Evaluation of active microorganisms and antibiotic susceptibility in community-acquired intraabdominal infections in children

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BACKGROUND: *In this study, we aimed to investigate the results of intraoperative culture and antibiogram in children who underwent surgery with the diagnosis of community-acquired intraabdominal infections (CA-IAIs) to determine the causative microorganisms and antibiotic susceptibility of the bacterial agents.*
METHODS: *Antibiotic susceptibility of isolated bacteria was investigated with disk diffusion method according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) suggestions directly from the patients' intraabdominal peritoneal fluid or tissues, aged <18 years.*
RESULTS: *Bacterial growth was found in 17 (34%) of the blood cultures taken before the operation and 38 (76%) of the intraoperative abdominal cultures. According to the isolated strains; 44 (80%) were Gram-negative and 11 (20%) were Gram-positive, however, the most commonly isolated microorganisms were Escherichia coli (52.72%), Klebsiella pneumonia (14.54%), and Enterobacter cloacae (5.45%); extended-spectrum beta-lactamase (ESBL) resistance was detected in 12 of the Escherichia coli strains (41.38%) and the rates of ampicillin-sulbactam, ceftriaxone, and cefotaxime resistance were 43.2%, 40.9%, and 6.8%, respectively.*
CONCLUSION: *In our study, ESBL-resistant gram-negative microorganisms in CA-IAIs presented as primary agents to be considered. Ampicillin-sulbactam, ceftriaxone and cefotaxime should not be preferred in the monotherapy of complicated CA-IAIs due to their high resistance rates, but they can be combined with aminoglycosides. Quinolones can be included in the treatment because of their low resistance rates. It is considered that routine intraoperative culture and evaluation of antibiotic susceptibility in complicated CA-IAIs will provide an insight into the outcomes of empirical treatment.*

KEY WORDS: Antimicrobial resistance, Intraabdominal infection, Surgery

Introduction

Community-acquired intraabdominal infections (CA-IAIs) are infections of intraabdominal organs and cavities that occur in patients with no history of hospitalization or surgery within the past three months [1]. In recent years, Gram-negative enteric bacteria, which are the most common causative agents of CA-IAIs, exhibit increased antibiotic resistance [2-4]. Resistant microorganisms and antibiotic susceptibilities should be defined to determine empirical antimicrobial therapy [5]; however, there are very few published studies in the literature due to surgeons neglecting to attend to the need to obtain intraoperative cultures [6,7].
In this study, we aimed to investigate the results of intraoperative culture and antibiogram in children who underwent surgery with the diagnosis of CA-IAIs to determine the causative microorganisms and antibiotic susceptibility of the bacterial agents.

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Materials and Methods

The patients under the ages of 18 years underwent surgery with the diagnosis of CA-IAIs in clinical Pediatric Surgery between March 2017- June 2018 were enrolled to the study. Patients having undergone abdominal surgery or been hospitalized and those followed up for more than 48 hours with antibiotic treatment within the past three months were excluded from the study. The demographic characteristics, complaints, physical examination results, laboratory results, radiological imaging methods, type of operation, microorganisms, and antibiotic susceptibility of the patients were recorded in the patient follow-up forms. Preoperative blood culture and intraoperatively intraabdominal peritoneal fluid or tissue were taken from patients. Antibiotic susceptibility of isolated bacteria was investigated with disk diffusion method according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) suggestions direction.

All of the patient data were recorded in *SPSS 20.0* for Windows for analysis. Features of the case groups were compared using the *Chi-square* test for two variables. Approval for the study was obtained from the Clinical Research Ethics Committee of Afyon Kocatepe University, Turkey (2017/2-23).

Results

A total of 50 patients (female, n=19; 38%, and male, n=31; 62%) with a mean age of 10.96 ± 4.67 years were included in the study. In our study, the most frequently reported complaints were abdominal pain (72%), nausea and vomiting (24%). Physical examination of the patients most frequently revealed right lower quadrant pain (n:35, 70%,), tenderness (n:34, 68%), and rebound pain (n:31, 62%).

According to the laboratory parameters of the patients at the time of presentation, 39 (78%) patients had leukocytosis, 11 (22%) had normal white blood cell counts, and 31 (62%) had high C-reactive protein (CRP) levels with the mean value being calculated as 11.02 ± 20.96 g/L. As the imaging modality used for diagnosis, ultrasonography (USG) was performed in 36 patients (72%) and computed tomography (CT) in 12 patients (24%).

