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Blood Culture Positivity in Patients with Acute Appendicitis – A Propensity-score Matched Prospective Cohort Study

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Abstract

Background

The prevalence of bacteraemia in acute appendicitis is unknown. We aimed to assess prevalence and predictive factors of bacteraemia in adult patients with appendicitis.

Methods

In this prospective propensity-score matched cohort study, patients were recruited as part of one single-centre prospective observational study assessing appendicitis microbiology in concurrence with two randomized controlled trials on non-operative treatment of uncomplicated acute appendicitis. All patients evaluated for enrollment in these three trials between April 2017 and December 2018 with both a confirmed diagnosis of appendicitis and available blood culture on admission were included in this study. Potential predictive factors of bacteraemia (age, sex, BMI, body temperature, C-reactive protein (CRP), leukocyte count, comorbidities, symptom duration, and appendicitis severity) were assessed. Prevalence of bacteraemia was determined by all available blood cultures followed by propensity-score matching using sex, age, BMI, CRP, leukocyte count, and body temperature of the patients without available blood culture.

Results

Out of the 987 patients with appendicitis, 271 patients had available blood culture and the prevalence of bacteraemia was 12% (n=33). Based on propensity score estimation, the prevalence of bacteraemia in the whole prospective appendicitis cohort was 9%. Bacteraemia was significantly more frequent in complicated acute appendicitis (15%; 29/189) compared with uncomplicated acute appendicitis (5%; 4/82) (p=0.015). Male sex (p=0.024) and higher body temperature (p=0.0044) were associated with bacteraemia.

Conclusion

Estimated prevalence of bacteraemia in patients with acute appendicitis was 9%. Complicated appendicitis, male sex, and higher body temperature were associated with bacteraemia in acute appendicitis.

Introduction

With an incidence of 100-200 cases per 1000.000 person years(1), acute appendicitis is one of the most common reasons for acute abdominal pain and abdominal infections are the second most common source of sepsis(2, 3). The over century-long paradigm of appendectomy as standard treatment for all acute appendicitis patients has recently been challenged by the effectiveness and safety of non-operative treatment of computed tomography (CT) confirmed uncomplicated acute appendicitis(4-12). With epidemiological and clinical data supporting the different disease hypothesis of uncomplicated and complicated acute appendicitis(5, 12-15), further research is needed on understanding and identifying these different forms of acute appendicitis. During the coronavirus pandemic (COVID-19), antibiotics were acknowledged as a safe alternative to surgery for uncomplicated acute appendicitis by the American College of Surgeons (COVID-19 Guideline for Triage of Emergency General Surgical Patients)(16) as nonoperative treatment would allow limiting inpatient bed use and reimplementation of health care resources.

To our knowledge, there are no reported studies on blood culture positivity in adult patients with appendicitis. There are studies assessing bacteraemia postoperatively after appendectomy(17) and many studies with specimens obtained from appendiceal lumen or swab samples from suppurative peritoneal fluid or periappendiceal abscess(18-20), but only few small studies on bacteraemia in patients with appendicitis on admission(20-22). In the early 1990's, a small retrospective study on children reported positive blood cultures of 17% and 8% in perforated and non-perforated acute appendicitis, respectively(23) . In a small prospective paediatric study, the prevalence of bacteraemia in patients with acute appendicitis was 6%(21). In a retrospective cohort of 1315 children, there were 288 patients with available blood culture data on admission with a blood culture positivity prevalence of 0.35%(22). A recent metagenome analysis study profiling bacterium in ascites and blood of patients with acute surgical abdomen found no positive blood cultures in patients with appendicitis (24).

Bridging the knowledge gaps in understanding the aetiology and pathophysiology of uncomplicated and complicated acute appendicitis is of utmost importance to be able to optimize the accuracy of the pre-intervention diagnosis of appendicitis severity allowing the assessment and tailoring of all available treatment options accordingly. The aim of this study was to assess the prevalence of blood culture positivity in a large prospective patient cohort with CT and/or clinically confirmed complicated or uncomplicated acute

appendicitis. We also aimed to evaluate potential predictive factors associated with blood culture positivity mainly focusing on the appendicitis severity.

