

# Blood culture positivity in patients with acute appendicitis: A propensity score-matched prospective cohort study

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## Abstract

**Background and objective:** The prevalence of bacteremia in acute appendicitis is unknown. We aimed to assess prevalence and predictive factors of bacteremia in adult patients with appendicitis.

**Methods:** In this prospective propensity score-matched cohort study, patients were recruited as part of one single-center 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 bacteremia (age, sex, body mass index (BMI), body temperature, C-reactive protein (CRP), leukocyte count, comorbidities, symptom duration, and appendicitis severity) were assessed. Prevalence of bacteremia 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 815 patients with appendicitis, 271 patients had available blood culture and the prevalence of bacteremia was 12% (n = 33). Based on propensity score estimation, the prevalence of bacteremia in the whole prospective appendicitis cohort was 11.1%. Bacteremia 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 bacteremia.

**Conclusions:** Estimated prevalence of bacteremia in patients with acute appendicitis was 11.1%. Complicated appendicitis, male sex, and higher body temperature were associated with bacteremia in acute appendicitis.

## Keywords

Blood culture, bacteremia, acute appendicitis, septicemia, blood stream infection

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## Context and Relevance

Acute appendicitis is one of the most common surgical emergencies, but studies on bacteremia

prevalence with appendicitis are lacking. This study assessed bacteremia prevalence and potential associated factors in adult patients presenting with complicated or uncomplicated acute

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appendicitis. Estimated propensity score-matched prevalence of bacteremia in patients with acute appendicitis was 11.1%. Complicated appendicitis, male sex, and higher body temperature were associated with blood culture positivity. This study underlines the importance of further increasing the understanding of etiology, pathophysiology, and differences in diagnostic and clinical findings of uncomplicated and complicated acute appendicitis enabling the optimization of different treatment alternatives.

## Introduction

With an incidence of 100–200 cases per 1,000,000 person years,<sup>1</sup> acute appendicitis is one of the most common reasons for acute abdominal pain, and abdominal infections are the second most common source of sepsis.<sup>2,3</sup> 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.<sup>4–12</sup> With epidemiological and clinical data supporting the different disease hypothesis of uncomplicated and complicated acute appendicitis,<sup>5,12–15</sup> 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)<sup>16</sup> as non-operative treatment would allow limiting inpatient bed use and reimplementation of health care resources.

To our knowledge, there is only one previous study from 1984<sup>17</sup> on blood culture positivity in adult patients with appendicitis focusing on the comparison of blood culture, appendicular lumen, intra-abdominal culture, and wound cultures. In this study, the prevalence of blood culture positivity was 5% (7 out of 140 patients with appendicitis), and there was no correlation between the degree of appendicitis and the incidence of positive blood cultures.<sup>17</sup> There are studies assessing bacteremia postoperatively after appendectomy<sup>18</sup> and many studies with specimens obtained from appendiceal lumen or swab samples from suppurative peritoneal fluid or periappendiceal abscess,<sup>19–21</sup> but only few small studies on bacteremia in pediatric patients with appendicitis on admission.<sup>22,23</sup> In the early 1990s, a small retrospective study on children reported positive blood cultures of 17% and 8% in perforated and non-perforated acute appendicitis, respectively.<sup>24</sup> In a small prospective pediatric study, the prevalence of bacteremia in patients with acute appendicitis was 6%.<sup>23</sup> 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%.<sup>22</sup> 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.<sup>25</sup>

