate based on pancreatic cultures in half the patients. Future clinical research and practice must consider antibiotic selective pressure due to prolonged therapy and coverage of *Enterococcus* and yeast. Improved guidelines on antimicrobial diagnostics and therapy could reduce inappropriate antibiotic use and improve clinical outcomes.

Keywords: necrotizing pancreatitis, antibiotics, antimicrobial, antifungal, microbiology

(*Ann Surg* 2023;278:e812–e819)

Antibiotic treatment remains the cornerstone of disease management when infected necrosis occurs in patients with necrotizing pancreatitis. However, optimal antibiotic use is challenging. Firstly, it remains difficult to differentiate between clinical deterioration caused by systemic inflammatory response syndrome (SIRS) or by sepsis due to infected necrosis.[1] Secondly, for targeted antibiotic therapy, microbiological cultures are required, but fine needle aspiration (FNA) is currently not routinely recommended, given the possibility of possible false-negative results and iatrogenic infection.[2]

While international guidelines do not recommend antibiotic prophylaxis,[2–4] empirical broad-spectrum antibiotics are recommended when infected necrosis is suspected based on clinical deterioration.[2–7] However, the worldwide use of broad-spectrum antibiotics may lead to antibiotic resistance.[8] Antimicrobial resistance is reported to be a leading cause of death around the world, indicating a health problem whose magnitude is at least as large as major diseases such as the human immunodeficiency virus.[9] Previous studies have concluded that there is an overuse and misuse of antibiotic regimens in patients with necrotizing pancreatitis.[10–13] However, the studies are either small and retrospective[11,13] or based only on questionnaires rather than clinical data[10,12] (the most recent data dates from 2013[12]). Since 2013, the treatment approach for infected necrosis has changed from invasive to less invasive interventions, with antibiotics playing a larger role. In the current era, there is limited understanding on the clinical impact of cultured microbes, antibiotic resistance, and antibiotic use. As a result, patients may keep receiving unnecessary or untargeted, broad-spectrum antibiotic therapy. To address this efficiency in clinical research, we evaluated the clinical impact of different pathogens and antibiotic use on clinical outcomes in the current era in a large prospective cohort of unselected patients with necrotizing pancreatitis.

MATERIALS AND METHODS

Study Design and Population

This study was a post-hoc analysis of patients included in the nationwide prospective registry of acute pancreatitis (PWN-CORE) of the Dutch Pancreatitis Study Group. A subset of these patients was also randomized in the TENSION study.[14] For the current study, all patients with necrotizing pancreatitis over 18 years of age, treated between January 1, 2010, and December 31, 2019, were selected, spanning 15 hospitals. Patients were excluded for which electronic medical records were unavailable, who exhibited signs of chronic pancreatitis according to the M-ANNHEIM criteria[15] or who were diagnosed with pancreatic carcinoma at admission. Approval was obtained for PWN-CORE by a central medical ethics committee and by the institutional review board of each participating hospital. For the current study, the medical ethics committee waived the need for additional ethical approval. This study was reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines[16] and conducted in accordance with the principles of the Declaration of Helsinki. All patients or their legal representatives gave written informed consent for the PWN-CORE registry.

Definitions

Acute pancreatitis was diagnosed according to the revised Atlanta classification.[17] Necrotizing pancreatitis was defined as either necrosis of pancreatic tissue or/and peripancreatic tissue demonstrated on a contrast-enhanced computed tomography (CT) or by a computed tomography severity index (CTSI)-score of 3 or higher.[17] An expert pancreatic radiologist (TLB) reviewed all abdominal radiologic images to determine the computed tomography severity index-score and to assess the presence and location of peripancreatic fluid collections and (peri)pancreatic necrosis.

Antibiotic use information was collected from the time of admission until 6 months postadmission. We included both antibacterial and antifungal therapy but excluded selective decontamination of the digestive tract. Broad-spectrum antibiotics included carbapenems, quinolones, metronidazole, and third-generation or higher-generation cephalosporins.

