Implications of Bacteriological Study in Complicated and Uncomplicated Acute Appendicitis

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Abstract

Background

The bacteriological sample in the presence of intraabdominal free fluid is necessary to adapt the antibiotherapy and to prevent the development of resistance. The aim of this study 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 predictors for complicated appendicitis.

Material and methods

We performed a single-centre, 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. 268 patients were analysed in term of medical history, parameters at admission, bacterial culture, antibiotic resistance and postoperative outcomes.

Results

The positive microbiological culture rate was significantly higher in CAA group (68.2 % vs. 53.4 %). The most frequently isolated bacteria in UAA and CAA cultures were *E. coli* (37.9 % and 48.6 %), bacteria from the *Streptococcus anginosus* group (9.3 % and 7.8 %), and *Bacteroides* spp. (5 % and 13.1 %). The most commonly observed resistances were against ampicillin (28.9 % and 21.7 %) and amoxicillin/clavulanic acid (16.4 % and 10.5 %) in UAA and CAA, respectively.

The predictors for complicated appendicitis were preoperative or intraoperative variables. Neither the culture results, the group of bacterial isolation nor the specific isolated bacteria predicted a complicated appendicitis.

Conclusion

CAA presented a higher rate of positive cultures with increased identification of Gram negative bacteria. There were not relevant differences in terms of antibiotic resistance.

Background

Complicated intra-abdominal infections represent a widespread problem, encountered worldwide, with appendicitis alone affecting in USA 300 000 patients/year and consuming > 1 million hospital days.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 aetiology is related usually to the presence of an appendicolith that obstructs the appendix lumina. Other pathologies that can produce an inflammation of the appendix are tumours (carcinoid tumours, 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. The antibiotic use can be considered as an adjunct to surgical intervention, and their appropriate use remain 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 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.

Material And Methods

Study design

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

The inclusion criteria for the 268 patients analysed were: 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.

The study was approved by the Ethics Committee of our institution.

Definitions

Uncomplicated acute appendicitis (UAA) - Catarrhal or phlegmonous inflammation of the appendix.

Complicated acute appendicitis (CAA) - 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 prescribed 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 at the second postoperative day to follow the dynamics of the inflammatory syndrome. Patient was discharged in the absence of relevant postoperative complications.

Variables

Baseline characteristics collected were: age, sex, nationality, Charlson Comorbidity Index (which predicts the ten-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 analysed were: heart rate (HR), systolic blood pressure (SBP), and temperature; and the C-reactive protein and the white cell blood count from the blood tests. The type of surgical intervention, the open or laparoscopic approach, and the need of drainage were the intraoperative variables analysed.

A positive bacteriological analysis was thoroughly evaluated to identify the specific bacteria and its resistance to 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 ClavienDindo classification, and the need of reintervention. Specific complications analysed were: postoperative ileus, acute kidney injury, bacteraemia, surgical site infection and caecal 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 normality test.

To evaluate the null hypothesis, the χ^2 test was used for categorical variables, the Student's *t* test was used for normal quantitative variables and the Mann–Whitney *U* test was used for non-normal quantitative variables.

To explore the risk factors for complicated appendicitis, all variables were tested in univariate logistic regression. Statistically significant variables in univariate analysis were then included in a multivariable logistic regression model, erasing non-significant outcomes until all variables were adjusted to each other.

in the final model. A p-value < 0.05 in a two-tailed statistical analysis was considered statistically significant. Statistical analysis was performed with the statistical software SPSS 23.0 for Windows (IBM SPSS Inc., Chicago, IL).

Results

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

The demographic analysis (Table 1) revealed that patients in the CAA group were older (38.5 years [IQR: 27–52] vs. 33.5 [25.3–41]), and there was a higher proportion of male patients in this group (71% vs. 56.5%). These differences were statistically significant. There were no statistically significant differences in the nationality between groups.

