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Implications of bacteriological study in complicated and uncomplicated acute appendicitis

Sorin Cimpean[1,2], Alberto Gonzalez Barranquero[3], Ion Surdeanu[2], Benjamin Cadiere[3], Guy-Bernard Cadiere[3]

[1]Royal Belgian Society for Surgery, Brussels; [2]Departement of General and Digestive Surgery, Iris Hospitals South, Brussels; [3]Departement of Surgery, Saint Pierre University Hospital, Brussels, Belgium

Purpose: Bacteriological sample in the presence of intraabdominal free fluid is necessary to adapt the antibiotherapy and to prevent the development of resistance. The aim was to evaluate the differences between uncomplicated (UAA) and complicated acute appendicitis (CAA) in terms of bacterial culture results and antibiotic resistance, and to evaluate the factors linked with CAA.

Methods: We performed a single-center, retrospective observational study of all consecutive patients who presented with appendicular peritonitis and underwent emergent surgery in a tertiary referral hospital in Brussels, Belgium, between January 2013 and December 2020. The medical history, parameters at admission, bacterial culture, antibiotic resistance, and postoperative outcomes of 268 patients were analyzed. UAA was considered catarrhal or phlegmonous inflammation of the appendix. CAA was considered gangrenous or perforated appendicitis.

Results: Positive microbiological cultures were significantly higher in the CAA group (68.2% vs. 53.4%). The most frequently isolated bacteria in UAA and CAA cultures were *Escherichia coli* (37.9% and 48.6%). Most observed resistances were against ampicillin (28.9% and 21.7%) and amoxicillin/clavulanic acid (16.4% and 10.5%) in UAA and CAA, respectively. A higher Charlson comorbidity index, an elevated white blood cell count, an open procedure, and the need for drainage were linked to CAA. Culture results, group of bacterial isolation, and most common isolated bacteria were not related to CAA.

Conclusion: CAA presented a higher rate of positive cultures with increased identification of gram-negative bacteria. Bacterial culture from the peritoneal liquid does not reveal relevant differences in terms of antibiotic resistance.

Keywords: *Appendicitis; Microbiology; Anti-bacterial agents; Bacteria*

INTRODUCTION

Complicated intraabdominal infections represent a widespread problem, encountered worldwide, with appendicitis alone affecting 300,000 patients/year and consuming >1 million hospital days in the United States [1]. The lifetime risk is estimated to be 8.6% in males and 6.7% in females [2].

This pathology is well known and the etiology is related usually with an obstruction of the appendix lumen. Other pathologies that can produce an inflammation of the appendix are tumors (carcinoid tumors and adenocarcinoma), intestinal parasites, and hypertrophied lymphatic tissue [3].

Acute appendicitis is treated by appendectomy and is usually followed by additional antibiotic treatment. In case of necrosis or perforation of the appendix with secondary peritonitis, the antibiotherapy is important for the treatment and prevention of the postoperative infectious complications. Antibiotic use can be considered as an adjunct to surgical intervention, and their appropriate use remains a critical aspect [4]. The bacteriological sample in case of presence of intraabdominal free fluid is necessary to adapt the antibiotherapy and to prevent the development of resistance. In case of simple appendicitis, restriction of antibiotic treatment

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Correspondence to: Sorin Cimpean, M.D.
Department of General and Digestive Surgery, Iris Hospitals South, Rue Jean Paquot 40, 1050 Ixelles, Brussels, Belgium
Tel: +32-460374077, Fax: +32-26414428
E-mail: sorin.cimpean.md@gmail.com
ORCID: https://orcid.org/0000-0001-6639-5170

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can be considered.

The bacterial flora in the appendix consists of a mixture of aerobes and anaerobes bacteria. In the literature, *Escherichia coli* and *Bacteroides fragilis* are most commonly associated with appendicitis, and the first line empiric antibiotic therapy is typically selected to target these bacteria [5]. Nevertheless, acute appendicitis is habitually a polymicrobial infection, with up to 14 different bacteria reported [6].

The aim of the study is to evaluate the differences between uncomplicated (UAA) and complicated acute appendicitis (CAA) in terms of bacterial culture results and antibiotic resistance. The secondary outcome was to evaluate the predictors for complicated appendicitis. The study also evaluates the clinical implication of the bacterial culture results of UAA and CAA in term of antibiotic resistance, and the risk factor of CAA.

METHODS

The study was approved by the Ethics Committee of Saint Pierre University Hospital. The verbal/oral informed consent was obtained in consultation, by telephone or by email from the patients or the legal representative.

Study design

We performed a single-center, retrospective observational study of all consecutive patients who presented with appendicular peritonitis and underwent emergent surgery in Saint Pierre University Hospital in Brussels, Belgium, between January 2013 and December 2020.

The inclusion criteria for the 268 patients analyzed were the patients over 15 years old, who underwent an appendectomy in an emergent surgery, with the presence of peritonitis of appendicular origin, and enough quantity of intraabdominal free fluid to allow the bacteriological sample.

The exclusion criteria were peritonitis of a distinct origin, conservative or percutaneous treatment of appendicular abscess, the absence of free fluid, the absence of bacteriological sample, or the absence of bacteriological analysis.

