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Does microbial resistance profile change in community-based intra-abdominal infections? Evaluation of the culture results of patients with appendicitis

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Most common origin of intra-abdominal infections in children is appendicitis. Microorganisms responsible for community-based and hospital-acquired intra-abdominal infections vary. The aim of this study was to evaluate microbial culture outcomes and antibiotic susceptibilities of these microorganisms in samples obtained intraoperatively from pediatric patients with appendicitis, and to define the infectious microorganisms responsible for the community-based intra-abdominal infections in our region, and their antibiotic susceptibilities. This study included 231 patients between 0 and 16 years of age, operated on due to appendicitis between 2014 and 2017. Appendicular tissues were sampled intraoperatively. Antibiogram was studied in case of reproduction in tissue culture. Forms included information on the age and gender of the patients, intra-abdominal event, bacterial growth in microbial culture and antibiogram, antibiotic switch during follow-up, duration of the treatment, complications and outcomes were recorded. No microbial growth was observed following inoculation of the samples obtained from appendiceal tissue of 24.7% patients, whereas growth was positive in 75.3%. Gram negative bacteria were isolated in 94.3% of the patients, whereas gram positive bacteria was isolated in 5.7%. Polymicrobial growth was observed in 2.2% of the patients. *E. coli* in 79.9%, *P. aeruginosa* in 5.2%, *Enterobacter cloacae* in 3.4%, *Coagulase-negative staphylococci* in 3.4%, *Klebsiella* spp. in 1.7%, *Citrobacter* spp. in 1.7%, *Enterococcus* spp. in 1.7%, *Comamonas testosteroni* in 1.2% of patients produced. ESBL positivity is present in 51 (36.7%) of 139 *E. coli* strains reproducing in appendiceal tissue culture. ESBL was positivity detected in one of the reproduced 3 *Klebsiella* spp. strains. In *E. coli*, ciprofloxacin resistance as 20.86%, ampicillin-sulbactam resistance as 83.45%, and co-trimoxazole resistance as 41% were found. Our study clearly demonstrates that the resistance profile varies in community-based intra-abdominal infections. Empirical treatment protocols should be revised in especially the patients admitted with septic presentation and where the source control is not possible.

Key words: intra-abdominal infections, antibiotic susceptibilities, appendicitis, children.

Most common origin of intra-abdominal infections in children is appendicitis. Microorganisms responsible for community-based and hospital-acquired intra-abdominal infections vary. Complicated appendicitis, gastrointestinal system perforations, intra-abdominal abscess and diverticula are the most common causes of community-based infections. In those infections, site of gastrointestinal perforation (stomach, duodenum, jejunum, ileum, appendix or colon) determines the infectious flora. *E. coli*, *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp. and occasionally *P. aeruginosa* are responsible for the infections of duodenum and farther jejunum; whereas anaerobic bacteria such as *B. fragilis*, *Clostridium* spp., or *Fusobacterium* spp. may be included in farther ileum as well.[1,2]

With the introduction of wide spectrum systemic intravenous antibiotics usage in the treatment of appendicitis, rates of mortality and morbidity have reduced dramatically[3]. Additionally, it has been demonstrated that non-surgical medical treatment of non-complicated appendicitis was possible in children.[4,5] Extended-spectrum β-lactamases (ESBLs) are being used at increasing rates worldwide, and therefore surveillance studies have gained importance.[6] Resistance of bacteria should be monitored for the definition of empirical antibiotic therapy protocols.

The aim of this study was to evaluate microbial culture outcomes and antibiotic susceptibilities of these microorganisms in samples obtained intraoperatively from pediatric patients with appendicitis, and to define the infectious microorganisms responsible for the community-based intra-abdominal infections in our region, and their antibiotic susceptibilities. Our study is important to contribute to a local consensus on empirical antibiotic regimen in community-based intra-abdominal infections in both patients operated due to appendicitis and community-based intra-abdominal infections.