Table 1
Baseline characteristics and surgical procedure

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%)	n (%)	p-value
	Median (IQR)	Median (IQR)	
Age (years)	33.5 (25.3–41)	38.5 (27–52)	0.018
Sex			0.016
Female	70 (43.5)	31 (29)	
Male	91 (56.5)	76 (71)	
Nationality			0.169
European, Belgian	59 (37.8)	44 (42.7)	
European, non-Belgian	42 (26.9)	35 (34)	
African	34 (21.8)	20 (19.4)	
Middle Eastern	7 (4.5)	2 (1.9)	
Asian	5 (3.2)	1 (1)	
American	9 (5.8)	1 (1)	
Charlson Comorbidity Index	0 (0–0)	0 (0–1)	0.017
Personal history of abdominal surgery	26 (16.1)	14 (13.1)	0.490
Personal history of other surgeries	18 (11.2)	10 (9.3)	0.631
Physical examination at admission			
HR (bpm)	87 (76–100.5)	95 (81–108)	0.007
Tachycardia (> 100 bpm)	48 (29.8)	46 (43)	0.027
SBP (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)	1.000

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%) Median (IQR)	n (%) Median (IQR)	p-value
Blood tests at admission			
C-reactive protein	29.2 (6.5–101)	97.5 (29.6–188.3)	0.000
White cell blood count	13 460 (8 216 – 16 170)	15 720 (12 040–18 500)	0.001
Surgical intervention			0.020
Appendectomy	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)	0.000
Drainage	83 (51.6)	84 (78.5)	0.000
Periappendicular	42 (26.1)	59 (55.1)	0.000
Pelvic	63 (39.4)	57 (53.3)	0.025
Other localization	6 (3.7)	4 (3.7)	1.000

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

Although the median Charlson Comorbidity Index 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-value = 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 heart rate in CAA group (95 bpm [81–108 bpm] vs. 87 bpm [76 100.5 bpm]), the prevalence of tachycardia in CAA group (48 [29. %] patients vs. 46 [4 %]) and an increased body temperature in the patients with CAA (18 patients (16. %) vs. 19 (11. %)).

The inflammatory syndrome was more important in CAA group and reflected by the levels of C-reactive protein (97.5 g/dL [29.6–188.3] vs. 29.2 g/dL [6.5–101] and white cell blood count (15 720/mm³ [12 040 – 18 500] vs. 13 460/mm³ [8 216 – 16 170/mm³]). These differences were statistically significant.

Surgical treatment

A higher proportion of surgeries were performed by laparoscopy in UAA group (156 [98.1%] patients vs. 91 [85%]). 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%] patients 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 abdominal drainage was more frequently used in CAA group (84 [78.5%] patients vs. 83 [51.6%]), and placed in periappendicular (59 [55. %] patients vs. 42 [26. %]) or pelvic position (63 patients [39. %] in UAA and 57 patients [53. %]) in CAA group, p-value = 0.025).

Bacterial culture

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

Table 2
Bacterial isolation, antibiotic resistance and antibiotic treatment

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%)	n (%)	p-value
	Median (IQR)	Median (IQR)	
Cultures			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
Specific bacterial isolation			
E. coli	61 (37.9)	52 (48.6)	0.082
Klebsiella spp.	7 (4.3)	4 (3.7)	1.000
Citrobacter spp.	1 (0.6)	2 (1.9)	0.566
Enterobacter	3 (1.9)	0	0.278
Eikenella spp.	1 (0.6)	1 (0.9)	1.000
Proteus mirabilis	1 (0.6)	2 (1.9)	0.566
Haemophilus spp.	2 (1.2)	1 (0.9)	1.000
Bacteroides spp.	8 (5)	14 (13.1)	0.018
Pseudomonas aeruginosa	9 (5.6)	10 (9.3)	0.241
Prevotella spp.	1 (0.6)	1 (0.9)	1.000
Enterococcus spp.	6 (3.7)	4 (3.7)	1.000
Strep. anginosus group	15 (9.3)	19 (17.8)	0.042
Other Streptococcus	2 (1.2)	2 (1.9)	0.678
Staphylococcus spp.	5 (3.1)	1 (0.9)	0.407
Other	7 (4.3)	2 (1.9)	0.324