Definitions

The abdominal fluid culture was obtained from a sample of peritoneal fluid (>1 mL) that was sent to the laboratory for Gram stain and culture. UAA was considered catarrhal or phlegmonous inflammation of the appendix. CAA was considered gangrenous or perforated appendicitis [7, 8].

Intervention

All patients with the diagnosis of acute appendicitis who underwent emergent surgery received amoxicillin/clavulanic acid as preoperative antibiotic treatment, in the absence of previous allergies. The periappendicular intraabdominal free fluid visualized during the surgery was collected in sterile conditions and was sent for bacteriological analysis. Postoperative antibiotics were prescript depending on the clinical condition of the patient and the state of the surgical field during the intervention. Tailored antibiotic therapy was adjusted according to the results of the antibiotic sensitivity testing, usually available 48 hours after the surgery, especially in cases of antibiotic resistance. A systematic blood test was performed on the second postoperative day to follow the dynamics of the inflammatory syndrome. The patient was discharged in the absence of relevant postoperative complications.

Variables

Baseline characteristics collected were age, sex, nationality, Charlson comorbidity index (CCI, which predicts the 10-year mortality for a patient according to their comorbid conditions), and personal history of abdominal surgery or other surgeries. At admission, the physical examination signs analyzed were heart rate (HR), systolic blood pressure, and temperature; and the C-reactive protein and the white blood cell (WBC) count from the blood tests. The type of surgical intervention, the open or laparoscopic approach, and the need for drainage were the intraoperative variables analyzed.

A positive bacteriological analysis was thoroughly evaluated to identify the specific bacteria and their resistance to the antibiotic. We also evaluated the antibiotic treatment prescribed, in the first, second, and third line.

Postoperative variables were the hospital stay, blood tests at 48 hours after surgery, overall morbidity, its severity according to the Clavien Dindo classification [9], and the need for reintervention. Specific complications analyzed were postoperative ileus, acute kidney injury, bacteremia, surgical site infection, and cecal perforation.

Statistical analysis

Categorical variables were described with numbers and percentages. Quantitative variables were described with mean and standard deviation if they followed a normal distribution and with median and interquartile range (IQR) if they followed a non-normal distribution. The Shapiro-Wilk test was used as a normality test.

To evaluate the null hypothesis, the chi-square test was used for categorical variables, the Student t-test was used for normal quantitative variables and the Mann-Whitney U-test was used for nonnormal quantitative variables.

All variables were tested in univariate logistic regression to explore the factors linked with complicated appendicitis, except for specific bacterial isolation with <10 positive cultures. Statistically significant variables in univariate analysis were then included in a multivariable logistic regression model, erasing nonsignificant outcomes until all variables were adjusted to each other in the final model. A P-value of <0.05 in a 2-tailed statistical analysis was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics ver. 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 834 patients were operated for acute appendicitis during the period of the study. We included 268 patients (161 with a UAA and 107 with a CAA) after excluding 566 patients according to the exclusion criteria, mainly due to the absence of sufficient

Table 1. Baseline characteristics and surgical procedure

Characteristic	Acute appendicitis		P-value
	Uncomplicated	Complicated	
No. of patients	161	107	
Age (yr)	33.5 (25.3–41.0)	38.5 (27.0–52.0)	0.018*
Sex			0.016*
Female	70 (43.5)	31 (29.0)	
Male	91 (56.5)	76 (71.0)	
Nationality			0.250
European, Belgian	59 (36.6)	44 (41.1)	
European, non-Belgian	42 (26.1)	35 (32.7)	
African	34 (21.1)	20 (18.7)	
Middle Eastern	7 (4.3)	2 (1.9)	
Asian	5 (3.1)	1 (0.9)	
American	9 (5.6)	1 (0.9)	
Unknown	5 (3.1)	4 (3.7)	
Charlson comorbidity index	0 (0–0)	0 (0–1)	0.017*
History of abdominal surgery	26 (16.1)	14 (13.1)	0.490
History of other surgeries	18 (11.2)	10 (9.3)	0.631
Physical examination at admission			
Heart rate (bpm)	87 (76–100.5)	95 (81–108)	0.007*
Tachycardia, > 100 bpm	48 (29.8)	46 (43.0)	0.027*
SAP (mmHg)	125 (118–138)	130 (118–140)	0.286
Hypotension, < 100 mmHg	8 (5)	7 (6.5)	0.583
Temperature (°C)	36.9 (36.5–37.4)	37 (36.7–37.5)	0.039*
Fever, > 37.8°C	19 (11.8)	18 (16.8)	0.243
Septic shock	4 (2.5)	2 (1.9)	> 0.999
Blood tests at admission			
C-reactive protein	29.2 (6.5–101.0)	97.5 (29.6–188.3)	< 0.001 *
WBC count (/mm^3)	13,460 (8,216–16,170)	15,720 (12,040–18,500)	0.001*
Surgical intervention			0.020*
Appendicectomy	158 (98.1)	99 (92.5)	
Cecectomy	1 (0.6)	7 (6.5)	
Ileocecal resection	2 (1.2)	1 (0.9)	
Laparoscopic procedure	156 (96.9)	91 (85)	< 0.001*
Drainage	83 (51.6)	84 (78.5)	< 0.001*
Periappendicular	42 (26.1)	59 (55.1)	< 0.001*
Pelvic	63 (39.4)	57 (53.3)	0.025*
Other localizations	6 (3.7)	4 (3.7)	> 0.999

Values are presented as number only, number (%), or median (interquartile range).
bpm, beats per minute; SAP, systolic arterial pressure; WBC, white blood cell.
*$P < 0.05$, statistically significant.

free fluid for bacteriological analysis.