Methods

Study Design

This prospective study was a pre-planned subgroup analysis of blood culture data collected at Turku University Hospital in Finland in the prospective observational cohort study MAPPAC(25) (Microbiology APPendicitis ACuta) and the concurrent randomized controlled trials APPAC II and APPAC III(6, 7). MAPPAC (NCT03257423) is a prospective clinical trial conducted in close synergy with the concurrent APPAC II (NCT03236961) and APPAC III (NCT03234296) randomized clinical trials (RCTs). The MAPPAC study has both a single-centre and multicentre arm and this blood culture study is part of the single-centre arm at Turku University Hospital. The aim of this study is to evaluate the microbiological and immunological aspects in the aetiology of uncomplicated and complicated acute appendicitis.(25) APPAC II is a multicentre, open-label, noninferiority RCT comparing oral moxifloxacin with intravenous ertapenem followed by oral levofloxacin and metronidazole in the management of CT-confirmed uncomplicated acute appendicitis aiming to demonstrate both the ability of oral antibiotics alone to manage acute appendicitis and the noninferiority of oral antibiotics compared with intravenous followed by oral antibiotics(7). APPAC III is a multicentre, double-blind, placebo-controlled, superiority RCT comparing antibiotic therapy (intravenous ertapenem followed by oral levofloxacin and metronidazole) with placebo in the treatment of CT-confirmed uncomplicated acute appendicitis aiming to evaluate the role of antibiotics in the resolution of uncomplicated acute appendicitis(6). All patients gave written informed consent. The trial protocol was approved by the ethics committee of Hospital District of Southwest Finland.

Study participants

Patients were recruited as part of one single-centre prospective observational study (MAPPAC) in concurrence with the two RCTs (APPAC II and III), in which all patients aged 18 to 60 years admitted to the emergency department with clinical suspicion of acute appendicitis and uncomplicated appendicitis confirmed by CT were evaluated for RCT enrollment. In addition to enrolling the patients with uncomplicated acute appendicitis evaluated for enrollment in the RCTs, the MAPPAC trial also enrolled patients with complicated acute appendicitis. All patients evaluated for enrollment in these three trials at Turku University Hospital between April 5th, 2017 and December 12th, 2018 with both a confirmed diagnosis of appendicitis and available blood culture on admission to the emergency room, were included in this study. In patients undergoing non-operative

treatment, appendicitis was confirmed by CT and in patients undergoing appendectomy, the diagnosis was confirmed both by CT and surgery with histology of the removed appendix. We selected all eligible patients within the original trial populations for the analyses performed in this predefined blood culture study assessing both the prevalence of blood culture positivity and the potential predictive factors for bacteraemia.

Outcome measures

To overcome the limitation of potential selection bias of not having blood cultures from the whole appendicitis patient cohort, we used propensity score matching of the patients in this large prospective patient cohort with CT and/or clinically confirmed complicated or uncomplicated acute appendicitis, but no blood culture data matching the patient population using sex, age, body mass index (BMI), C-reactive protein (CRP), leukocyte count, and body temperature.

Potential predictive factors associated with blood culture positivity were evaluated in this study and the effect of appendicitis severity was our primary variable. Other characteristics evaluated were age, sex, BMI, body temperature, CRP, leukocyte count, duration of symptoms, and clinically significant comorbidities potentially having an impact on the blood culture positivity. A detailed list of the evaluated comorbidities is presented in Supplementary table S1. Our definitions of uncomplicated and complicated acute appendicitis were performed according to all our APPAC trials (4, 6, 7, 25). The criteria for a radiological diagnosis of uncomplicated and complicated acute appendicitis are defined in Table 3. All clinical diagnosis were assessed in a blinded manner by 2 investigators unaware of the other's evaluation (S.S and J.H.). In cases of disagreement, the clinical diagnosis was reviewed by a third investigator (P.S.). The presence of an appendicolith has been shown to be associated with a more complicated course of the disease (9, 12). As the definitions of complicated appendicitis are not yet internationally uniform and standardized, we also performed a subgroup analysis classifying patients presenting only with an appendicolith but no other complications as uncomplicated.