For the current study, we made a distinction between a proven and nonproven infection according to predefined criteria and following a standard diagnostic work-up (ie, blood cultures, urine cultures, chest x-ray). This distinction was based on the notes of the treating clinician. Proven infections included pneumonia, cholangitis, cholecystitis, urinary tract infection, infected (peri-)pancreatic necrosis, and other less prevalent infections. All definitions are provided in Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/SLA/E397. Nonproven infections were defined as instances of clinical suspicion for one of the aforementioned infections or fever of unknown origin but without meeting the criteria for proven infections. Infected necrosis was considered proven when (1) gas configurations were present on contrast-enhanced CT before the first pancreatic intervention or (2) either FNA or the first drainage procedure from pancreatic of peripancreatic fluid resulted in a positive culture. If infection of the pancreatic necrosis could not be proven according to our criteria, but there was a clinical suspicion according to the treating clinician, we defined this as suspected infected necrosis (nonproven infection).

We only included cultures that were directly obtained from percutaneous catheter drains within 24 hours after the intervention or during radiologic, endoscopic or surgical intervention (including FNA) to describe the microbiological pathogens in infected pancreatic necrosis and to distinguish relevant cultures from drain colonization. Antimicrobial therapy consisted of both antibiotics and antifungals but did not include selective decontamination of the digestive tract. Antibiotic susceptibility was defined as reported by the local microbiology laboratories. When a susceptibility report was missing, the susceptibility was additionally interpreted by a clinical microbiologist (ES) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines[18] (Supplementary Text S2, Supplemental Digital Content 1, http://links.lww.com/SLA/E397). Multidrug-resistant bacteria are described in Supplementary Text S3, Supplemental Digital Content 1, http://links.lww.com/SLA/E397.

Data Collection

Using a standardized case-record form, clinical data were collected prospectively during the initial hospital admission, and follow-up data was collected retrospectively. Data regarding (indications for) antibiotics, clinical outcomes (ie, interventions, organ failure, mortality, readmissions and length of hospital stay) was collected from the date of admission until the last date of data collection (January 2020) or death. If, at any time before or during follow-up, a patient was transferred to another hospital, all the required follow-up data was retrieved from that institution. All data were collected by 1 author (H.C.T.) and subsequently verified by a second author (F.v.d.B.). Discrepancies were resolved by consensus during research meetings of the Dutch Pancreatitis Study Group. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical Analysis

The timing and indication of all antimicrobial therapies were reported as descriptive data. We separately assessed antibiotic use early in the disease (< 7 and <14 d after admission), when it was less likely that patients had already developed infected necrosis. Antibiotics and their susceptibility were reported for patients in whom a pancreatic culture was obtained. Microbiological pathogens and their characteristics obtained from pancreatic cultures were described and compared. Descriptive data was reported as a mean with SD when normally distributed and as a median with interquartile ranges (P25-P75) when not normally distributed. Categorical data was shown as frequencies and percentages. When multivariate analyses were not deemed possible, predefined as less than 40 events of the outcome, univariate analyses were performed using Fisher exact test or χ^2 test for categorical data and the Student *t*-test or the Mann-Whitney *U* test for continuous data. To adjust for potential confounding factors, generalized linear models were constructed to explore the effect and duration of antibiotics on microbiological findings and clinical outcomes. We also constructed generalized linear models to explore the association between microbiological pathogens and clinical outcomes. The variables included as covariates varied by the clinical outcome, including variables that were considered to be associated with a poor clinical course. The selection was based on clinical reasoning and was reported for each variable in Supplementary Table S4, Supplemental Digital Content 1, http://links.lww.com/SLA/E397. If applicable, we calculated odds ratios (OR) with their respective 95%-confidence intervals (CI). A P value <0.05 was considered statistically significant. Statistical analysis was performed using R (R version 3.6.1 (2019-07-05)).

RESULTS

Between 2010 and 2019, 1593 patients with acute pancreatitis across the 15 participating hospitals were registered in the PWN-CORE registry and screened for eligibility. In total, 401 patients with necrotizing pancreatitis were included in the present study (Fig. 1). Clinical characteristics are provided in Table 1, and clinical outcomes and interventions are provided in Table 2. The median follow-up was 46 months (P25-P75: 28-66).