The demographic analysis (Table 1) revealed that patients in the CAA group were older (38.5 years [IQR, 27.0–52.0 years] vs. 33.5 years [IQR, 25.3–41.0 years]), and there was a higher proportion of male patients in this group (71.0% vs. 56.5%). These differences were statistically significant. There were no statistically significant differences in the nationality between groups.

Patients in the UAA group presented more personal history of abdominal surgeries (26 [16.1%] vs. 14 [13.1%]) and more personal history of other surgeries (18 [11.2%] vs. 10 [9.3%]), with no statistical significance.

Although the median CCI was 0 for both groups, the IQR was discretely higher in the CAA group (0–1 vs. 0–0), thus there was a statistically significant difference (P = 0.017).

Initial evaluation of the patients

The general condition of the patients was evaluated at the hospital admission and the patient parameters were evaluated. The analysis of the clinical parameters found statistically significant differences, with an increased HR in the CAA group (95 beats per minute [bpm] [IQR, 81.0–108.0 bpm] vs. 87 bpm [IQR, 76.0–100.5 bpm]), the prevalence of tachycardia in the CAA group (48 [29.8%] vs. 46 [43.0%]) and an increased body temperature in the patients with CAA (18 [16.8%] vs. 19 [11.8%]).

The inflammatory syndrome was more important in the CAA group and reflected by the levels of C-reactive protein (97.5 g/dL [IQR, 29.6–188.3 g/dL] vs. 29.2 g/dL [IQR, 6.5–101.0 g/dL]) and WBC count (15,720/mm^3 [IQR, 12,040–18,500/mm^3] vs. 13,460/mm^3 [IQR, 8,216–16,170/mm^3]). These differences were statistically significant.

Surgical treatment

A higher proportion of surgeries were performed by laparoscopy in the UAA group (156 [96.9%]vs. 91 [85.0%]). Patients with UAA received more appendectomies (158 [98.1%] vs. 99 [92.5%]) and ileocecal resections (2 [1.2%] vs. 1 [0.9%]), while the CAA group presented more cecectomies (7 [6.5%] vs. 1 [0.6%]).

The CAA presented more contamination of the peritoneal cavity and the drainage was considered useful by the surgeon in most patients. The drain was placed in case of presence of cloudy or purulent peritoneal liquid. The abdominal drainage was more frequently used in the CAA group (84 [78.5%] vs. 83 [51.6%]), and placed in periappendicular (59 [55.1%] vs. 42 [26.1%]) or pelvic position (63 [39.1%] in UAA and 57 [53.3%] in the CAA group; P = 0.025).

Bacterial culture

The positive microbiological culture rate was, as expected, significantly higher in the CAA group (73 [68.2%] vs. 86 [53.4%]) (Table 2). Statistically significant differences were observed in the bacterial isolation, with an increased proportion of gram-negative bacteria in CAA cultures (65 [60.7%]vs. 76 [47.2%]), while there were no differences in the proportion of gram-positive or anaerobic bacteria between groups.

The most frequently isolated bacteria in UAA cultures were *E. coli* (61 [37.9%]), bacteria from the *Streptococcus anginosus* group (15 [9.3%]), *Pseudomonas aeruginosa* (9 [5.6%]), *Bacteroides* spp. (8 [5.0%]), and *Klebsiella* spp. (7 [4.3%]). In the CAA group the most frequently isolated bacteria were *E. coli* (52 [48.6%]), bacteria from the *S. anginosus* group (19 [7.8%]), *Bacteroides* spp. (14 [13.1%]), *P. aeruginosa* (10 [9.3%]), and *Klebsiella* spp. (4 [3.7%]).