Blood cultures were performed at the Department of Clinical Microbiology of Turku University Hospital using the Bactec™ FX blood culture system (BD Diagnostic Systems, Heidelberg, Germany) and identification of bacteria were done with Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) using the MALDI Biotyper® instrument and MBT Compass Library (Bruker Daltonics, Bremen, Germany). All microbes found in blood cultures and all antimicrobial treatments were documented.

Statistics

Prevalence of blood culture positivity was calculated directly from the 271 patients with available blood culture data. Propensity scoring was used to match this subpopulation to patients with acute appendicitis but no available blood culture using sex, age, BMI, CRP (categorised below and above reference limit), leukocyte count (categorized below and above reference limit), and body temperature (categorised below or above 37.5 °C).

Categorical variables were summarised with counts and percentages, continuous variables with mean and standard deviation (SD). In addition, range was reported for age. Association between blood culture positivity (positive/negative) versus appendicitis severity (uncomplicated/complicated), sex, comorbidities, duration of symptoms (categorised), and antibiotics (categorised) was examined using Fisher's exact test. Comparison of age, BMI, body temperature, CRP, and leukocyte count between the blood culture positivity groups was performed using one-way analysis of variance. Square root transformation was used to CRP and leukocyte count to fulfil the assumption of normality. Normality assumption was checked from studentized residuals. Confidence intervals (CI) of 95% were calculated. All statistical tests were performed as 2-sided, with a significance level set at 0.05. The analyses were programmed using SAS software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

From April 2017 and December 2018, there were a total of 987 patients with confirmed acute appendicitis and out of these, 299 (30%) patients had blood culture samples taken on admission to emergency department. After exclusion there were 271 eligible patients. The remaining 271 eligible patients with both acute appendicitis and available blood culture on admission were divided according to presence or absence of bacteraemia. Figure 1 shows the patient flow; patient demographics and baseline characteristics are presented in Table 1. Of the 271 patients with blood culture data, the majority (70%, 189/271) of the patients presented with complicated acute appendicitis and 30% (82/271) of the patients had uncomplicated acute appendicitis.

Among 271 eligible patients with both confirmed appendicitis and available blood culture on admission, 33 patients (12%, 33/271) had bacteraemia. The mean age of these 33 patients was 48 years (range 20 to 69 years) and 24 (73%) were male. Of these 33 patients with bacteraemia, 31 had appendectomy and two patients with uncomplicated acute appendicitis were treated with antibiotics only. In this large prospective patient cohort (n=987), the propensity score matched prevalence of bacteraemia was 9%.

When comparing the prevalence of blood culture positivity, it was significantly more common in complicated acute appendicitis compared with uncomplicated acute appendicitis. Bacteraemia was diagnosed in 15% (29/189) and 5% (4/82) of the patients with complicated acute appendicitis and uncomplicated acute appendicitis, respectively (p=0.015). Out of these 33 patients, 24 had complicated acute appendicitis presenting as perforation, gangrene of the appendix, or periappendicular abscess. Out of the four patients having uncomplicated acute appendicitis and bacteraemia, there was one woman and three men aged between 24 and 41 years with body temperature between 38°C to 39°C, CRP ranged from 52 to 131 mg/L, and leukocyte count from 8.2 to 29.9 $10^9/L$. Two of these patients had ulcerative colitis. Two out of these four were treated with appendectomy and the other two with antibiotics and all of them had oral antibiotics for one week. All four patients experienced an uneventful recovery with no need for further medical or surgical treatment. Medical reports were searched in January 2020 and none of these four patients had a recurrence or a readmission to the hospital for any abdominal problems. In addition, five patients with bacteraemia and complicated acute appendicitis presented with only an appendicolith and no other signs of complicated appendicitis. When analysing the patients with only an appendicolith but no other complications as uncomplicated, the prevalence

of bacteraemia remained significantly more frequent in complicated acute appendicitis 16% (24/150) compared with uncomplicated acute appendicitis 7% (9/121) ($p=0.039$).