Material and Methods

Study population and design

The study protocol was approved by the Ethics Committee of our institute (date: 22/03/2016, report number: 06/24) and written or verbal consent was obtained from the parents of all participants. This study was planned as a prospective study. This study included 231 patients between 0 and 16 years of age, operated in the Pediatric Surgery Department of Fırat University due to appendicitis between September 2014 and September 2017. Children with previous abdominal operations, antibiotic usage within the recent 3 months and those with a history of hospitalization were excluded. Follow-up forms were created for the patients. Forms included information on the age and gender of the patients, intra-abdominal event (abscess formation, acute appendicitis, suppurative appendicitis, perforated appendicitis), bacterial growth in microbial culture and antibiogram, antibiotic switch during follow-up, duration of the treatment, complications and outcomes were recorded. Appendicular tissues were sampled intraoperatively and sent to laboratory. Samples were inoculated into blood agar and Eosin-Metylene Blue (EMB) agar plaques, incubated at 37°C for 72 hours. Examinations were performed at 24th, 48th and 72nd hours.

Bacterial identification and antimicrobial susceptibility testing

All of the samples were analyzed in the clinical laboratory of Firat University Hospital (Elazig, Turkey). For bacterial identification, the isolates were analyzed by automated VITEC-2 compact system (Biome´rieux, France). To assess antimicrobial susceptibility, the minimum inhibitory concentrations (MICs) of ceftriaxone, ceftazidime (CAZ), cefotaxime (CTX), ertapenem, imipenem, ampicillin-sulbactam, piperacillin-tazobactam, amikacin, ciprofloxacin, and co-trimoxazole were determined using dehydrated MicroScan broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[7] Susceptibility interpretations were based on the CLSI M100-S23 clinical breakpoints.[8] We used the ATCC 25922 strain of *E. coli*, the ATCC 27853 strain of *P. aeruginosa*, and the ATCC 700603 strain of *Klebsiella* spp. as reference strains in each set of MIC tests for quality control. We determined the susceptibilities of *coagulase-negative staphylococci* (CNS), isolates to vancomycin, linezolid, oxacillin, and daptomycine by E-test method. We determined the susceptibilities of *Enterococcus* spp., and *Streptococcus* spp. isolates to vancomycin, linezolid, and daptomycine by E-test method and we determined the MIC of the strains.

Detection of extended-spectrum β-lactamase

Phenotypic identification of ESBL-producing strains of *E. coli*, *Klebsiella* spp. was performed according to the CLSI recommendations[8]. We defined ESBL production as a decrease in the MICs for CTX and CAZ of >8-fold when tested in combination with clavulanic acid relative to the MICs for CTX and CAZ in the absence of clavulanic acid.

Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v22 (SPSS Inc.,

Table I. Microorganisms Reproducing Apendix Culture and Their Distribution.

Bacteria	n (%)
E. coli	139 (79.9)
P. aeruginosa	9 (5.2)
Enterobacter cloacae	6 (3.4)
Coagulase-negative staphylococci	6 (3.4)
Klebsiella spp.	3 (1.7)
Citrobacter spp.	3 (1.7)
Enterococcus spp.	3 (1.7)
Comamonas testosteroni	2 (1.2)
Hafnia alvei	1 (0.6)
Streptococcus spp.	1 (0.6)
Edwardsiella ictaluri	1 (0.6)

Chicago, IL, USA). Parametric tests (Chi-square and Fisher's exact chi-square tests) were applied to data of normal distribution and non-parametric tests (T-test, Mann-Whitney and Wilcoxon tests) were applied to data of questionably normal distribution. Continuous data were presented as mean±standard deviation. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

Results

A total of 231 patients had undertaken appendectomy during the study period. Mean age was 10.74±3.50 years. Among the patients, 152 (65.8%) were male and 79 (34.2%) were female. Diagnosis was acute appendicitis in 44 patients (19%), suppurative appendicitis in 117 (50.6%) and perforated appendicitis in 70 (30.4%). No microbial growth was observed following inoculation of the samples obtained from appendiceal tissue of 57 (24.7%) patients, whereas growth was positive in 174 (75.3%). Gram negative bacteria were isolated in 164 (94.3%) of the patients, whereas gram positive bacteria was isolated in 10 (5.7%). Polymicrobial growth was observed in 5 patients (2.2%), and the dominant colony was included in the form. *Klebsiella pneumoniae* was the microbial agent in 2 patients and it was *Klebsiella oxytoca* in 1 patient. The enterococci detected in the bacterial cultures included 1 case with *E. avium*, 1 case with *E. raffinosus*, and 1 case with *E. faecalis*. Distribution of the microorganism growth in bacterial cultures among the patients with bacterial growth, are presented in Table I.