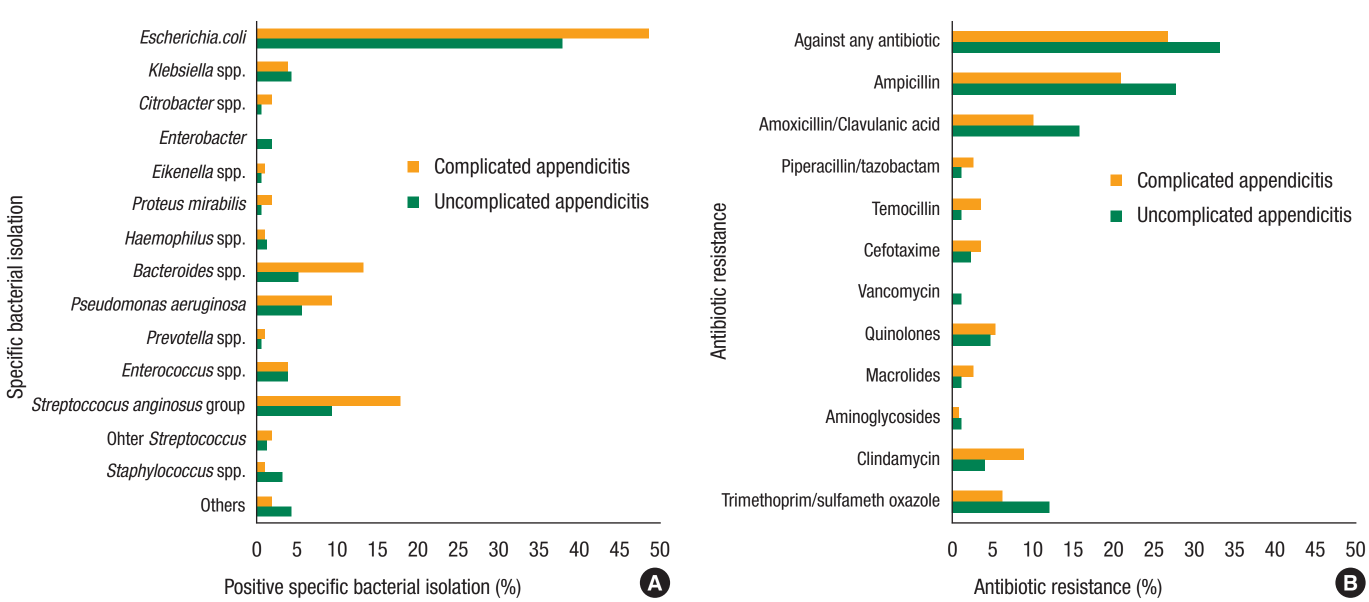

Fig. 1. Specific bacterial isolation (A) and antibiotic resistance (B) in complicated (grey) and uncomplicated appendicitis (black). Statistically significant differences were marked in bold.

Table 2. Bacterial isolation, antibiotic resistance, and antibiotic treatment

Variable	Acute appendicitis		P-value
	Uncomplicated (n = 161)	Complicated (n = 107)	
Culture			0.016*
Negative	75 (46.6)	34 (31.8)	
Positive	86 (53.4)	73 (68.2)	
Bacterial isolation			
Gram-negative	76 (47.2)	65 (60.7)	0.030*
Gram-positive	26 (16.1)	24 (22.4)	0.196
Strict anaerobes	18 (11.2)	22 (20.6)	0.035*
1st line antibiotic treatment			0.013*
None	7 (4.3)	2 (1.9)	
Monotherapy	154 (95.7)	100 (93.5)	
Combined therapy	0 (0)	5 (4.7)	
1st line antibiotic treatment			
None	7 (4.3)	2 (1.9)	0.098
Amox/clav	152 (94.4)	96 (89.7)	
Amox/clav-metronidazole	0 (0)	1 (0.9)	
Amox/clav-ornidazole	0 (0)	1 (0.9)	
Cefuroxime-metronidazole	0 (0)	1 (0.9)	
Cefuroxime-ornidazole	0 (0)	2 (1.9)	
Clindamycin	2 (1.2)	1 (0.9)	
Levofloxacin	0 (0)	1 (0.9)	
Piperacillin/tazobactam	0 (0)	2 (1.9)	
Resistance 1st line antibiotic treatment	27 (16.8)	10 (9.3)	0.084
2nd line antibiotic treatment			0.889
None	132 (80.2)	86 (80.4)	
Monotherapy	11 (6.8)	9 (8.4)	
Combined therapy	18 (11.2)	12 (11.2)	
2nd line antibiotic treatment			
None	132 (82.0)	86 (80.4)	0.763
Amox/clav-metronidazole	0 (0)	1 (0.9)	
Amox/clav-ornidazole	6 (3.7)	4 (3.7)	
Amox/clav-doxycycline	1 (0.6)	0 (0)	
Cefuroxime-metronidazole	1 (0.6)	0 (0)	
Cefuroxime-ornidazole	1 (0.6)	0 (0)	
Ceftriaxone-doxycycline	2 (1.2)	0 (0)	
Doxycycline	0 (0)	1 (0.9)	
Levofloxacin	3 (1.9)	2 (1.9)	
Levofloxacin-ornidazole	4 (2.5)	4 (3.7)	
Ciprofloxacin-ornidazole	3 (1.9)	3 (2.8)	
Piperacillin/tazobactam	8 (5.0)	5 (4.7)	
Ornidazole	0 (0)	1 (0.9)	

(*Continued to the next*)

Table 2. Continued

Variable	Acute appendicitis		P-value
	Uncomplicated (n = 161)	Complicated (n = 107)	
Resistance 2nd line antibiotic treatment	0 (0)	1 (0.9)	0.399
3rd line antibiotic treatment			0.337
None	159 (98.8)	103 (96.3)	
Monotherapy	1 (0.6)	1 (0.9)	
Combined therapy	1 (0.6)	1 (0.9)	
3rd line antibiotic treatment			0.552
None	159 (98.8)	103 (96.3)	
Levofloxacin-ornidazole	1 (0.6)	1 (0.9)	
Ciprofloxacin-ornidazole	0 (0)	1 (0.9)	
Piperacillin/tazobactam	1 (0.6)	1 (0.9)	
Ceftazidime-vancomycin-ornidazole-anidulafungin	0 (0)	1 (0.9)	
Resistance 3rd line antibiotic treatment	0 (0)	0 (0)	> 0.999
Antibiotic treatment duration (day)	5.0 (2–7)	5.5 (3–7)	0.002*
Antibiotic treatment > 1 wk	19 (11.8)	22 (20.6)	0.051

Values are presented as number (%) or median (interquartile range).
Amox/clav, amoxicillin/clavulanic acid.
*$P < 0.05$, statistically significant.