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%)	n (%)	p-value
	Median (IQR)	Median (IQR)	
Antibiotic resistance			
Against any antibiotic	55 (34.6)	29 (27.9)	0.254
Ampicillin	46 (28.9)	23 (21.7)	0.189
Amoxicillin/clavulanic acid	26 (16.4)	11 (10.5)	0.178
Piperacillin/tazobactam	2 (1.2)	3 (2.8)	0.391
Temocillin	2 (1.2)	4 (3.7)	0.221
Cefotaxime	4 (2.5)	4 (3.7)	0.718
Vancomycin	2 (1.2)	0	0.519
Quinolones	8 (5)	6 (5.6)	0.837
Macrolides	2 (1.2)	3 (2.8)	0.391
Aminoglycosides	2 (1.2)	1 (0.9)	1.000
Clindamycin	7 (4.3)	10 (9.3)	0.100
Trimethoprim/sulfamethoxazole	20 (12.6)	7 (6.5)	0.110
1st line antibiotic treatment			0.013
None	7 (4.3)	2 (1.9)	
Monotherapy	154 (95.7)	100 (93.5)	
Combined therapy	0	5 (4.7)	

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%)	n (%)	p-value
	Median (IQR)	Median (IQR)	
1st line antibiotic treatment			0.098
None	7 (4.3)	2 (1.9)	
Amoxicillin/clavulanic acid	152 (94.4)	96 (89.7)	
Amox/clav - Metronidazole	0	1 (0.9)	
Amox/clav - Ornidazole	0	1 (0.9)	
Cefuroxime - Metronidazole	0	1 (0.9)	
Cefuroxime - Ornidazole	0	2 (1.9)	
Clindamycin	2 (1.2)	1 (0.9)	
Levofloxacin	0	1 (0.9)	
Piperacillin/tazobactam	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)	

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%)	n (%)	p-value
	Median (IQR)	Median (IQR)	
2nd line antibiotic treatment			0.763
None	132 (82)	86 (80.4)	
Amox/clav - Metronidazole	0	1 (0.9)	
Amox/clav - Ornidazole	6 (3.7)	4 (3.7)	
Amox/clav - Doxycycline	1 (0.6)	0	
Cefuroxime - Metronidazole	1 (0.6)	0	
Cefuroxime - Ornidazole	1 (0.6)	0	
Ceftriaxone - Doxycycline	2 (1.2)	0	
Doxycycline	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 (4.9)	5 (4.7)	
Ornidazole	0	1 (0.9)	
Resistance 2nd line antibiotic treatment	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	1 (0.9)	
Piperacillin/tazobactam	1 (0.6)	1 (0.9)	
Ceftazidime - Vancomycin - Ornidazole - Anidulafungin	0	1 (0.9)	

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%)	n (%)	p-value
	Median (IQR)	Median (IQR)	
Resistance 3rd line antibiotic treatment	0	0	1.000
Antibiotic treatment duration (days)	5 (2–7)	5.5 (3–7)	0.002
Antibiotic treatment > 1 week	19 (11.8)	22 (20.6)	0.051

The most frequently isolated bacteria in UAA cultures were *E. coli* (61 patients [37.9%]), bacteria from the *Streptococcus anginosus group* (15 patients [9.3%]), *Pseudomonas aeruginosa* (9 patients [5.6%]), *Bacteroides spp.* (8 patients [5%]), and *Klebsiella spp.* (7 patients [4.3%]). In the CAA group the most frequently isolated bacteria were *E. coli* (52 patients [48.6%]), bacteria from the *Strep. anginosus group*, (19 patients [7.8%]), *Bacteroides spp.* (14 patients [13.1%]), *P. aeruginosa* (10 patients [9.3%]) and *Klebsiella spp.* (4 patients [3.7%]). Other isolated bacteria were *Citrobacter spp.*, *Enterobacter*, *Eikenella spp.*, *Proteus mirabilis*, *Haemophilus spp.*, *Prevotella spp.*, *Enterococcus spp.*, other *Streptococcus*, and *Staphylococcus spp.*

Antibiotic treatment

No significant differences were observed between the two groups in terms of antibiotic resistance, with an overall rate of antibiotic resistance of 34.6% (55/161) in UAA and 27.9% (29/107) in CAA. The most commonly resistances observed were against ampicillin (28.9% [46/161] and 21.7% [23/107]), and amoxicillin/clavulanic acid (16.4% [26/161] and 10.5% [11/107]) in UAA and CAA, respectively. Other relevant resistances found were against trimethoprim/sulfamethoxazole (12.6% [20/161]) clyndamicin (9.3% [10/107]) in the CAA group. There was a low resistance rate against quinolones (5% [8/161] and 5.6% [6/107]) in both groups.