Antibiotics were started in 321 patients (80%), after a median of 5 days (P25-P75: 1-13) following admission. At the start of antibiotic treatment (ie, for all indications), 221 of the 321 patients (69%) did not have a proven infection. Of these patients, 154/221 (70%) eventually developed an infection after a median of

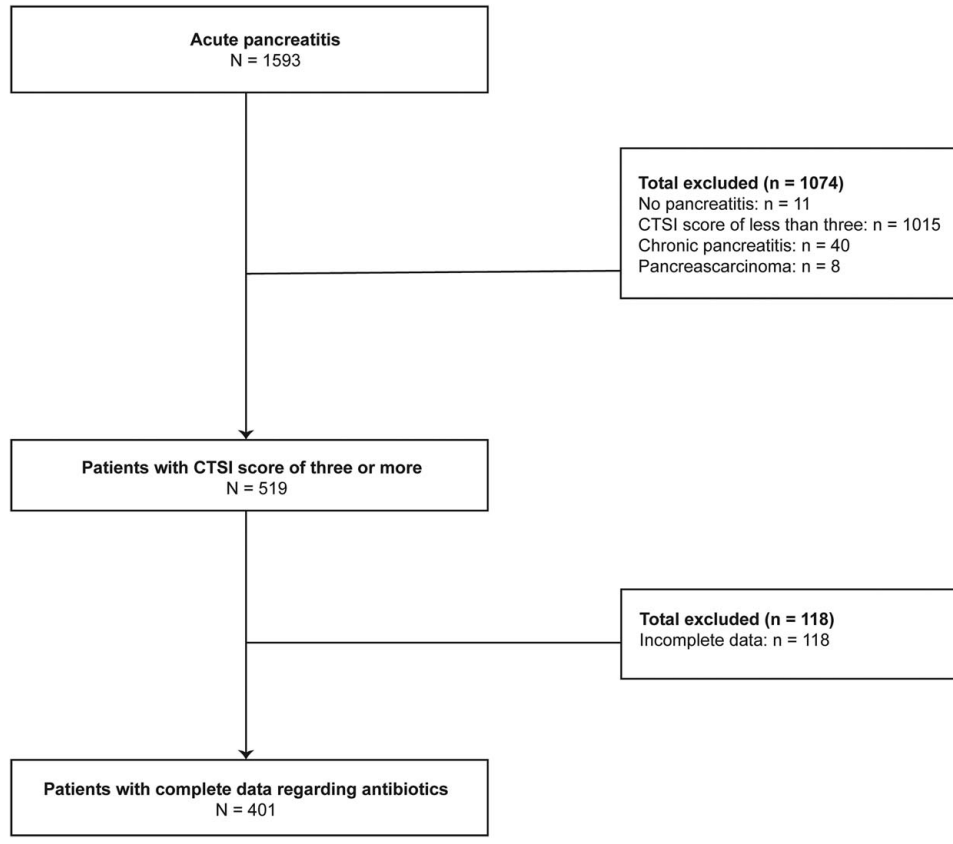

FIGURE 1. Inclusion flowchart.

TABLE 1. Clinical Characteristics in 401 Patients with Necrotizing Pancreatitis

	Overall N = 401, n (%)
Age (y)	59 (48–69)
Male sex	244 (61)
Etiology	
Biliary	187 (47)
Alcohol	61 (15)
Post-ERCP	43 (11)
Idiopathic	64 (16)
Other	46 (11)
Medical history	
Cardiovascular	174 (43)
Pulmonary	53 (13)
Chronic renal	17 (4)
Diabetes mellitus	47 (12)
ASA*	
1	133 (33)
2	176 (44)
3	78 (20)
4	4 (1)
Smoking, yes†	83 (21)
Alcohol use‡	192 (65)
BMI§	28.3 (24.8–31.6)
Laboratory values‖	
Leukocytes¶ (10^9/l)	17.8 (13.9–22.2)
CRP# (mg/l)	288 (191 – 352)
Imaging severity	
CT severity index**	6 (4–8)
Parenchymal necrosis	172 (67)
Pattern parenchymal necrosis††	
Right	4 (2)
Left	14 (8)
Central	78 (45)
Subtotal	27 (16)
Diffuse	47 (27)
Extent of necrosis‡‡	
< 30%	91 (23)
30-50%	37 (9)
> 50%	43 (11)
Follow-up (m)	46 (28–66)