Other isolated bacteria were *Citrobacter* spp., *Enterobacter, Eikenella* spp., *Proteus mirabilis, Haemophilus* spp., *Prevotella* spp., *Enterococcus* spp., other *Streptococcus,* and *Staphylococcus* spp. (Fig. 1).

Antibiotic treatment

No significant differences were observed between the 2 groups in terms of antibiotic resistance, with an overall rate of antibiotic resistance of 34.2% (55 of 161) in the UAA group and 27.1% (29 of 107) in the CAA group. The most common resistances observed were against ampicillin (46 [28.6%] and 23 [21.5%]) and amoxicillin/clavulanic acid ([26 [16.1%] and 11 [10.3%]) in the UAA and CAA groups, respectively. Other relevant resistances found were against trimethoprim/sulfamethoxazole (20 [12.4%]) and clindamycin (10 [9.3%]) in the UAA and CAA groups, respectively. There was a low resistance rate against quinolones (8 [5.0%] and 6 [5.6%]) in the UAA and CAA groups, respectively (Fig. 1).

More patients in the UAA group received monotherapy as the first line of antibiotic treatment (154 [95.7%] vs. 100 [93.5%]) and none received combined therapy (0 patients vs. 5 [4.7%]). Most patients received amoxicillin/clavulanic acid as the first line of treatment (94.4% in the UAA group and 89.7% in the CAA group). There were resistances to the first line of antibiotic treatment in 27 patients (16.8%) from the UAA group vs. 10 patients (9.3%) from the CAA group, without statistically significant differences.

Table 3. Postoperative outcomes

Variable	Acute appendicitis		P-value
	Uncomplicated (n = 161)	Complicated (n = 107)	
Morbidity	11 (6.8)	21 (19.6)	0.002*
CD classification of 30-day complications			0.012*
Grade I	2 (1.2)	6 (5.6)	
Grade II	4 (2.5)	9 (8.4)	
Grade III	5 (3.1)	6 (5.6)	
Reintervention	3 (1.9)	4 (3.7)	0.442
Specific complication			
Postoperative ileus	4 (2.5)	6 (5.6)	0.204
Acute kidney injury	0 (0)	1 (0.9)	0.399
Bacteremia	0 (0)	1 (0.9)	0.399
Surgical site infection	8 (5)	14 (13.1)	0.018*
Cecal perforation	1 (0.6)	1 (0.9)	> 0.999
Blood tests at 48 hr			
C-reactive protein	111.9 (28.9–215.7)	202.4 (96.6–316.0)	0.001*
WBC count*	8,660 (6,715–10,980)	8,695 (6,335–12,052)	0.447
Hospital stay (day)	3 (2–5)	5 (3–6)	< 0.001*

Values are presented as number (%) or median (interquartile range).
CD, Clavien-Dindo; WBC, white blood cell.
*$P < 0.05$, statistically significant.

For the second line of antibiotics, most patients received piperacillin/tazobactam (5.0% in the UAA group and 4.7% in the CAA group). There was only 1 resistance to this line of treatment in the CAA group (0.9%), without statistically significant differences.

The third line of treatment was not necessary mostly for patients with UAA (159 [98.8%] vs. 103 [96.3%]). Levofloxacin-ornidazole and piperacillin/tazobactam were the most commonly used antibiotics in both groups. The median antibiotic duration was statistically significantly higher in the CAA group (5.5 days [IQR, 3–7 days] vs. 5 days [IQR, 2–7 days]).

Postoperative outcomes

In term of postoperative outcomes, the morbidity was significantly higher for patients with CAA (21 [19.6%] vs. 11 [6.8%]). Thirty-day complications according to Clavien-Dindo classification revealed a significant difference for the CAA group, with a higher proportion of grade I, II, and III complications. There was a higher proportion of surgical site infections in the CAA group (14 [13.1%] vs. 8 [5.0%]) as a specific complication.

The C-reactive protein level at 48-hour postoperative blood test was higher in the CAA group (202,4 mg/dL [IQR, 96.6–316.0 mg/dL] vs. 111.9 mg/dL [IQR, 28.9–215.7 mg/dL]), with a similar WBC count between groups.

The hospital stay was significantly longer in the CAA group (5 days [IQR, 3–6 days]) than in the UAA group (3 days [IQR, 2–5 days]) (Table 3).

Analysis of factors linked with complicated appendicitis

All variables were evaluated as factors linked with complicated appendicitis. Variables with statistical significance in univariate analysis to predict complicated appendicitis and the results from the most common specific bacterial isolation are shown in Table 4. Once adjusted in multivariate analysis the risk factors related to complicated appendicitis were the CCI, the WBC count at admission, the need for an open procedure, and the need for surgical drainage. All variables that could be considered risk factors were tested in univariate logistic regression to explore if they were linked with complicated appendicitis, except for specific bacterial isolation with < 10 positive cultures (Table 4). Neither the culture results, the group of bacterial isolation, or the specific isolated bacteria could predict complicated appendicitis.

DISCUSSION

Acute appendicitis is the most common cause of acute peritonitis, with 7% of cases of secondary diffuse peritonitis. In case of complicated appendicitis, perforated appendicitis with peritonitis, the morbidity is increased. Diffuse peritonitis represents the most severe grade of CAA, and it is still considered an important cause of morbidity (10%) and mortality (1%–2.5%) [10].