Among the 238 patients (88%; 238/271) with a negative blood culture finding, the mean age of the patients was 45 years (range 16 to 89 years), 120 (50%) were male, 160 (67%) had complicated appendicitis, and 78 (33%) had uncomplicated appendicitis. Out of these 160 patients with complicated appendicitis, 34 presented with only an appendicolith and no other signs of complicated appendicitis.

Higher body temperature and male sex were the only two factors associated with blood culture positivity in patients with appendicitis, no other measured parameters had any association with blood culture positivity. Mean body temperature in patients with bacteraemia was 38.2°C (SD 0.9) and without bacteraemia 37.8°C (SD 0.7), ($p=0.0044$). Out of the patients with bacteraemia, 73% (24/33) were male and in patients without bacteraemia, 50% (120/238) were male, ($p=0.024$). Complicated acute appendicitis in the 271 patients with available blood culture on admission was significantly more common in men compared with women, 77% (111/144) vs. 61% (78/127), respectively ($p=0.0056$). Association of higher body temperature and blood culture positivity was similar in men and women [37.8°C (SD 0.7) and 37.9°C (SD 0.8), respectively], making it an independent factor predicting blood culture positivity. When comparing the association of blood culture results to both sex and body temperature, the mean body temperature in men with bacteraemia was 38.1°C (SD 0.8) and without bacteraemia 37.8°C (SD 0.7) and in women 38.6°C (SD 1.1) and 37.8°C (SD 0.7), respectively. There was no statistical difference between men and women in the association of body temperature and blood culture results ($p=0.53$). Duration of symptoms had no association with blood culture positivity ($p=0.21$), even though longer duration of symptoms was associated with complicated appendicitis ($p=0.0001$).

A total of 14 different bacteria were found in blood cultures (Table 2). There were 46 different isolated bacteria in 33 episodes of bacteraemia: 25 anaerobes, 13 Gram-negative aerobes and 8 Gram-positive aerobes. The most common bacteria were *Bacteroides fragilis* ($n=13$) and *Escherichia coli* ($n=12$). There was a variety of different antibiotics ($n=17$) used in this study partially based on the ongoing concurrent RCTs.

Discussion

In this prospective cohort on 271 patients with both confirmed acute appendicitis and available blood culture on admission, the prevalence of bacteraemia was 12 %. In the propensity-score matched larger cohort of all 987 patients with appendicitis, the prevalence was 9 %. Blood culture positivity was significantly associated with complicated acute appendicitis compared to uncomplicated acute appendicitis. To our knowledge, this is the first study assessing blood culture positivity in adult patients with acute appendicitis. Compared to earlier studies of bacteraemia prevalence our results were of the same magnitude. One retrospective study on children reported bacteraemia of 17% and 8% in perforated and non-perforated acute appendicitis, when in our study bacteraemia was diagnosed in 15% and 5%, respectively. There was huge variety in the overall prevalence in the earlier studies ranging from 0.35% to 17%, and as all these other studies were performed in pediatric populations, they are not directly comparable to our study with adult patients. Both epidemiological and clinical studies have shown that non-operative treatment for uncomplicated acute appendicitis is efficient, safe and cost-effective.(4, 5, 7-9, 26-29) This underlines the importance of understanding the aetiology, pathophysiology, and diagnostic and clinical findings of uncomplicated and complicated acute appendicitis enabling the optimization of different treatment alternatives for patients with the extremely common surgical emergency of appendicitis.

Other predictive factors of bacteraemia were male sex and higher body temperature, the majority (73%) of the patients with bacteraemia in our study were male. In our study, complicated appendicitis was significantly more common in men compared with women, 77% (111/144) vs. 61% (78/127), respectively. The higher risk for complicated appendicitis in men could explain the association of male sex and blood culture positivity and there might not be association between male sex and bacteraemia. In our study longer duration of symptoms was a risk factor for having complicated appendicitis, but there was no statistically significant difference in blood culture results. Association of higher body temperature and blood culture positivity was similar in both sexes, making it an independent factor predicting blood culture positivity.