ESBL positivity is present in 51 (36.7%) of 139 *E. coli* strains reproducing in appendiceal tissue culture. It was observed in one of the 3 *Klebsiella* spp. strains (33.3%) as well. When the ESBL positivity rates in *E.coli* were examined by years, the tendency to increase was observed with 32.5%, 39.3% and 37.2% respectively. However, there was no statistically significant difference ($p>0.05$). Susceptibility of different gram negative bacteria to various antibiotic agents are demonstrated in Table II.

Methicillin resistance was detected in 2 of CNS (33.3%). In 1 of these strains, linezolid and daptomycin resistance were observed as well. In 1 of the 3 enterococci grown (33.3%) (*E. raffinosus*), vancomycin and linezolid resistance were observed. The streptococcus strain detected in 1 patient was found to be susceptible to penicillin and other antimicrobial agents.

No complication was observed in 215 (93.1%) patients, superficial surgical site infection was observed in 10 (4.3%), intra-abdominal abscess was observed in 1 (0.4%), intra-abdominal abscess+ileus were observed in 1 (0.4%), ileus was observed in 2 (0.9%) and superficial surgical site infection+ileus were observed in 2 (0.9%) (Table III). Complications were observed in 13 of 70 patients with perforated appendicitis in, 2 of 117 patients with suppurative appendicitis and 1 of 44 patients with acute appendicitis.

Cefazolin+metronidazole were used for surgical prophylaxis in acute and suppurative appendicitis. When the source control was sufficient in perforated appendicitis, treatment of cefotaxim+metronidazole was started for 4-7 days. Antibiotic revision was made in 3 patients due to the complications observed under initial antibiotic therapy. Among those, *E. coli* growth was detected in all of them and ESBL positivity was detected in two of them. Intra-abdominal abscess was observed in both of these patients. Two cases belonged to the perforated appendicitis group. One patient had a concomitant ileus. Antibiotic revision was made in one patient with superficial wound site infection as well. Patients with ESBL positive *E. coli* growth were compared to those with

Table II. Susceptibility of Gram Negative Bacteria to Various Antibiotic Agents.

	Ertapenem	Imipenem	Ampicillin - sulbactam	Ceftriaxone	Ciprofloxacin	Amikacin	Piperacillin -tazobactam	Ceftazidime	Co-trimoxazole
E. coli (n: 88)	84 (95.5)	87 (98.9)	23 (26.1)	79 (89.8)	77 (87.5)	84 (95.5)	81 (92.0)	82 (93.2)	56 (63.6)
ESBL+*E. coli* (n: 51)	42 (82.4)	50 (98)	-	3 (5.9)	33 (64.7)	38 (74.5)	33 (64.7)	27 (52.9)	25 (49.0)
P. aeruginosa (n: 9)	-	9 (100)	-	-	9 (100)	9 (100)	9 (100)	8 (88.9)	-
Enterobacter cloacae (n: 6)	5 (83.3)	6 (100)	-	3 (50)	5 (83.3)	5 (83.3)	6 (100)	4 (66.7)	3 (50.0)
Comamonas testosteroni (n: 2)	2 (100)	2 (100)	1 (50)	-	2 (100)	2 (100)	2 (100)	1 (50)	2 (100)
Klebsiella spp. (n: 3)	2 (66.7)	2 (66.7)	-	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)
Citrobacter spp. (n: 3)	3 (100)	3 (100)	1 (33.3)	-	3 (100)	3 (100)	3 (100)	3 (100)	2 (66.7)