Bridging the knowledge gaps in understanding the etiology 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<sup>26</sup> (Microbiology APPendicitis ACuta) and the concurrent randomized controlled trials APPAC II and APPAC III.<sup>6,7</sup> 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-center and multicenter arm and this blood culture study is part of the single-center arm at Turku University Hospital. The aim of this study is to evaluate the microbiological and immunological aspects in the etiology of uncomplicated and complicated acute appendicitis.<sup>26</sup> APPAC II is a multicenter, 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.<sup>7</sup> APPAC III is a multicenter, 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.<sup>6</sup> 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-center prospective observational study (MAPPAC) in concurrence with the two RCTs (APPAC II and III), in which all patients aged 18–60 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 between 5 April 2017 and 10 December 2018 in these three trials at Turku University Hospital with a written informed consent, a confirmed diagnosis of appendicitis, and available blood culture on admission to the emergency room were included in this prospective sub-study. At Turku University Hospital, the aim was to obtain blood culture samples on all patients with confirmed appendicitis evaluated for participation in the three clinical trials. After completing enrollment, the inclusion criteria for this study were confirmed diagnosis of acute appendicitis (without previous episodes of acute appendicitis) and available blood culture taken on admission to the emergency room. Patients with acute appendicitis without available blood culture samples prior to any antibiotics on admission were excluded from 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 bacteremia.

Despite the study protocol instructions to retrieve blood cultures from all patients with suspected acute appendicitis evaluated for enrollment in the MAPPAC, APPAC II, and APPAC III trials, this was performed in only 37% (n=299) of the cases based on the major challenges caused by the acute care surgery setting of the trial. As a post hoc analysis plan to overcome this limitation of potential selection bias, we decided to use propensity score matching from the whole patient cohort presenting with acute appendicitis.

## 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.<sup>4,6,7,26</sup> The

**Table 1.** 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 >6 mm 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: >3 mm 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

criteria for a radiological diagnosis of uncomplicated and complicated acute appendicitis are defined in Table 1. All clinical diagnosis were assessed in a blinded manner by two 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.<sup>9,12</sup> 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 was 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 (categorized below and above reference limit), leukocyte count (categorized below and above reference limit), and body temperature (categorized below or above 37.5°C). The matched cohort (n=544)

consisted of patients with confirmed acute appendicitis, but no available blood culture. For patients with an available blood culture sample (blood culture positivity  $n=31$ ) and all of the propensity score matching parameters  $n=259$ ).

Categorical variables were summarized with counts and percentages, and 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 (categorized), and antibiotics (categorized) 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 for CRP and leukocyte count to fulfill the assumption of normality. Normality assumption was checked from studentized residuals.

Confidence intervals (CIs) of 95% were calculated. All statistical tests were performed as two-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 815 patients with confirmed acute appendicitis and out of these, 299 (37%) patients had blood culture samples taken. 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 the presence or absence of bacteremia. Fig. 1 shows the patient flow; patient demographics and baseline characteristics are presented in Table 2. 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 bacteremia. The mean age of these 33 patients was 48 years (range, 20–69 years) and 24 (73%) were male. Of these 33 patients with bacteremia, 31 had appendectomy and 2 patients with uncomplicated acute appendicitis were treated with antibiotics only. In this large prospective patient cohort ( $n=815$ ), the propensity score–matched prevalence of bacteremia was 11.1%.