In some studies, gram-negative bacteria are more common in acute appendicitis compared to gram-positive [11,12]. García-Marín [13] found that the culture-positive rate was higher in

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Table 4. Analysis of risk factors related to complicated appendicitis

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.022 (1.005–1.039)	0.009*	1.022 (1.005–1.039)	0.009*
Sex		0.017*		
Female	Reference			
Male	1.887 (1.120–3.174)			
Nationality		0.249		
European, Belgian	Reference			
European, non-Belgian	1.117 (0.617–2.025)			
African	0.789 (0.401–1.551)			
Middle Eastern	0.383 (0.076–1.934)			
Asian	0.268 (0.030–2.378)			
American	0.149 (0.018–1.120)			
Charlson comorbidity index	1.459 (1.114–1.911)	0.006*	1.333 (1.003–1.771)	0.048*
History of abdominal surgery	0.782 (0.782–1.576)	0.491		
History of other surgeries	0.819 (0.363–1.850)	0.631		
Physical examination at admission				
Heart rate (bpm)	1.018 (1.004–1.033)	0.010*		
Tachycardia, > 100 bpm	1.775 (1.066–2.958)	0.028*		
SAP (mmHg)	1.005 (0.990–1.019)	0.540		
Hypotension, < 100 mmHg	1.339 (0.471–3.807)	0.584		
Temperature (°C)	1.383 (0.994–1.924)	0.054		
Fever, > 37.8°C	1.512 (0.753–3.035)	0.245		
Septic shock	0.748 (0.135–4.155)	0.740		
Blood tests at admission				
C-reactive protein	1.005 (1.002–1.007)	< 0.001*		
WBC count (/mm^3)	1.00008 (1.00003–1.00014)	< 0.001*	1.00007 (1.00001–1.00013)	0.027*
Surgical intervention				
Appendicectomy	Reference			
Cecectomy	11.172 (1.354–92.174)	0.025*		
Ileocecal resection	0.798 (0.071–8.916)	0.855		
Laparoscopic procedure	0.182 (0.065–0.514)	0.001*	0.218 (0.073–0.648)	0.006*
Drainage	3.432 (1.970–5.980)	< 0.001*	2.571 (1.421–4.653)	0.002*
Culture		0.016*		
Negative	Reference			
Positive	1.872 (1.123–3.122)			
Bacterial isolation				
Gram-negative	1.731 (1.054–2.843)	0.030*		
Gram-positive	1.501 (0.809–2.787)	0.198		
Strict anaerobes	2.056 (1.043–4.052)	0.037*		
1st line antibiotic treatment	0.870 (0.704–1.075)	0.197		
Resistance 1st line antibiotic treatment	0.512 (0.237–1.106)	0.089		

(Continued to the next page)

Table 4. Continued

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Bacterial specific isolation				
Escherichia coli	1.550 (0.945–2.543)	0.083		
Klebsiella spp.	0.854 (0.244–2.993)	0.806		
Bacteroides spp.	2.879 (1.163–7.124)	0.022*		
Pseudomonas aeruginosa	1.741 (0.683–4.439)	0.246		
Enterococcus spp.	1.003 (0.276–3.643)	0.996		
Streptoccocus anginosus group	2.102 (1.016–4.347)	0.045*		

OR, odds ratio; CI, confidence interval; bpm, beats per minute; SAP, systolic arterial pressure; WBC, white blood cell.
*$P < 0.05$, statistically significant.

CAA than in UAA, identifying a higher frequency of gram-positive cocci and anaerobic bacteria with different isolates and susceptibilities. Parthiban and Harish [14] in a microbiology study of the appendicectomy specimen showed that anaerobes acted as the commonest organism involved in appendicitis and postoperative wound infection. Moreover, the presence of anaerobes caused a higher incidence of complicated appendicitis. Lafi et al. [15] found that the most common bacteria found in a bacteriological study of acute appendicitis were *E. coli, B. fragilis,* and *Staphylococcus aureus*. For Chen et al. [3], the most commonly involved bacteria were *E. coli*, followed by *Klebsiella pneumoniae, Streptococcus* spp., *Enterococcus* spp., and *P. aeruginosa*. The presence of *P. aeruginosa* was associated with wound infection, despite antibiotic prophylaxis, highlighting that special consideration for the clinical and biological evolution of these patients was necessary when this pathogen was found [16]. In our study, the most frequently identified bacteria were gram-negative, especially in the setting of CAA, without statistically significant differences between groups in the presence of gram-positive or anaerobes. However, there was no association between the group of bacterial isolation or the specific isolated bacteria and the presentation of a CAA.

In recent years, multiple studies revealed that in case of UAA, the antibiotics only can be a reliable treatment. APPAC (Appendicitis Acuta) randomized clinical trial found that in case of UAA, the antibiotic treatment for did not require appendectomy during the 1-year follow-up period, and those who required appendectomy did not experience significant complications [17,18]. In case of simple appendicitis, the inferiority of nonoperative therapy vs. appendectomy could equally be related to the type of antibiotic used. Current evidences show that resistance of *E. coli* to amoxicillin plus clavulanic acid is increasing [19].