The surgical diagnoses was acute appendicitis in 20 (11.8%), perforated appendicitis in 15 (30%), gangrenous appendicitis in 8 (16%), invagination in 2 (4%), perforated meckel diverticulum in 1 (2%), 1 (2%) intestinal obstruction, 1 (2%) intraabdominal abscess, 1 (2%) necrotizing enterocolitis (NEC), and 1 (2%) ovarian cyst rupture. The types of operation was appendectomy 40 (80%), laparotomy 6 (12%) and laparoscopy 4 (8%).

In the study, 17 (34%) of the blood cultures obtained before the operation were found to be positive and 33

TABLE I - *The distribution of microorganisms isolated from blood cultures.*

Microorganisms	Number (n)	(%)
Escherichia coli	5	29.42
ESBL (+) Escherichia coli	3	17.65
Klebsiella pneumoniae	3	17.65
Klebsiella oxytoca	1	5.88
Enterobacter cloacae	2	11.76
Pseudomonas aeruginosa	1	5.88
Staphylococcus hominis	1	5.88
Staphylococcus epidermidis	1	5.88
Total	17	100

TABLE II - *The distribution of microorganisms isolated from abdominal cultures.*

Microorganisms	Number (n)	(%)
Escherichia coli	12	31.58
ESBL (+) Escherichia coli	9	23.68
Klebsiella pneumoniae	2	5.27
ESBL (+) Klebsiella pneumoniae	1	2.63
Klebsiella oxytoca	1	2.63
Pseudomonas aeruginosa	1	2.63
Enterobacter cloacae	1	2.63
Morganella morganii	2	5.27
Staphylococcus hominis	2	5.26
MR Staphylococcus hominis	1	2.63
Staphylococcus epidermidis	2	5.26
MR Staphylococcus epidermidis	1	2.63
Enterokok faecium	2	5.27
Staphylococcus hemoliticus	1	2.63
Total	38	100

MR: Methicillin resistance; ESBL: Extended spectrum beta lactamase

TABLE III - *The distribution of microorganisms isolated.*

	Number (n)	(%)
Gram-negative microorganisms		
Escherichia coli	17	30.91
ESBL (+) Escherichia coli	12	21.82
Klebsiella pneumoniae	5	9.09
ESBL (+) Klebsiella pneumoniae	1	1.81
Klebsiella oxytoca	2	3.64
Enterobacter cloacae	1	1.81
ESBL (+) Enterobacter cloacae	2	3.64
Pseudomonas aeruginosa	2	3.64
Morganella morganii	2	3.64
Total	44	80
Gram-positive microorganisms		
Staphylococcus hominis	3	5.45
MR Staphylococcus hominis	1	1.82
Staphylococcus epidermidis	3	5.45
MR Staphylococcus epidermidis	1	1.82
Enterokok faecium	2	3.64
Staphylococcus hemoliticus	1	1.82
Total	11	20
Total	55	100

MR: Methicillin resistance; ESBL: Extended spectrum beta lactamase

TABLE IV - *The antibiotic susceptibility rates of Gram-negative microorganisms isolated as CA-IAI agents.*

Antibiotic	Number (n)	(%)
Ampicillin-sulbactam	25	56.8
Ceftriaxone	26	59.1
Cefotaxime	26	59.1
Cefepime,	28	63.6
Piperacillin-tazobactam,	32	72.7
Ertapenem,	42	100
İmipenem,	44	100
Ciprofloxacin	41	93.2
Gentamicin	38	88.4
Amikacin	42	97.7
Trimetoprim- sulfomethoxazole	28	65.1

(66%) were negative for bacterial growth. The distribution of microorganisms isolated from blood cultures is shown in Table I. Furthermore, of the intraoperative abdominal cultures, 38 (76%) were positive and 12 (24%) were negative for bacterial growth. Table II presents the distribution of microorganisms isolated from abdominal cultures.

According to the results, bacterial positivity was present in a total of 55 cultures. According to the isolated strains, 44 (80%) were Gram-negative and 11 (20%) were Gram-positive. The most commonly isolated microorganisms were *Escherichia coli (E. coli)* in 52.7%, followed by *Klebsiella pneumonia* in 14.5%, and *Enterobacter cloacae* in 5.5%. Extended-spectrum beta-lactamases ESBL positivity was detected in 12 of *E. coli* strains (41.4%), two of *E. cloacae* strains (66.6%), and one of *K. pneumonia* strains (16.7%). The distribution of microorganisms is shown in Table III.