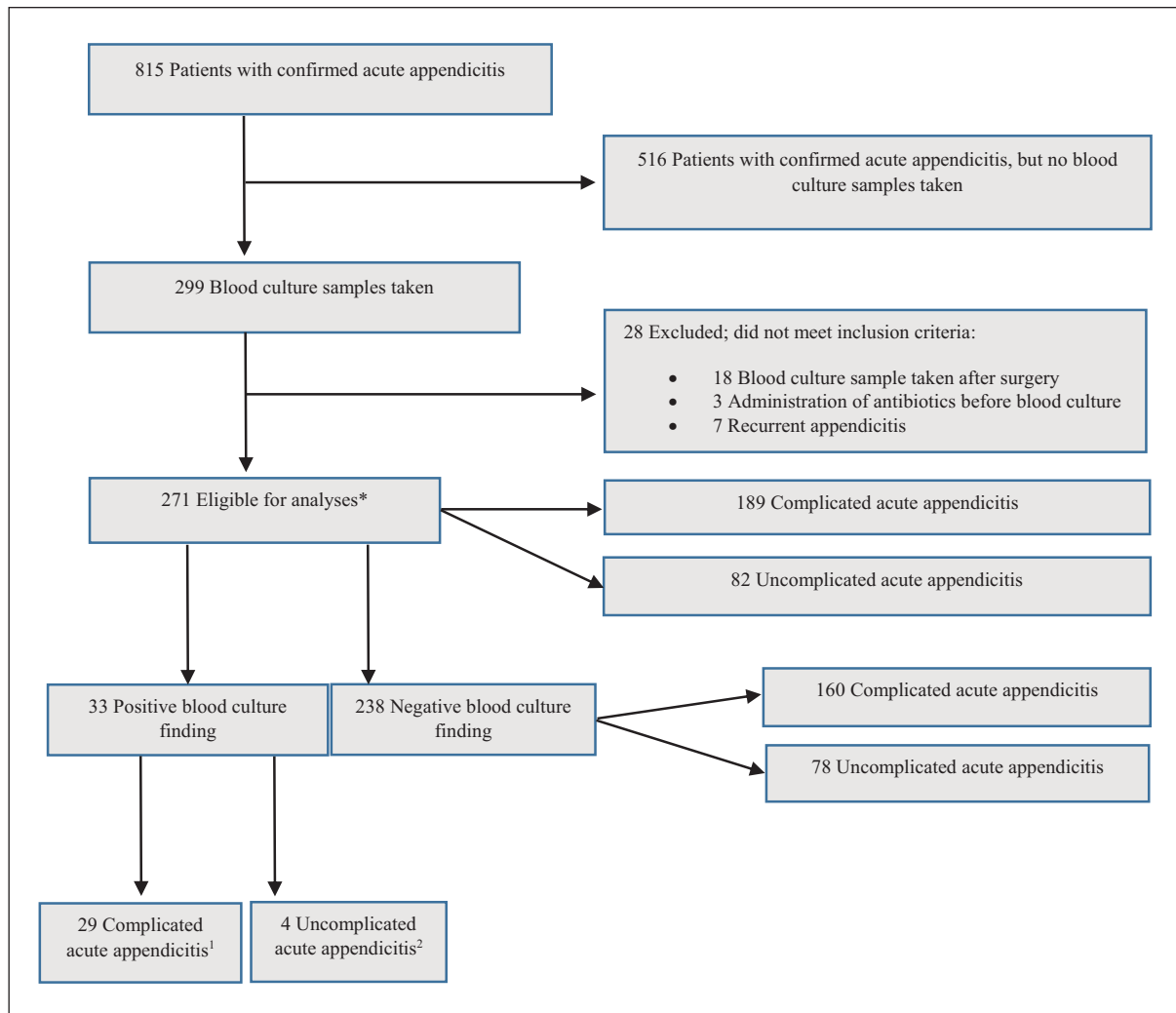
When comparing the prevalence of blood culture positivity, it was significantly more common in complicated acute appendicitis compared with uncomplicated acute appendicitis. Bacteremia was diagnosed in 15% (29/189) and 5% (4/82) of the patients with complicated acute appendicitis and uncomplicated acute 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. In addition, five patients with bacteremia and complicated acute appendicitis presented with only an appendicolith and no other signs of complicated appendicitis. When analyzing the patients with only an appendicolith but no other complications as uncomplicated, the prevalence of bacteremia remained significantly more frequent in complicated acute appendicitis 16% (24/150) compared with uncomplicated acute appendicitis 7% (9/121) ( $p=0.039$ ). Out of the four patients having uncomplicated acute appendicitis and bacteremia, there was one woman and three men aged between 24 and 41 years with body temperature between 38°C and 39°C, CRP ranged from 52 to 131 mg/L, and leukocyte count from 8.2 to 29.9 10<sup>9</sup>/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 1 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.

Among the 238 patients (88%; 238/271) with a negative blood culture finding, the mean age of the patients was 45 years (range, 16–89 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 bacteremia was 38.2°C (SD, 0.9) and without bacteremia 37.8°C (SD, 0.7) ( $p=0.0044$ ). Out of the patients with bacteremia, 73% (24/33) were male and in patients without bacteremia, 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) versus 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 with both sex and body temperature, the mean body temperature in men with bacteremia was 38.1°C (SD, 0.8) and without bacteremia 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





**Fig. 1.** Flow chart of study patients.

<sup>1</sup>All 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, tumor, or clear intraoperative finding of gangrene supported by histopathology.