There were two patients with bacteraemia and uncomplicated acute appendicitis treated without source control, i.e., without appendectomy, and interestingly both of these patients had an uneventful recovery from their appendicitis. Recent studies have shown that uncomplicated acute appendicitis may also resolve by only symptomatic treatment (6, 30). However, the notion that rare cases of patients with uncomplicated acute

appendicitis could also present with bacteraemia and have uneventful recovery after non-operative treatment without source control may somewhat challenge the need for a longer course of intravenous antibiotics for all patients with bacteraemia. Two additional patients with blood culture positivity were treated with appendectomy receiving only preoperative antibiotics as their blood culture results were obtained only after discharge without a clinical need for treatment alteration. In a search of electronic hospital records in January 2020, these two patients had recovered from appendicitis without complications or recurrent infections. A total of 14 different bacteria were present in the blood cultures. Most bacteria found were expected pathogens like *E. coli* and *B. fragilis* that are commonly involved in gastrointestinal septicaemia and bacteraemia. Amongst other bacteria there were both pathogenic bacteria and normal microbiota of mouth and other parts of gastrointestinal tract.

This study has several limitations. First, only 30% (299/987) of the patients with confirmed appendicitis had their blood culture taken in the emergency department on admission despite the instructions to retrieve blood cultures from all patients with suspected complicated acute appendicitis evaluated for enrollment in the MAPPAC trial and from all patients with uncomplicated acute appendicitis enrolled in the APPAC II and III RCTs. This limitation is not driven by non-compliance to the study protocol, but the acute care setting of the study with a large variety of physicians at the emergency department not remembering the instructions and thus from a clinical perspective, the majority (70%) of the blood cultures were retrieved from patients with complicated acute appendicitis. However, we aimed to overcome this limitation of potential selection bias by using propensity score matching using the whole patient cohort with acute appendicitis. Second limitation is that in this study population men had a higher risk for complicated appendicitis possibly explaining the association of male sex and bacteraemia, but due to the sample size and lack of blood culture samples on admission in the whole patient cohort this issue cannot be determined by our study.

The main strength of our study is the large prospective patient cohort (n=987) enabling both the propensity score-matching and assessment of predictive factors due to prospective data collection of all essential clinical parameters. Another strength is the accuracy of the differential diagnosis between uncomplicated and complicated acute appendicitis in every patient with either CT and/or surgery with histology of the removed appendix partially based on the synergy of the concurrent three trials (MAPPAC, APPAC II, and APPAC III).

In summary, estimated overall prevalence of blood culture positivity in patients with acute appendicitis was 9%. Complicated appendicitis, male sex, and higher body temperature were associated with blood culture positivity in acute appendicitis.

Author Contributions

SS, PS and TH accessed and verified the data. PS, HM, and AJH conceived of the study. EL did the analysis. PS led all both of the APPAC randomized trials and PS and AJH led the prospective cohort study MAPPAC from which the study data are derived. SS and TH wrote the first manuscript. All authors gave critical input into interpretation and revised the manuscript.

Declaration of interests

PS reports personal fees from Merck and Orion Pharma, outside the submitted work. HM reports personal fees from Astellas, Merck, Pfizer and Roche Diagnostics, outside the submitted work. All other authors declare no competing interests.

Data sharing

A complete de-identified patient dataset, accompanied by the original trial protocol (MAPPAC), will be made available to researchers on request. Individuals wishing to access the data should send a request to the corresponding author.