More patients in UAA group received monotherapy as a first line of antibiotic treatment (154 [95.7%] patients vs. 100 [93.5%]) and none received combined therapy (0 patients vs. 5 [4.7%]). Most patients received amoxicillin/clavulanic acid as a first line of treatment (94.4% in UAA and 89.7% in CAA). There were resistances to the first line of antibiotic treatment in 16.8% of patients (27/161) from the UAA group vs. 9.3% (10/107), without statistically significant differences.

For the second line of antibiotics, most patients received Piperacillin/Tazobactam (4.9% in UAA and 4.5% in CAA). There was only one resistance to this line of treatment in CAA group (0.9%), without statistically significant differences.

The third line of treatment was not necessary mostly for patients with UAA (159 [98.8%]) patients 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 CAA (5.5 days [IQR: 3–7] vs. 5 days [IQR: 2–7]).

Postoperative outcomes

In term of postoperative outcomes, the morbidity was significantly higher for patients with CAA (21 [19.6%] patients 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 CAA group (14 [13.1%] patients vs. 8 [5%]) as specific complication. (Table 3)

Table 3
Postoperative outcomes

	Uncomplicated appendicitis n : 161	Complicated appendicitis n : 107	
	n (%)	n (%)	p-value
	Median (IQR)	Median (IQR)	
Morbidity	11 (6.8)	21 (19.6)	0.002
30-day complications according to Clavien-Dindo classification			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 complications			
Postoperative ileus	4 (2.5)	6 (5.6)	0.204
Acute kidney injury	0	1 (0.9)	0.399
Bacteriemia	0	1 (0.9)	0.399
Surgical site infection	8 (5)	14 (13.1)	0.018
Cecal perforation	1 (0.6)	1 (0.9)	1.000
Blood tests at 48 hours			
C-reactive protein	111.9 (28.9–215.7)	202.4 (96.6–316.0)	0.001
White cell blood count *	8 660 (6 715 – 10 980)	8 695 (6 335 – 12 052)	0.447
Hospital stay (days)	3 (2–5)	5 (3–6)	0.000

The C-reactive protein level at 48h postoperative blood test, was higher in CAA group (202,4 mg/dl (96.6–316.0) vs. 111.9 mg/dl (28.9–215.7), with a similar white cell blood count between groups.

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

Analysis of risk factors for complicated appendicitis

All variables were evaluated as predictors for complicated appendicitis. Variables with statistical significance in univariate analysis to predict a complicated appendicitis and all the results from specific bacterial isolation are shown in Table 4. Once adjusted in multivariate analysis the predictors for complicated appendicitis were: the Charlson Comorbidity Index, the white blood cell count at admission, the need of an open procedure and the need of surgical drainage. Neither the culture results, the group of bacterial isolation or the specific isolated bacteria could predict a complicated appendicitis. These results are shown in Table 5.

Table 4
Univariate analysis of predictors for complicated appendicitis

	Odds ratio	95% Confidence Interval	p-value
Age	1.022	1.005–1.039	0.009
Sex			
Female	Reference		0.017
Male	1.887	1.120–3.174	
Charlson Comorbidity Index	1.459	1.114–1.911	0.006
Physical examination at admission			
FC (bpm)	1.018	1.004–1.033	0.010
Tachycardia (> 100 bpm)	1.775	1.066–2.958	0.028
Blood tests at admission			
C-reactive protein	1.005	1.002–1.007	0.000
White cell blood count	1.000081	1.000025–1.000137	0.000
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
Drainage	3.432	1.970–5.980	0.000
Cultures			
Negative	Reference		0.016
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

	Odds ratio	95% Confidence Interval	p-value
Bacterial specific isolation			
E. coli	1.550	0.945–2.543	0.083
Klebsiella spp.	0.854	0.244–2.993	0.806
Citrobacter spp.	3.048	0.273–34.036	0.365
Enterobacter	0	ND	0.999
Eikenella spp.	1.509	0.093–24.395	0.772
Proteus mirabilis	3.048	0.273–34.036	0.365
Haemophilus spp.	0.750	0.067–8.376	0.815
Bacteroides spp.	2.879	1.163–7.124	0.022
Pseudomonas aeruginosa	1.741	0.683–4.439	0.246
Prevotella spp.	1.509	0.093–24.395	0.772
Enterococcus spp.	1.003	0.276–3.643	0.996
Strep. anginosus group	2.102	1.016–4.347	0.045
Other Streptococcus	1.514	0.210–10.917	0.681
Staphylococcus spp.	0.294	0.034–2.555	0.267
Other	0.419	0.085–2.057	0.289