<sup>2</sup>Out of the four patients two were treated with appendectomy and two were treated with antibiotics only.

\*Patient treatment: Emergency appendectomy (n=240), initial antibiotics for CT-confirmed uncomplicated acute appendicitis (n=28), and periappendicular abscess with initial antibiotics followed by interval appendectomy (n=3).

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 3). There were 46 different isolated bacteria in 33 episodes of bacteremia: 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 bacteremia was 12%. In the propensity score-matched larger cohort of all 815 patients with appendicitis, the prevalence was 11.1%. Blood culture positivity was significantly associated with complicated acute appendicitis compared to uncomplicated acute appendicitis. To our knowledge, there is only one previous study assessing blood culture positivity in adult patients with acute appendicitis.<sup>17</sup> The bacteremia prevalence rate in this study<sup>17</sup> and the earlier studies mainly in pediatric patient cohorts<sup>22–24</sup> are corroborated by the outcomes of this study. One retrospective study on children reported bacteremia of 17% and 8% in perforated and non-perforated acute appendicitis,<sup>24</sup> when in our study bacteremia 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%,<sup>22–24</sup> and as all these other studies were performed in pediatric populations, they are not

**Table 2.** Patient demographics and baseline characteristics.

	Bacteremia	No bacteremia	All patients available with blood culture	Propensity score population	p value*
N	33	238	271	544	
Complicated	29 (88%)	160 (67%)	189 (70%)	248 (46%)	0.015
Uncomplicated	4 (12%)	78 (33%)	82 (30%)	296 (54%)	
Sex, male	24 (73%)	120 (50%)	144 (53%)	270 (50%)	0.024
Sex, female	9 (27%)	118 (50%)	127 (47%)	274 (50%)	
Age, years, mean (range)	48 (20–69)	45 (16–89)	45 (16–89)	40 (16–95)	0.26
Body mass index, kg/m <sup>2</sup> , mean (SD)	27.7 (4.7)	27.9 (5.3)	27.8 (5.2)	26.8 (5.0)	0.83
CRP, mg/L, median (Q1, Q3)	65 (22, 158)	68 (25, 144)	67 (25, 146)	30 (11, 60)	0.78
WBCs, ×10 <sup>9</sup> /L, median (Q1, Q3)	13.7 (9.1, 17.7)	13.8 (11.1, 16.2)	13.7 (11.0, 16.4)	12.6 (10.3, 15.2)	0.30
Temperature, °C, mean (SD)	38.2 (0.9)	37.8 (0.7)	37.8 (0.8)	37.3 (0.6)	0.0044
Comorbidity <sup>a</sup> (N)	3 (9%)	25 (10%)	28		1.00
Duration of symptoms <sup>b</sup> (N)	32	237	269	214	0.21
<12 h	4	49	53	82	
12–24 h	12	70	82	66	
24–48 h	10	47	57	37	
>48 h	6	71	77	29	

CRP: C-reactive protein; WBC: white blood cell count.

<sup>a</sup>Included comorbidities: inflammatory bowel disease, diabetes, systemic immunosuppressive medicine for any reason, multiple sclerosis, Addison's disease, polymyalgia rheumatica, rheumatoid arthritis, malignancy, coronary heart disease.

<sup>b</sup>Duration 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 categorized in four categories: <12 h, 12–24 h, 24–48 h, and >48 h before admission.

\*Fisher's exact test.

**Table 3.** Bacteria found in blood cultures.

Organism	n = 46 isolates in 33 episodes of blood stream infection (%)
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> <sup>a</sup>	1 (2)
Aerobic or facultative anaerobic gram-negative rods	13 (28)
<i>Escherichia coli</i>	12 (26)
<i>Citrobacter koseri</i>	1 (2)

<sup>a</sup>A possible skin contamination as described in blood culture answer.