Table IV presents the antibiotic susceptibility rates of Gram-negative microorganisms isolated as CA-IAI agents. Antibiotic treatments and prognosis were evaluated in patients with ESBL-positive agent growth. The medicines prescribed were ampicillin-sulbactam and amikacin in five patients (41.7%), ampicillin-sulbactam in three (25%), cefazole in two (16.7%), ampicillin-sulbactam and gentamicin in one patient (8.3%), and cefotaxime in another patient (8.3%).

Complete recovery was observed in seven patients who had been treated with cefazole, cefotaxime or ampicillin-sulbactam alone for acute appendicitis. Complete recovery was observed in three patients who had received combination therapy for perforated appendicitis. However, one patient that had been diagnosed with complicated perforated appendicitis and treated with ampicillin-sulbactam alone developed a surgical site infection. Antibiotic treatments and prognosis of the ESBL-positive patients are shown in Table V.

Discussion

Appendicitis is the most common cause of CA-IAIs that require emergency surgical interventions in the pediatric group [8]. In the current study, appendicitis was the most common surgical diagnosis in patients who had undergone surgery with the preliminary diagnosis of CA-IAIs (86%). Undertaking a careful history and detailed physical examination is important in distinguishing simple diseases from emergencies requiring surgical interventions, especially acute appendicitis. In various studies, the frequency of two or more findings of vomiting, right lower quadrant pain, tenderness and defense was found to be significantly higher in appendicitis [9]. Similarly, in our study, the most common complaints of nausea and vomiting were accompanied by right lower quadrant pain, defense and rebound findings.

Leukocyte count and CRP value can be used for diagnostic purposes in patients suspected of intraabdominal infections and assist physicians in deciding whether to apply surgical or antibiotic treatment to the patient [10,11]. In our study, leukocytosis was detected in the majority of the patients (n = 39, 78%). In various studies, it has been reported that high CRP levels in acute appendicitis assist in the diagnostic process and are mostly increased in perforation cases [12,13]. In our study, the CRP value was high in 31 patients (62%), and the mean CRP

TABLE V - *Antibiotic treatments and prognosis of the ESBL-positive patients*

Diagnosis	Treatment	Microorganism	Prognosis
Acute appendicitis	Sefazol	ESBL (+) E. coli	Complete recovery
Acute appendicitis	Sefazol	ESBL (+) E. coli	Complete recovery
Acute appendicitis	Cefotaxime	ESBL (+) E. coli	Complete recovery
Perforated appendicitis	Ampicillin-sulbactam	ESBL (+) E. coli	İnfection
Perforated appendicitis	Ampicillin-sulbactam+Amikacin	ESBL (+) E. coli	Complete recovery
Perforated appendicitis	Ampicillin-sulbactam +Amikacin	ESBL (+) E. coli	Complete recovery
Perforated appendicitis	Ampicillin-sulbactam +Amikacin	ESBL (+) E. coli	Complete recovery
Acute appendicitis	Ampicillin-sulbactam	ESBL (+) E. coli	Complete recovery
Acute appendicitis	Ampicillin-sulbactam +Gentamicin	ESBL (+) E. coli	Complete recovery
Acute appendicitis	Ampicillin-sulbactam +Amikacin	ESBL (+) E. coli	Complete recovery
Acute appendicitis	Ampicillin-sulbactam	ESBL (+) E. Cloacae	Complete recovery

E. coli: Escherichia coli; E.Cloacae: Enterobacter Cloacae

value was calculated as 11.02 ± 20.96 g/L. A high CRP value was detected in 86.7% of the patients diagnosed with perforated appendicitis.

USG and CT are the most commonly used radiological modalities in the diagnosis of intraabdominal infections [14], with the latter having a higher sensitivity than the former [15]. However, USG has important advantages, such as being portable, easy to apply as a bedside procedure, fast, inexpensive, and radiation-free; therefore, it remains to be the first choice in diagnosis in Turkey [16]. However, being operator-dependent is a major disadvantage of USG. In the current study, 36 patients (72%) were diagnosed by USG and 12 patients (24%) by CT.

Intraabdominal infections are usually caused by Gram-negative bacteria. The bacterial agents that should be primarily considered in patients with CA-IAIs are *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and rarely *Pseudomonas aeruginosa* strains. *E. coli* is the most frequently isolated bacterium in CA-IAIs [17,18].