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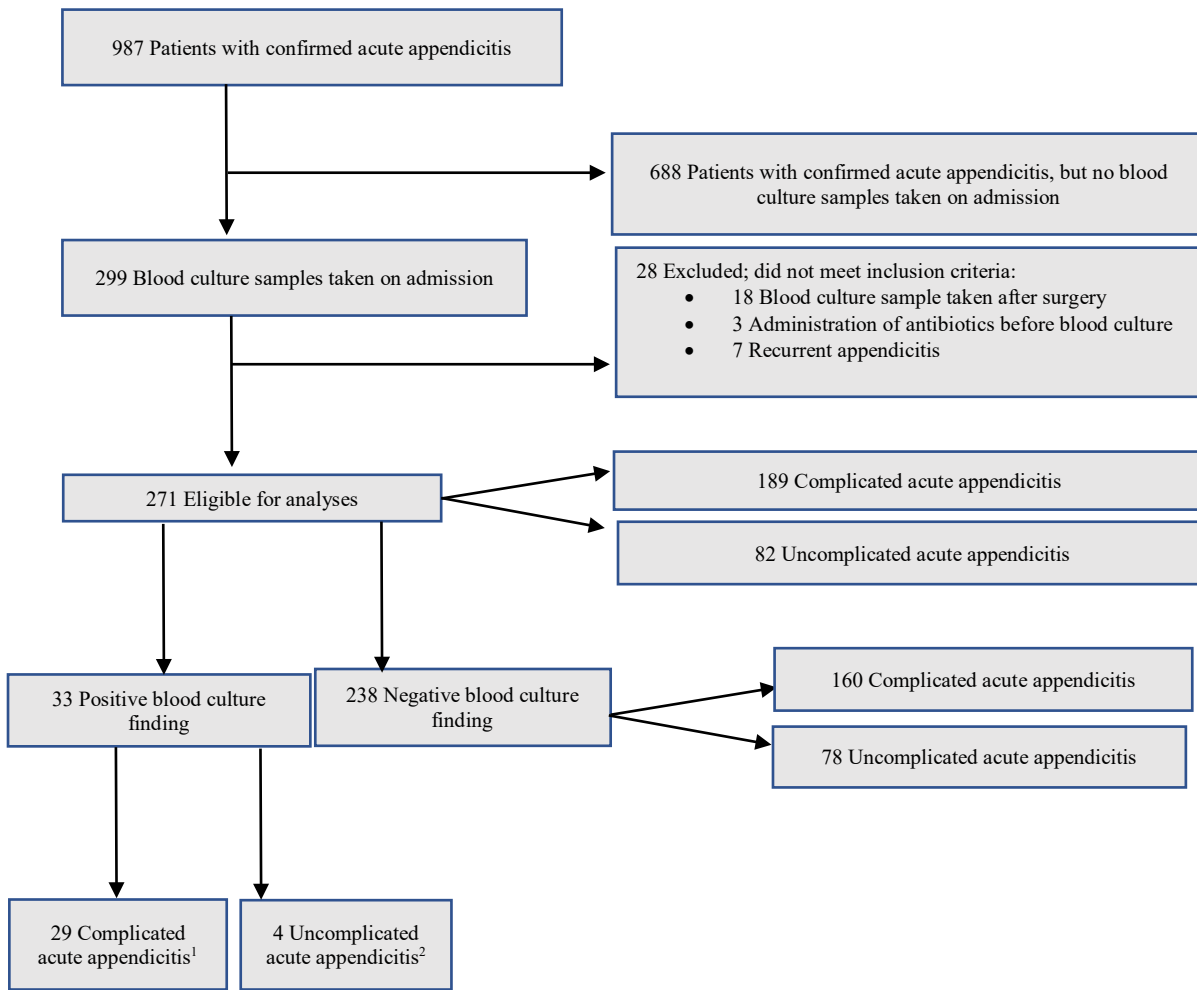
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Figure 1: Flow chart of study patients



¹All 29 patients were treated with appendectomy, and 2 patients received only preoperative dose of antibiotics. Appendicitis was considered as complicated when presenting with an appendicolith, perforation, periappendicular abscess, tumour, or clear intraoperative finding of gangrene supported by histopathology.

²Out of the 4 patients 2 were treated with appendectomy and 2 were treated with antibiotics only.