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.<sup>4,5,7–9,27–30</sup> This underlines the importance of understanding the etiology, 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 bacteremia were male sex and higher body temperature, and the majority (73%) of the patients with bacteremia in our study were male. In our study, complicated appendicitis was significantly more common in men compared with women, 77% (111/144) versus 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 bacteremia. 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. The only previous study on adults by Lau et al. reported predictive factors associated with increased incidence of septic complications to include late appendicitis, a positive wound culture at the end of operation, longer duration of symptoms (over 36 h), and higher patient age (over 50 years).<sup>17</sup>

There were two patients with bacteremia and uncomplicated acute appendicitis treated without source control, that is, 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.<sup>6,31</sup> However, the notion that rare cases of patients with uncomplicated acute appendicitis could also present with bacteremia 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 bacteremia. Two additional patients with blood culture positivity and complicated acute appendicitis 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 septicemia and bacteremia. Among 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% (299/815) 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 bacteremia, 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=815) 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 11.1%.

Complicated appendicitis, male sex, and higher body temperature were associated with blood culture positivity in acute appendicitis.

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## Author contributions

S.S., P.S., and T.H. accessed and verified the data. P.S., H.M., and A.J.H. conceived of the study. E.L. did the analysis. P.S. led all both of the APPAC randomized trials and P.S. and A.J.H. led the prospective cohort study MAPPAC from which the study data are derived. S.S. and T.H. wrote the first manuscript. All authors gave critical input into interpretation and revised the manuscript.

## 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.

## Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P.S. reports personal fees from Merck and Orion Pharma, outside the submitted work. H.M. reports personal fees from Astellas, Merck, Pfizer, and Roche Diagnostics, outside the submitted work. All other authors declare no competing interests.

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## Supplemental material

Supplemental material for this article is available online.

## References

1. Ferris M, Quan S, Kaplan BS et al: The global incidence of appendicitis: A systematic review of population-based studies. *Ann Surg* 2017;266(2):237–241.
2. Fagerström A, Paajanen P, Saarelainen H et al: Non-specific abdominal pain remains as the most common reason for acute abdomen: 26-year retrospective audit in one emergency unit. *Scand J Gastroenterol* 2017;52(10):1072–1077.