Data is presented as n (%)

E. coli growth according to the complications, and a statistically non-significant difference was observed ($p>0.05$).

Median duration of hospital stay was 7 days (min: 3, max: 16) in patients with perforated appendicitis. Median durations of hospital stay in suppurative and acute appendicitis were 3 (min: 2, max: 7) and 3 (min: 2, max: 5) days, respectively. Statistically significant difference was observed between the durations of hospital stay in patients with perforated appendicitis and acute or suppurative appendicitis ($p<0.05$). All patients were discharged with wellness.

Discussion

Studies on the agents of intra-abdominal infections among pediatric patients are few in number. An important part of the intra-abdominal infections in pediatric patients comprises appendicitis[1]. Medical treatment is a valuable alternative to surgical intervention in patients with non-complicated appendicitis. However, both community-based microbial agents of intra-abdominal infections should clearly be known and each hospital should have information about microorganism resistance profile on its own region for the selection of antibiotic therapy. This is enabled via local epidemiological studies. A guideline was published by Surgical Infection Society (SIS) on intra-abdominal infections in 1992. This guideline was revised in 2002 and was reprinted by a co-working of SIS and Infectious Diseases Society of America (IDSA) in 2009, which included recent studies. According to this guideline, routine aerobic or anaerobic microbial culture is optional in low-risk patients with community-based infections. However, this may be helpful in the detection of epidemiological alterations in the resistance patterns of the pathogens in community-based intra-abdominal infections (evidence level: B-II). In case of an important resistance to a local, widely used antibiotic for a common infectious agent in the community (such as *E. coli*) (10-20% of the isolates are resistant), microbial culture and susceptibility tests should routinely be performed in patients with perforated appendicitis or other complicated intra-abdominal infections (B-III). Again according to this guideline, ampicillin-sulbactam is not recommended in community-based *E. coli* infections due to high resistance (B-II). Quinolone-resistant *E. coli* is wide and quinolones should not be used unless a 90% or higher sensitivity is not demonstrated in hospital surveillances (A-II). In children, intra-

Table III. Distribution of Complications According to the Pathology of Appendicitis.

Complications	Total	Pathology of Appendicitis		
		Acute	Suppurative	Perforated
No complication	215 (93.1)	43 (97.7)	115 (98.2)	57 (81.5)
Wound site infection	10 (4.3)	1 (2.3)	1 (0.9)	8 (11.4)
Intra-abdominal abscess	1 (0.4)	-	-	1 (1.4)
Ileus	2 (0.9)		1 (0.9)	1 (1.4)
Intra-abdominal abscess+ileus	1 (0.4)	-	-	1 (1.4)
Wound site infection+ileus	2 (0.9)	-	-	2 (2.9)
Total	231 (100)	44 (100)	117 (100)	70 (100)

Data is presented as n (%)

abdominal sampling for microbial culture is recommended during drainage, in order to select a highly tolerated and safe agent with a limited spectrum during gradual reduction of the oral therapy (B-II). In cases with no response to the treatment and continued infection, anaerobic microbial culturing is recommended (C-III)[9]. Recommendations in the recent guidelines published by both Surgical Infection Society and World Emergency Surgery Society are parallel to those in the guidelines of IDSA[10,11]. No study has so far been conducted in our region on the causes of community-based intra-abdominal infections and antibiotic susceptibility of these agents other than our previous study on 44 pediatric patients.[12]