Table 1: Patient Demographics and Baseline characteristics

	Bacteraemia	No bacteraemia	All patients available with blood culture	p value*
N	33	238	271	
Complicated	29 (88 %)	160 (67 %)	189 (70 %)	0.015
Uncomplicated	4 (12 %)	78 (33 %)	82 (30 %)	
Sex, male	24 (73 %)	120 (50 %)	144 (53 %)	0.024
Sex, female	9 (27 %)	118 (50 %)	127 (47 %)	
Age, years, mean (range)	48 (20–69)	45 (16–89)	45 (16–89)	0.26
Body mass index, kg/m ² , mean (SD)	27.7 (4.7)	27.9 (5.3)	27.8 (5.2)	0.83
CRP ¹ , mg/L, median (Q1, Q3)	65 (22, 158)	68 (25,144)	67 (25, 146)	0.78
WBCs ² , per μ L, median (Q1, Q3)	13700 (9100,17700)	13800 (11100,16200)	13700 (11000,16400)	0.30
Temperature, °C, mean (SD)	38.2 (0.9)	37.8 (0.7)	37.8 (0.8)	0.0044
Comorbidity ³ (N)	3 (9 %)	25 (10 %)	28	1.00
Duration of symptoms ⁴ (N)	32	237	269	0.21
under 12 hours	4	49	53	
12 to 24 hours	12	70	82	
24 to 48 hours	10	47	57	
over 48 hours	6	71	77	

¹CRP, C-reactive protein

²WBC, White blood cell count

³Included comorbidities: Inflammatory bowel disease, diabetes, systemic immunosuppressive medicine for any reason, multiple sclerosis, Addison's disease, polymyalgia rheumatica, rheumatoid arthritis, malignancy, coronary heart disease

⁴Duration of symptoms was documented in 269 of 271 patients. Two patients, one in both groups, could not give precise information about the symptoms because of their medical condition (dementia, drug abuse). Duration of symptoms was categorised in four categories: under 12 hours, 12 to 24 hours, 24 to 48 hours and over 48 hours before admission.

*Fischer's Exact Test

Table 2: Bacteria found in blood cultures

Organism	n = 46 isolates in 33 episodes of BSI (%)
Anaerobic bacteria	25 (54)
<i>Bacteroides fragilis</i>	13 (28)
<i>Clostridium</i> species	3 (7)
<i>Alistipes onderdonkii</i>	2 (4)
<i>Eggerthella lenta</i>	2 (4)
<i>Odoribacter splanchnicus</i>	2 (4)
<i>Parabacteroides distasonis</i>	1 (2)
<i>Parvimonas micra</i>	1 (2)
<i>Solobacterium moorei</i>	1 (2)
Aerobic or facultative anaerobic gram-positive cocci	8 (17)
<i>Streptococcus</i> species	4 (9)
<i>Staphylococcus</i> species	2 (4)
<i>Enterococcus avium</i>	1 (2)
<i>Micrococcus luteus</i> *	1 (2)
Aerobic or facultative anaerobic gram-negative rods	13 (28)
<i>Escherichia coli</i>	12 (26)
<i>Citrobacter koseri</i>	1 (2)

*A possible skin contamination as described in blood culture answer

Table 3. Structured radiological report including radiological criteria and categorization of acute appendicitis.

1) Appendix Visualization

Report one of the following:

Not visualized/ Partly or unclearly visualized/ Completely visualized

2) Appendix transverse diameter (mm):

3) Probability of appendicitis

Report one of the following:

Not likely/ Rather unlikely/ Rather likely/ Very likely

4) Categorization of the appendicitis

Report either I or II, if any:

I Uncomplicated appendicitis: transverse diameter > 6mm with typical findings

-wall thickening and enhancement

-periappendiceal edema and/or minor amount of fluid

II Complicated appendicitis: Above-mentioned criteria for appendicitis with at least one of the following:

-Appendicolith: > 3mm stone within appendix

-Abscess: periappendiceal walled of collection with enhancing walls

-Perforation: appendiceal wall enhancement defect and

periappendiceal excess of fluid and/or infectious phlegmon and/or extraluminal air

-Tumor: tumor-like prominence of appendix

5) Other diagnosis: Report if any

Diverticulitis/ Complicated ovarian cyst/ Pelvic inflammatory disease/ Colitis/ Ileitis /Intestinal obstruction or ileus/ Ureter stone/

Hydronephrosis/ Tumor/ Other diagnosis