There is a real concern about the antibiotic resistance of the bacteria. The resistant and virulent microorganisms might be a result of antibiotic exposure or the application of invasive and prolonged medical and surgical treatment [20]. The presence of multidrug-resistant bacteria can contribute to additional morbidity [21]. In a study from 2010, 25% of children with gangrenous or ruptured appendicitis were insensitive to the antimicrobial regime used [22]. *E. coli* and mixed anaerobes are the predominant organisms identified in secondary peritonitis from appendicitis in children. In case of an inadequate empirical antibiotic and amoxicillin/clavulanate resistance of the bacteria, postoperative infectious complications might increase [23].

The initial empirical therapy should target all of the microorganisms likely to be involved, on the basis of the suspected risk factors [24]. Empiric antibiotic treatment is effective in most patients, early (blood or intraabdominal) culturing is very useful to guide antibiotic modification in abdominal infection [25]. If the postoperative evolution of the patient is not optimal, the results of the bacterial culture are critical, especially in the actual tendency of increased occurrence of multidrug resistant bacterial strains [26].

Andersen et al. [27] in a review of literature found that the antibiotic prophylaxis is effective in the prevention of postoperative complications in appendectomies patients, whether the administration is given pre-, peri- or postoperatively. Kimbrell et al. [28] in a study on postoperative antibiotic administration in CAA suggest that the use of postoperative prophylactic antibiotics more than 24 hours in patients does not prevent the development of an abscess. Obinwa et al. [23] in a study on the microbiology of secondary bacterial peritonitis due to appendicitis found that inadequate initial empirical antibiotic and amoxicillin/clavulanate resistant *E. coli* may contribute to increased postoperative infectious complications. The study recommended a triple antibiotic combination of amoxicillin/clavulanate, gentamicin, and metronidazole as an empiric treatment in CAA.

The prospective multicenter study "MUSTANG (Multicenter Study of the Treatment of Appendicitis in America: Acute, Perforated, and Gangrenous)" on the duration of antibiotherapy found that there was no evidence of an association between the duration of 24 hours vs. 96 hours for CAA and an increased rate of SSI [29]. A study from the Netherlands (2014) concluded that 3 days of antibiotics led to a similar rate of infectious complications of 5 days or more [30,31]. van den Boom et al. [32] in a meta-analysis revealed that there were no differences in the incidence of intraabdominal abscess with ≤3 days vs. >3 days of antibiotic treatment, but there was a reduction with >5 days of treatment. Xu et al. [33] in a retrospective analysis of 93 patients who underwent appendectomy found that the average stay of patients receiving fluoroquinolones was 2.6 days shorter than patients who received cephalosporins. In our study, the median duration of the antibiotic treatment was 5 days for UAA and 5.5 days for CAA. Therefore, the duration could have been optimized in the UAA but might have been optimal for the CAA group. In our institution, the antibiotics were discontinued, in concertation with the infectiology team accordingly to the type of bacteria culture and type of antibiotic.

In conclusion, the bacterial culture allows for not only evaluating the immediate impact of the antibiotics treatment and evaluating the resistance, but also evaluating the preoperative empirical treatments in order to reduce patients' morbidity. CAA presented a higher rate of positive cultures with increased identification of gram-negative bacteria. *E. coli*, bacteria from the *S. anginosus* group, and *Bacteroides* spp. were the most commonly isolated bacteria, without relevant differences in terms of antibiotic resistance.