In our study, *E. coli* growth was observed in 139 (79.9%) patients and ESBL positivity was detected in 51 (36.7). In a previous study conducted in the Marmara region of our country, 33 pediatric patients with perforated appendicitis were evaluated and *E. coli* growth was observed in 26 (87%) patients, and ESBL positivity was detected in 8 (31%).[13] Resistance rates among gram negative bacteria are increasing each day. The recent, as well as largest study conducted on the subject was SMART, which included data from 44 hospitals of 16 countries from Europe. A total of 1259 strains of infectious intra-abdominal agents were included in the study in the pediatric patient group.[14] Among community-based infections, *E. coli* was detected at a rate of 75.4% which was similar to our study. However, in community-based strains of *E. coli,* ESBL positivity was observed to be 5.5%. The reason for that may be the collection of the data for the strains in SMART study between 2011 and 2014, and their increasing resistance within years. However, in community-based infections, this rapid increase in the resistance may be improper antibiotic therapy as well. In another study conducted in Pacific Island, intra-abdominal microbial cultures of 144 cases with perforated appendicitis including 47 pediatric patients, were evaluated[15]. Microbial growth was detected in 74% of the samples, which was similar to the rate in our study. In 81% of the cases with microbial growth, *E. coli* was the isolated agent. ESBL positivity was not investigated. In a multi-center study conducted in China, gram negative bacteria isolated from patients with intra-abdominal infection, and their susceptibilities were investigated between 2012 and 2013.[16] Community-based intra-abdominal infection cause of ESBL positive *E.coli* was detected at a rate of 55.6%. The rate of community-based ESBL positive *E. coli* among cases with intra-abdominal infection-related appendicitis was 46%. In a study investigating the microbial culture results of pediatric patients with appendicitis in Ireland, *E. coli* was found to be the infectious agent at a rate of 81% and no ESBL positivity was detected[17]. However, data of the study belonged to years 1995-2008. Many risk factors have been defined for ESBL positivity in pediatric patients. These include low birth weight, stay in pediatric or newborn intensive care unit, histories of invasive intervention, delayed intubation time or antibiotic therapy.[18-22] However, our patients were community-based and those with any type of antibiotic therapy 3 months prior to the treatment were excluded. High ESBL positive *E. coli* rates observed in our study, despite this fact may, be due to the frequent usage of antimicrobial agents in the childhood and to the recent nature of our data. It has been emphasized in a study that ESBL positive *enterobactericia* could be transmitted from the child to other individuals in the house in cases it has been carried more than 4 years, and in turn it might contribute to an ESBL positivity spread in the community.[23] As mentioned, significant differences are observed between centers, which demonstrates the importance of interregional variability.

Another important aspect of our study is the low number of cases necessitating antibiotic revision despite high ESBL positivity rates. Importance of source control is obvious at that point.[10] In patients with community-based intra-abdominal infection and low risk, and when satisfactory clinical outcome is observed via source control and initial therapy, afterwards no antibiotic revision is needed even in the presence of the pathogens not suspected and treated at the beginning (B-III). In our study, antibiotic revision was needed in only 3 patients since all were operated due to appendicitis with previous source control and good clinical response. However, high rates of resistance should be considered and empirical therapy should be started in patients with acute appendicitis, who are planned to be given medical treatment only. When a 10-20% or higher resistance is observed to the isolates of a frequent intra-abdominal pathogen, this antibiotic agent should not be used. Ampicilin-sulbactam and ciprofloxacin usage is not recommended. According to our data, although fluoroquinolone usage is common among pediatric patients in our country, resistance of *E. coli* to ciprofloxacin was found to be 20.86%. Resistance to ampicillin-sulbactam was found to be 83.45%. Likewise, co-trimoxazole should not be used due to high resistance.

Ertapenem, which is known to be effective in community-based ESBL positive microorganisms, is an important alternative in intra-abdominal infections. Its potential to be used alone in intra-abdominal infections is an important advantage. No efficacy on *P. aeruginosa* may be counted as a disadvantage, however, this microorganism is not common among community-based infections.[10] Ertapenem was considered to be safe and effective in the empirical treatment of community-based intra-abdominal infections in patients especially not considered for surgery and who admit with a septic presentation.

As a conclusion, our study clearly demonstrates that the resistance profile varies in community-based intra-abdominal infections. Empirical treatment protocols should be revised in especially the patients admitted with septic presentation and where the source control is not possible. The fact that our study is the only central data center and the small number of complication rates, restricts the evaluation of effect of resistance on clinical outcomes. Further studies with larger sample sizes are needed on the subject.

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