Data are presented as n (%) or median (interquartile range: P25-P75).
Missing patients:
* = 10.
† = 148.
‡ = 107.
§ = 263.
¶ = 39.
‖Highest value within 48 hours after admission.
= 37.
** = 146.
†† = 144.
‡‡ = 144.
ASA, American Society of Anesthesiologists; BMI, body mass index; CRP, c-reactive protein; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; N, number.

TABLE 2. Pancreatic Interventions and Clinical Outcomes in 401 Patients With Necrotizing Pancreatitis

	Overall N = 401, n (%)
Clinical outcomes	
Death pancreatitis related	28 (7)
Hospital stay length, overall	44 (20–79)
Initial	23 (13–51)
Readmission	259 (65)
Length hospital stay readmission	20 (7–43)
Infected necrosis	198 (49)
Timing infected necrosis after admission	29 (19–47)
Gas configurations on CT	34 (14)
Positive pancreatic culture	111 (46)
Both gas configurations and positive pancreatic culture	53 (22)
ICU-admission	157 (39)
Length of ICU-stay	12 (4–35)
Organ failure	124 (31)
Transient SOF	24 (21)
Persistent SOF	84 (72)
Transient MOF	14 (12%)
Persistent MOF	63 (54)
Extra pancreatic infections before IPN or pancreatic intervention	
Pneumonia	74 (18)
Urinary tract infection	73 (18)
Interventions	
Pancreatic intervention or FNA	204 (51)
Percutaneous catheter drainage	119 (60)
No. PCD	3 (1–5)
Endoscopic transluminal drainage	121 (61)
No. of ETD	1 (1–1)
Necrosectomy	93 (47)
ETN	58 (29)
No. of ETN	2 (1–4)
Surgical necrosectomy	41 (21)
No. of SN	1 (1–2)
Need for additional intervention	150 (75)
Total number of pancreatic interventions for IPN	3 (2–5)

Data are presented as n (%) or median (interquartile range: P25-P75).
CT indicates computed tomography; ETD, endoscopic transluminal drainage; ETN, endoscopic transluminal necrosectomy; FNA, fine needle aspiration; ICU, intensive care unit; IPN, infected pancreatic necrosis; MOF, multiple organ failure; PCD, percutaneous catheter drainage; SN, surgical necrosectomy; SOF, single organ failure.

10 (IQR 3–29) days following the start of antibiotics. Infected necrosis was the most common first proven infection following initiation of antibiotics (n = 92, 60%). In 251 of 321 patients (63%), antibiotics were started within 14 days following admission, with no proven infection in 178 (71%) patients. In those first 14 days, pneumonia was the most common proven infection (n = 21, 30%). The median duration of antibiotic use was 27 days (P25-P75: 15-48). Indications at the different time points for starting antibiotics in the disease course are given in Table 3.

Antifungals were started in 74 of 401 patients (23%) after a median of 33 days (P25-P75: 19-51), 8 of the 74 (11%) had no proven fungal infection. In the 66 (89%) patients with a proven fungal infection, antifungals were most often started for a yeast-positive pancreatic culture (n = 47, 71%). The median duration of antifungals was 15 days (P25-P75: 7-24). Information on *Clostridioides difficile* is provided in Supplementary Text S5, Supplemental Digital Content 1, http://links.lww.com/SLA/E397.