Table 5
Multivariate analysis of predictors for complicated appendicitis

	Odds ratio	95% Confidence Interval	p-value
Charlson Comorbidity Index	1.333	1.003–1.771	0.048
Blood tests at admission	1.000068	1.000008–1.000129	0.027
White cell blood count			
Laparoscopic procedure	0.218	0.073–0.648	0.006
Drainage	2.571	1.421–4.653	0.002

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 complicated AA, and it is still considered an important cause of morbidity (10%) and mortality (1–2.5%). 9

In some studies, Gram-negative bacteria are more common in acute appendicitis compared to Gram-positive. 10,11 Garcia-Martin found that the culture-positive rate was higher in CAA than in UAA, identifying a higher frequency of gram-positive cocci and anaerobic bacteria with different isolates and susceptibilities. 12 Parthiban et al. 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. 13 Lafi et al. found that the most common bacteria found in a bacteriological study of AA were *E. coli*, *B. fragilis* and *Staphylococcus aureus*. 14 For Chen et al., the most commonly involved bacteria were *E. coli*, followed by *K. 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 to the clinical and biological evolution of these patients was necessary when this pathogen was found. 15 In our study the most frequently identified bacterias 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 not an association between the group of bacterial isolation or the specific isolated bacteria and the presentation of a CAA.

Operative/ nonoperative treatment

In recent years, multiples studies revealed that in case of UAA, the antibiotics only can a reliable treatment. APPAC 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. 16, 17 In case of simple appendicitis, the inferiority of non-operative therapy versus 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. 18

There is a real concern on 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. 19 The presence of multidrug-resistant bacteria can contribute to additional morbidity. 20 In one study from 2010, 25% of children with gangrenous or ruptured appendicitis were insensitive to the antimicrobial regime used. 21 *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, post-operative infectious complications might increase. 22

Empiric /prophylactic antibiotherapy

The initial empirical therapy should target all of the microorganisms likely to be involved, on the basis of the suspected risk factors. 23 Empiric antibiotic treatment is effective in most patients, early (blood or intra-abdominal) culturing is very useful to guide antibiotic modification in abdominal infection. 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 multi-drug resistance bacterial strains. 24

Andersen et al. 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 post-operatively. 25 Kimbrell et al. 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. 26 Obinwa et al. 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 post-operative infectious complications. The study recommended a triple antibiotic combination of amoxicillin-clavulanate, gentamicin and metronidazole as an empiric treatment in CAA. 22

Duration of antibiotherapy

The prospective multi-centre study “MUSTANG” on the duration of antibiotherapy found that there was no evidence of an association between the duration of 24 h versus 96 h for CAA and an increased rate of SSI. 27 A study from Netherlands (2014) concluded that 3 days of antibiotics led to a similar rate of infectious complications 5 days or more. 30, 31 van den Boom et al. in a meta-analysis revealed that there were no differences in the incidence of intraabdominal abscess with ≤ 3 vs. >3 days of antibiotic treatment, but there was a reduction with > 5 days of treatment. 28 Xu et al. 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. 29 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 optimised in the UAA but might have been optimal for the CAA group.

Conclusion

CAA presented a higher rate of positive cultures with increased identification of Gram negative bacteria. *E. coli*, bacteria from the *Streptococcus 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 a complicated appendicitis.

Declarations

Ethical Approval and Consent to participate:

The study was approved by the Ethical Committee of Saint Pierre University Hospital.

All methods were carried out in accordance with relevant guidelines and regulations.

Informed consent:

Informed consent was obtained from all participants or, if participants are under 16, from a parent and/or legal guardian.

Availability of data and materials:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

No competing interests exist for any of the authors.

Authors' contributions:

Sorin Cimpean: Conceptualization, Methodology, Software.:Alberto Gonzalez Barranquero: Data curation, Writing- Original draft preparation.:Ion Surdeanu: Visualization, Investigation .:Benjamin Cadiere: Writing- Reviewing and Editing.:Guy Bernard Cadiere: Supervision, Validation,

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