The predictors for complicated appendicitis were preoperative or intraoperative variables, while the culture results, the group of bacterial isolation or the specific isolated bacteria did not predict complicated appendicitis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. van Rossem CC, Schreinemacher MH, van Geloven AA, Bemelman WA; Snapshot Appendicitis Collaborative Study Group. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. JAMA Surg 2016;151:323-9.
2. Snyder MJ, Guthrie M, Cagle S. Acute appendicitis: efficient diagnosis and management. Am Fam Physician 2018;98:25-33.
3. Chen CY, Chen YC, Pu HN, Tsai CH, Chen WT, Lin CH. Bacteriology of acute appendicitis and its implication for the use of prophylactic antibiotics. Surg Infect (Larchmt) 2012;13:383-90.
4. Boueil A, Guégan H, Colot J, D'Ortenzio E, Guerrier G. Peritoneal fluid culture and antibiotic treatment in patients with perforated appendicitis in a Pacific Island. Asian J Surg 2015;38:242-6.
5. Jeon HG, Ju HU, Kim GY, Jeong J, Kim MH, Jun JB. Bacteriology and changes in antibiotic susceptibility in adults with community-acquired perforated appendicitis. PLoS One 2014;9:e111144.
6. Abdurrazzaaq A, Afuwape O, Ademola A, Fasina O. Bacterial pattern in acute appendicitis. Ann Afr Surg 2018;15:8-13.
7. Parthiban N, Harish M. A study on microbiology culture of acute appendicectomy specimen and its correlation with wound infection. Int Surg J 2017;4:2212-5.
8. David A, Dodgion C, Zein Eddine SB, Davila D, Webb TP, Trevino CM. Perforated appendicitis: Short duration antibiotics are noninferior to traditional long duration antibiotics. Surgery 2020;167:475-7.
9. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-96.
10. Gomes CA, Sartelli M, Podda M, Di Saverio S, Coccolini F, Segovia-Lohse HA, et al. Laparoscopic versus open approach for diffuse peritonitis from appendicitis ethiology: a subgroup analysis from the Physiological parameters for Prognosis in Abdominal Sepsis (PIPAS) study. Updates Surg 2020;72:185-91.
11. Aziz MA, Lah SU, Hussain S, Hussain M, Shah W. Bacteriology of acute appendicitis and its implication for rationale use of antibiotics. Pak J Med Health Sci 2020;14:1472-5.
12. Naher HS, Ktab FK. Bacterial profile associated with appendicitis. Int Res J Med Sci 2013;1:1-4.
13. García-Marín A, Pérez-López M, Martínez-Guerrero E, Rodríguez-Cazalla L, Compañ-Rosique A. Microbiologic analysis of complicated and uncomplicated acute appendicitis. Surg Infect (Larchmt) 2018;19:83-6.
14. Bennion RS, Baron EJ, Thompson JE Jr, Downes J, Summanen P, Talan DA, et al. The bacteriology of gangrenous and perforated appendicitis: revisited. Ann Surg 1990;211:165-71.
15. Lafi SA, Al-Alossi MM, Aldulaymi HR. Appendicitis: bacteriological aspect and some other factors. Al Anbar Med J 2009;7.
16. Khan MS, Chaudhry MB, Shahzad N, Tariq M, Memon WA, Alvi AR. Risk of appendicitis in patients with incidentally discovered appendicoliths. J Surg Res 2018;221:84-7.
17. Guinane CM, Tadrous A, Fouhy F, Ryan CA, Dempsey EM, Murphy B, et al. Microbial composition of human appendices from patients following appendectomy. mBio 2013;4:e00366-12.
18. Cohn SM. Antibiotic therapy vs. appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. In: Cohn SM, Rhee P, editors. 50 Landmark papers [Internet]. Boca: CRC Press; 2019 [cited 2022 Feb 2]. Available from: https://www.taylorfrancis.com/books/9781000075236/chapters/10.1201/9780429316944-18.

19. Podda M, Cillara N, Di Saverio S, Lai A, Feroci F, Luridiana G, et al. Antibiotics-first strategy for uncomplicated acute appendicitis in adults is associated with increased rates of peritonitis at surgery: a systematic review with meta-analysis of randomized controlled trials comparing appendectomy and non-operative management with antibiotics. Surgeon 2017;15:303-14.
20. Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection. Br J Surg 2017;104:e14-23.
21. Reinisch A, Malkomes P, Habbe N, Bechstein WO, Liese J. Bad bacteria in acute appendicitis: rare but relevant. Int J Colorectal Dis 2017;32:1303-11.
22. Akingboye AA, Davies B, Tien T. Pus samples in complicated appendicitis: an important investigation or a waste of resources: a prospective cohort study. Scand J Surg 2019;108:55-60.
23. Obinwa O, Casidy M, Flynn J. The microbiology of bacterial peritonitis due to appendicitis in children. Ir J Med Sci 2014;183:585-91.
24. Montravers P, Blot S, Dimopoulos G, Eckmann C, Eggimann P, Guirao X, et al. Therapeutic management of peritonitis: a comprehensive guide for intensivists. Intensive Care Med 2016;42:1234-47.
25. Son JT, Lee GC, Kim HO, Kim T, Lee D, Lee SR, et al. Routine intraoperative bacterial culture may be needed in complicated appendicitis. Ann Coloproctol 2020;36:155-62.
26. Deodatus JA, Paas SF, Wagenvoort GH, de Kubber MM. Case report: appendicitis induced Staphylococcus aureus and Klebsiella pneumoniae bacteremia in a young healthy male. Int J Emerg Med 2021;14:36.
27. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. Cochrane Database Syst Rev 2005;2005:CD001439.
28. Kimbrell AR, Novosel TJ, Collins JN, Weireter LJ, Terzian HW, Adams RT, et al. Do postoperative antibiotics prevent abscess formation in complicated appendicitis? Am Surg 2014;80:878-83.
29. Bou Zein Eddine S, Dodgion CM, Qian S, Trevino C, De Moya MA, Yeh DD, et al. Complicated appendicitis: are extended antibiotics necessary?: a post hoc analysis of the EAST Appendicitis "MUSTANG" Study. J Surg Res 2020;247:508-13.
30. van den Boom AL, de Wijkerslooth EM, van Rosmalen J, Beverdam FH, Boerma EG, Boermeester MA, et al. Two versus five days of antibiotics after appendectomy for complex acute appendicitis (APPIC): study protocol for a randomized controlled trial. Trials 2018;19:263.
31. Goyal V, Pathania S, Goyal V, Sandhu HP. A prospective evaluation of prevalence of microbial flora and significance of intraoperative peritoneal culture of fungus in perforation peritonitis. Int J Med Res Rev 2015;3:1317-21.
32. van den Boom AL, de Wijkerslooth EM, Wijnhoven BP. Systematic review and meta-analysis of postoperative antibiotics for patients with a complex appendicitis. Dig Surg 2020;37:101-10.
33. Xu S, Yu X, Li Y, Shi D, Huang J, Gao Q, et al. Analysis of antibiotics selection in patients undergoing appendectomy in a Chinese tertiary care hospital. Springerplus 2016;5:1839.