Infected Necrosis and Antimicrobial Therapy

Overall, in 260 of 401 patients (65%), antimicrobial therapy was administered for either suspected or proven infected necrosis after a median of 17 days (P25-P75: 8-29) following admission. Meropenem was the most prescribed antibiotic (n = 76, 29%), followed by cefuroxime (n = 43, 17%) (Table S6, Supplemental Digital Content 1, http://links.lww.com/SLA/E397). Infected necrosis was proven in 198 of 401 patients (49%) after a median of 29 days (P25-P75: 19-47). In 179 of the 198 (90%) patients, antibiotics were started for a median duration of 11 days (P25-P75: 6-19) at a median of 20 days (P25-P75: 9-39) before confirmation

TABLE 3. Indications for Antimicrobial Therapy in 401 Patients with Necrotizing Pancreatitis

	First AB N = 321 (80%), n (%)	First AB within 7 d after Admission N = 197 (62%), n (%)	First AB within 14 d after Admission N = 251 (78%), n (%)	AB before diagnosis infected pancreatic necrosis N = 179 (91%), n (%)	First AF N = 74 (23%)
No proven infection	221 (69)	148 (75)	178 (71)	129 (72)	8 (11)
Fever e.c.i.	68 (30)	61 (41)	64 (36)	41 (32)	0 (0)
Suspected infected pancreatic necrosis	108 (48)	46 (31)	70 (39)	70 (54)	0 (0)
Suspected pneumonia	29 (13)	23 (16)	27 (15)	9 (7)	0 (0)
Suspected cholangitis	16 (7)	14 (9)	15 (8)	6 (5)	0 (0)
Suspected cholecystitis	1 (0.4)	1 (1)	1 (1)	1 (1)	0 (0)
Suspected urinary tract infection	1 (0.4)	1 (1)	1 (1)	0 (0)	0 (0)
Prophylactic during procedure	2 (1)	2 (1)	2 (1)	2 (2)	0 (0)
Broad coverage of potential yeast	NA	NA	NA	NA	8 (100)
Proven infection	100 (31)	49 (25)	73 (29)	50 (28)	66 (89)
Infected pancreatic necrosis	24 (24)	4 (8)	9 (13)	11 (22)	47 (75)
Pneumonia	24 (25)	16 (33)	21 (30)	16 (32)	5 (8)
Cholangitis	13 (14)	12 (25)	12 (17)	4 (8)	0 (0)
Cholecystitis	3 (3)	3 (6)	3 (4)	2 (4)	0 (0)
Urinary tract infection	17 (18)	6 (12)	13 (18)	8 (16)	0 (0)
Other	19 (19)*	8 (8)†	8 (11)‡	3 (6)§	14 (17)‖

Data are presented as n (%), mean (±SD), or median (interquartile range: P25-P75).

Note: data were available for all 401 patients unless differently specified behind the characteristic:

*Other: phlebitis n = 4, parotitis n = 3, line infection n = 3, spleen abscess = 1, clostridium difficile infection n = 1, secondary peritonitis due to duodenal perforation n = 2, gastric perforation n = 1, infected ascites n = 1, bacteremia e.c.i. n = 3.

†Other: phlebitis n = 2, parotitis n = 2, line infection n = 1, spleen abscess n = 1, secondary peritonitis due to duodenal perforation n = 1, gastric perforation n = 1.

‡Other: phlebitis n = 4, parotitis n = 3, line infection n = 2, spleen abscess n = 1, secondary peritonitis due to duodenal perforation n = 2, gastric perforation n = 1, bacteremia e.c.i. n = 2.

§Other: phlebitis n = 3, parotitis n = 3, line infection n = 2, Clostridioides difficile n = 1.

‖Other: bacteremia n = 5, candida esophagitis n = 7, candida in sputum n = 5, line infection n = 2.

AB indicates antibacterial therapy; AF, antifungal therapy; N number.

of infected necrosis; 125 of the 179 (70%) patients received broad-spectrum antibiotics. A total of 29 of 198 patients (15%) with proven infected necrosis were treated with antibiotics alone and did not undergo an invasive intervention.