3. Leppaniemi A, Kimball EJ, De Laet I et al: Management of abdominal sepsis: A paradigm shift. *Anaesthesiol Intensive Ther* 2015;47(4):400–408.
4. Salminen P, Paajanen H, Rautio T et al: Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: The APPAC randomized clinical trial. *JAMA* 2015;313(23):2340–2348.
5. Salminen P, Tuominen R, Paajanen H et al: Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. *JAMA* 2018;320(12):1259–1265.
6. Sippola S, Gronroos J, Sallinen V et al: A randomised placebo-controlled double-blind multicentre trial comparing antibiotic therapy with placebo in the treatment of uncomplicated acute appendicitis: APPAC III trial study protocol. *BMJ Open* 2018;8(11):e023623.
7. Sippola S, Haijanen J, Gronroos J et al: Effect of oral moxifloxacin vs intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: The APPAC II randomized clinical trial. *JAMA* 2021;325(4):353–362.
8. Styrd J, Eriksson S, Nilsson I et al: Appendectomy versus antibiotic treatment in acute appendicitis: A prospective multicenter randomized controlled trial. *World J Surg* 2006;30(6):1033–1037.
9. Vons C, Barry C, Maitre S et al: Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: An open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377(9777):1573–1579.
10. Sallinen V, Akl EA, You JJ et al: Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. *Br J Surg* 2016; 103(6): 656–667.
11. Davidson GH, Flum DR, Talan DA et al: Comparison of Outcomes of antibiotic Drugs and Appendectomy (CODA) trial: A protocol for the pragmatic randomised study of appendicitis treatment. *BMJ Open* 2017;7(11):e016117.
12. Flum DR, Davidson GH, Monsell SE et al: A randomized trial comparing antibiotics with appendectomy for appendicitis. *N Engl J Med* 2020;383(20):1907–1919.
13. Atema JJ, van Rossem CC, Leeuwenburgh MM et al: Scoring system to distinguish uncomplicated from complicated acute appendicitis. *Br J Surg* 2015;102(8):979–990.
14. Livingston EH, Fomby TB, Woodward WA et al: Epidemiological similarities between appendicitis and diverticulitis suggesting a common underlying pathogenesis. *Arch Surg* 2011;146(3):308–314.
15. Livingston EH, Woodward WA, Sarosi GA et al: Disconnect between incidence of nonperforated and perforated appendicitis: Implications for pathophysiology and management. *Ann Surg* 2007;245(6):886–892.
16. American College of Surgeons: COVID 19: And elective case triage guidelines for surgical care. American College of Surgeons, 2020, [https://www.facs.org/media/33km00ma/guidance\\_for\\_triage\\_of\\_nonemergent\\_surgical\\_procedures\\_general\\_surgery.pdf](https://www.facs.org/media/33km00ma/guidance_for_triage_of_nonemergent_surgical_procedures_general_surgery.pdf)
17. Lau WY, Teoh-Chan CH, Fan ST et al: The bacteriology and septic complication of patients with appendicitis. *Ann Surg* 1984;200(5):576–581.
18. Nordentoft T, Bringstrup FA, Bremmelgaard A et al: Effect of laparoscopy on bacteremia in acute appendicitis: A randomized controlled study. *Surg Laparosc Endosc Percutan Tech* 2000;10(5):302–304.
19. Song DW, Park BK, Suh SW et al: Bacterial culture and antibiotic susceptibility in patients with acute appendicitis. *Int J Colorectal Dis* 2018;33(4):441–447.
20. Jeon HG, Ju HU, Kim GY et al: Bacteriology and changes in antibiotic susceptibility in adults with community-acquired perforated appendicitis. *PLoS ONE* 2014;9(10):e111144.
21. Garcia-Marin A, Perez-Lopez M, Martinez-Guerrero E et al: Microbiologic analysis of complicated and uncomplicated acute appendicitis. *Surg Infect* 2018;19(1):83–86.
22. Thompson GC, Morrison E, Ross M et al: The use of routine blood cultures in pediatric appendicitis. *Pediatr Emerg Care* 2017;33(12):e160–e163.
23. Juric I, Primorac D, Zagar Z et al: Frequency of portal and systemic bacteremia in acute appendicitis. *Pediatr Int* 2001; 43(2):152–156.
24. Ruff ME, Friedland IR, Hickey SM: *Escherichia coli* septicemia in non-perforated appendicitis. *Arch Pediatr Adolesc Med* 1994;148(8):853–855.
25. Wu SC, Rau CS, Liu HT et al: Metagenome analysis as a tool to study bacterial infection associated with acute surgical abdomen. *J Clin Med* 2018;7(10):346.
26. Vanhatalo S, Munukka E, Sippola S et al: Prospective multicentre cohort trial on acute appendicitis and microbiota, aetiology and effects of antimicrobial treatment: Study protocol for the MAPPAC (Microbiology APPendicitis ACuta) trial. *BMJ Open* 2019;9(9):e031137.
27. Haijanen J, Sippola S, Tuominen R et al: Cost analysis of antibiotic therapy versus appendectomy for treatment of uncomplicated acute appendicitis: 5-year results of the APPAC randomized clinical trial. *PLoS ONE* 2019;14(7):e0220202.
28. Livingston EH: Antibiotic treatment for uncomplicated appendicitis really works: Results from 5 years of observation in the APPAC trial. *JAMA* 2018;320(12):1245–1246.
29. Sakran JV, Mylonas KS, Gryparis A et al: Operation versus antibiotics: The “appendicitis conundrum” continues—A meta-analysis. *J Trauma Acute Care Surg* 2017;82(6):1129–1137.
30. Sippola S, Gronroos J, Tuominen R et al: Economic evaluation of antibiotic therapy versus appendicectomy for the treatment of uncomplicated acute appendicitis from the APPAC randomized clinical trial. *Br J Surg* 2017;104(10):1355–1361.
31. Park HC, Kim MJ, Lee BH: Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. *Br J Surg* 2017;104(13): 1785–1790.