An FNA or pancreatic intervention was performed in 204 patients (51%). A pancreatic culture was obtained in 176 of these 204 patients (86%). In 165 of the 204 patients (66%), the pancreatic culture was obtained during the initial intervention. Of these, 128 (78%) received empirical antibiotics at the time of culturing, and 102 of the 128 (80%) received antibiotics for more than 24 hours before culturing (Supplementary Table S7, Supplemental Digital Content 1, http://links.lww.com/SLA/E397). In 62 of the 128 patients (48%), the micro-organisms were either partially (n = 24, 39%) or completely unsusceptible (n = 38, 61%) to the antibiotics that were started empirically. Broad-spectrum antibiotics, as recommended in the current guidelines, were administered in 55 of the 62 patients (89%). This was comparable to the group of patients in which the micro-organisms were susceptible to the antibiotics (n = 55 (78%); $P = 0.96$). *Enterococcus* spp, specifically *Enterococcus Faecium*, was more often found in patients in whom the micro-organisms were (partially) unsusceptible ($P = 0.03$) (Table S8, Supplemental Digital Content 1, http://links.lww.com/SLA/E397). In these patients, antibiotics were adjusted according to the antibiotic susceptibility profile for 53 patients (85%), with no adjustments made for the remaining 9 patients (15%).

Micro-organisms Identified in Pancreatic Samples

An FNA was performed in 41 of 401 patients (10%), with positive results in 31 of 41 patients (76%). A follow-up culture was obtained from the first pancreatic intervention in 23 of 31 patients (74%), with similar micro-organisms identified as in the FNA in 11 cultures (48%). Between FNA and the first pancreatic intervention, 17 of the 23 patients (74%) received antimicrobial therapy for a median of 13 days (P25-P75: 4 -17).

Overall, the culture was positive at least one time during the study period in 164 of the 176 patients (93%) in whom a pancreatic sample was obtained. In 147 of 176 patients (80%), cultures were obtained within 24 hours after invasive pancreatic intervention (Table S9, Supplemental Digital Content 1, http://links.lww.com/SLA/E397). Cultures were polymicrobial in 75 of 146 patients (51%). Gram-negative bacteria were isolated in 91 of 146 patients (62%), with *Escherichia coli* most often reported (n = 48, 33%). Gram-positive bacteria were isolated in 100 patients (68%), with *E faecium* (n = 47, 32%) most often reported. Yeast were found in 30 patients (20%), with *Candida albicans* (n = 22) most often reported. In 3 patients (2%), multidrug-resistant bacteria were found: ESBL-E (n = 2) and tobramycin and ciprofloxacin-resistant *Morganella* spp (n = 1).

Additional pancreatic intervention was performed in 150 of the 204 patients (74%) after a median of 11 days (P25-P75: 6-18) following the first intervention. In 130 of these 150 patients (87%), antimicrobial therapy was administered between the first and second intervention for a median of 6 days (P25-P75: 3-10). The reported micro-organisms in the cultures of the repeated intervention are described in Supplementary Table S10, Supplemental Digital Content 1, http://links.lww.com/SLA/E397. A substantial increase in the presence of multidrug-resistant bacteria [most often ESBL (n = 5, 56%) and yeast was identified (n = 9, 14%) and n = 17 (27%), respectively].

Clinical Associations of Antibiotics and Micro-organisms

Univariate comparisons of clinical outcomes and interventions are provided in Supplementary Table S11, Supplemental Digital Content 1, http://links.lww.com/SLA/E397.

The duration of antibiotic therapy overall and before a pancreatic culture was associated with the finding of *Enterococcus* spp (adjusted OR 1.08 (95% CI 1.03-1.16; $P = 0.01$ and adjusted OR 1.01 (95% CI 1.00-1.02; $P = 0.04$)). The finding of *Enterococcus* spp in the first pancreatic culture was associated with a higher rate of new or persistent organ failure (adjusted OR 3.68 (95% CI 1.61-8.79; $P < 0.01$). Higher mortality rates were associated with pancreatic infections with *Enterococcus* spp, isolated in either the initial or repeat pancreatic culture (adjusted OR 5.78 (95% CI 1.46-38.73; $P = 0.03$) and adjusted OR 4.47 (95% CI 1.40 – 1.724; $P = 0.02$)). Covariates included in the generalized linear models are provided in Supplementary Table S4, Supplemental Digital Content 1, http://links.lww.com/SLA/E397.

DISCUSSION

We found that antibiotics are started in a large proportion of patients with necrotizing pancreatitis, often without a proven infection. In patients with infected necrosis, half of the identified micro-organisms were partially or not at all susceptible to the empirically started antibiotics. The prolonged duration of antibiotics was associated with more *Enterococcus* spp as a cultured pathogen, while the presence of *Enterococcus* spp in pancreatic tissue was associated with increased organ failure and mortality.

In line with previous studies,[10–13] antibiotics are still widely and inconsistently administered early in the disease course (80%) in contradiction to current guidelines.[2–4] The drawback of these studies is that they are either small and retrospective[11,13] or based solely on questionnaires rather than clinical data.[10,12] In addition, all the studies suffer from a lack of current data, with the most recent data dating from 2013.[12] Nevertheless, our findings show that clinical practices regarding the administration of antibiotics have not been improved since the early 2000s. This continues overuse and misuse of antibiotics and the associated avoidable, negative patient outcomes and underlines the importance of bringing these findings to the forefront.

In a similar vein, antimicrobial therapy is not indicated for SIRS without a proven infection (generally <14 d after the onset of disease)[1]; however, three-quarters of the patients received antimicrobial therapy within this time frame. This is presumably influenced by the challenges to clinically distinguish between SIRS and sepsis and the lack of knowledge regarding the timing of infections in necrotizing pancreatitis. These challenges further highlight the need for more accurate tools to accurately distinguish between inflammation and infection, which will inform when to withhold antibiotic treatment.

In line with previous research, our study shows gastrointestinal microbiota, particularly *E. faecium* and *E. coli*,[19] dominate the pancreatic cultures. Although carbapenems, specifically meropenem, were most frequently used as the empirical antibiotic when infected necrosis was suspected, *E. faecium* – which is intrinsically not susceptible to carbapenems – was 1 of the most frequently isolated micro-organisms. Since *Enterococcus* spp and fungi are generally not susceptible to the recommended empirical broad-spectrum antibiotics, it is likely that there is ongoing migration of gastrointestinal micro-organisms during antibiotic treatment. As a result, empirical therapy is likely insufficient to treat those patients and therefore cannot be treated with antibiotics alone. We also found an increased rate of organ failure and mortality in patients infected with *Enterococcus* spp, further underlining the potential benefit of targeted antibiotic treatment. In comparative literature, enterococcal bacteraemia was also associated with increased mortality rates.[20,21] One study found inappropriate antibiotic therapy to be an independent risk factor for mortality in enterococcal bacteraemia.[22] However, these findings should be interpreted with caution. Despite performing multivariate analyses, it remains unclear whether prolonged antibiotic usage and subsequently potential organ failure and mortality, can be prevented in these complex patients. Furthermore, antibiotic selective pressure may explain these results: prolonged treatment leads to the selection of opportunistic pathogens such as *Enterococcus* spp. Nevertheless, our findings suggest that for patients with suspected infected necrosis, obtaining early, multiple, and repeat cultures from pancreatic necrosis to adjust empirical antimicrobial therapy should be considered instead of treating the blind with a wide range of antibiotics. Furthermore, empirical coverage of *Enterococcus* could play a potential role in antibiotic stewardship and future research.

Based on the first culture, only half (50%) of patients received adequate antimicrobial therapy. The lack of adequate therapy can be explained by previous treatment with antibiotics that treat the sensitive pathogens. Furthermore, it remains unknown if every identified micro-organism is clinically relevant. Since all patients underwent pancreatic intervention due to clinical stagnation or clinical deterioration, it seems plausible that the untreated pathogens are clinically relevant and therefore should be treated.

Culture-based antimicrobial therapy could potentially increase the number of patients who can be treated without invasive interventions and reduce the severity of clinical outcomes due to suboptimally treated micro-organisms. While we found that 15% of the patients could be treated with antibiotics alone, the POINTER trial showed that 35% of the patients in the postponed drainage group could be treated with antibiotics alone, without drainage.[23] This difference could be explained by the design and focus of the POINTER trial, in which all patients with infected necrosis were closely prospectively monitored on a daily basis and randomized when possible, compared with prospectively monitoring once or twice a week in our cohort. In daily clinical practice, however, it is common and according to the guidelines to immediately schedule a drainage procedure in case of infected necrosis. However, in the POINTER trial, the effect of antibiotics was awaited, given the patients a chance to recover before the drainage procedure. Furthermore, targeted antibiotic therapy was started in a subset of patients based on FNA. Routine FNA could be a potential solution to prevent 'blind' antibiotic treatment, an approach currently discouraged by the guidelines.[2] In our study, half of the patients' FNA culture results differed from the subsequent culture following the pancreatic intervention; this result may be explained either by the growth of new micro-organisms under antimicrobial therapy or by only a limited part of the collection sampled through FNA. This emphasizes the importance of FNAs in multiple locations of the collection and the importance of obtaining cultures during each pancreatic intervention.

As compared with the current literature, the incidence of multidrug-resistant bacteria in the first pancreatic tissue sample was relatively low.[24] This may be explained by the restrictive antibiotic policies in the Netherlands. However, an increase in the presence of multidrug-resistant bacteria and yeast was found in repeat pancreatic cultures. This result is worrisome, particularly

for countries with less restrictive antibiotic policies, as (1) multidrug-resistant bacteria and yeast infections are associated with prolonged hospitalization and poor prognosis[25–31] and (2) antibiotic resistance, the most commonly used antibiotics for infected necrosis are gradually losing their effectiveness.[8] If found in the cultures, empirical fungal therapy and treatment of the yeast should be potentially considered. Notably, the current national guidelines only recommend consideration of empirical fungal therapy in selected individual cases.[32]

The results of this study should be interpreted in light of some limitations. Firstly, this is a post-hoc analysis of prospectively collected data. Although all data has been carefully collected and evaluated, a part of the data regarding antimicrobial therapy was retrospectively collected from electronic records. Secondly, the percentage of patients with infected necrosis in our cohort was relatively high as compared with the literature.[33,34] This could be explained by our focus on several prospective studies on invasive intervention in patients with infected necrosis during the study period.[14] Thirdly, data from the Netherlands, a country with low antibiotic resistance may not be fully generalizable to countries with higher levels of antibiotic resistance.[35] Strengths of this study include the fact that this is the first multicenter study on the whole spectrum of antimicrobial therapy and its clinical impact in a large sample size of patients with acute necrotizing pancreatitis in recent real-world clinical practice. Nevertheless, even in the Netherlands, where care for pancreatitis patients is to a great extent centrally organized within the Dutch Pancreatitis Study Group, there remains meaningful opportunity to improve in the use of antibiotics. We can extrapolate that there is probably significant potential to improve the use of antibiotics in many other countries with similar healthcare organizations. As mentioned earlier, this magnitude of the opportunity underlines the importance to make the current guidelines and recommendations regarding antibiotic use known to all of those who treat patients with acute pancreatitis. This can be achieved via presentations at national and international conferences and by implementing stricter antibiotic policy regulations in hospitals (e.g., establish one responsible department).

In conclusion, this study shows the current extensive use of antibiotics in patients with acute necrotizing pancreatitis early in the disease course, when infected necrosis rarely occurs. Half of the patients with infected necrosis received inappropriate empiric antimicrobial treatment. Our findings emphasize the need for clear guidelines the use of antimicrobial resources and diagnostic testing (i.e., FNA), with a potential role for empirical coverage of *Enterococcus* and yeast infections guided by antibiotic stewardships. Furthermore, prospective observational studies and large, pragmatic randomized trials are needed to define more clear indications, timing, and duration of antibiotic treatment in patients with both sterile and infected acute necrotizing pancreatitis.

ACKNOWLEDGMENTS

The authors thank Zachary Del Duca for reviewing the manuscript for grammar and style.

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