In a study investigating Gram-negative bacillus susceptibilities in IAIs in Europe, the responsible pathogen was reported to be *E. coli* in 49.3%, *K. pneumonia* in 10.5%, and *Pseudomonas* spp. in 8.6% of the samples [3]. In another study conducted in China, *E. coli* was detected at a rate of 47.3%, *K. pneumonia* at 17.2%, and *Pseudomonas* spp. at 10.1% [4].

Similarly, *E. coli* (n = 29, 52.7%), *K. pneumonia* (n = 6, 10.9%) and *E. cloacae* were the most frequent agents isolated in our study.

The risk factors for community-acquired ESBL-producing bacteria include renal insufficiency, hospitalization and antibiotic use within the last three months, surgical operation, mechanical ventilation, history of hospitalization in the intensive care unit, being male, diabetes mellitus, recurrent urinary tract infection, and urinary catheterization [19,20].

For the patients included in our study, male gender (66.6%) was identified as a risk factor.

Treatment guidelines have been prepared to recommend treatment according to the severity of intraabdominal infections. In this regard, in 2009, the latest guidelines of the American Infectious Diseases Society of America (IDSA) were published. According to the IDSA guidelines, obtaining a culture is not recommended as a routine procedure in patients with CA-IAIs and is left to the discretion of the physician. However, it is emphasized that CA-IAI-associated pathogens can be useful in determining local resistance rates and guiding the treatment of patients. Routine culture and susceptibility studies are recommended in complicated IAI cases if there is significant resistance (10-20%) to a commonly used antimicrobial regimen in a commonly isolated strain (e.g., *E. coli*) [18]. In Turkey, there are not sufficient studies on antibiotic susceptibility in CA-IAIs. This is due to the surgeons in our country lacking awareness about intraoperative sample collection, thinking that it is unnecessary to obtain a culture, as well as technical infrastructure deficiencies and organizational problems. Baykam *et al.* [6] observed that a culture sample was obtained from only 12 (5.1%) of 233 operated patients (56 diagnosed with complicated IAIs) despite preparing a study protocol with surgeons. Six of these materials had bacterial growth, of which half had ceftriaxone resistance.

Antibiotics used in empirical therapy in CA-IAIs should be effective against Gram-negative enteric bacteria. Increasing antibiotic resistance is observed in these microorganisms in many geographic regions. These include ampicillin-sulbactam resistance, which is common throughout the world [3]. According to the IDSA guidelines, ampicillin-sulbactam is not recommended for treatment when the resistance rate is high [18].

In a study evaluating intraoperative culture and antibiogram results in children undergoing appendectomy in Turkey, the rate of ampicillin-sulbactam resistance was found to be 58.7% [7]. In another study, ampicillin-sulbactam susceptibility was reported in 386 (47%) of 823 *E. coli* strains isolated from different samples, including peritoneal fluid [19]. The use of aminoglycosides in combination with ampicillin is recommended to prevent treatment failure in CA-IAIs of mild and moderate severity [20]. In the current study, the rate of ampicillin-sulbactam resistance was 43.2%. In such cases, ampicillin-sulbactam is not a good option in empirical treatment, and it should be combined with aminoglycosides.

Increasing the use of quinolone in pediatrics is currently under consideration. The use of ciprofloxacin has even been approved in children with a complicated urinary tract infection and pyelonephritis [21]. IDSA guidelines state that quinolones should not be used unless there is evidence that quinolone-resistant *E. coli* is common and quinolone sensitivity is 90% according to hospital surveillance [18]. In a study conducted in Taiwan, the sensitivity of *E. coli* to quinolones was determined to be 82-85%, and the use of quinolones in the treatment of CA-IAIs was recommended [22].

In our study, quinolone susceptibility was found to be 93.2% and we consider that this antibiotic should be preferred in empirical treatment.

In recent years, ESBL resistance has been increasing in community-acquired microorganisms. Although ESBL-producing strains show *in vitro* susceptibility to third- and fourth-generation cephalosporins, treatment failure may occur. Therefore, considering ESBL positivity is of great importance in the empirical antibiotic approach [23]. In a study reporting data obtained from Turkey, ESBL production was high in *E. coli* strains isolated from complicated urinary tract infections (43.7%) [24]. In our study, among the Gram-negative microorganisms isolated, 12 of *E. coli* strains (41.4%) had ESBL positivity. In addition, due to this high ESBL positivity rate, we detected 40.9% resistance to third-generation cephalosporins (ceftriaxone and cefotaxime), and thus these antibiotics should not be preferred in empirical treatment.

According to the IDSA guidelines, appropriate source control is essential in the treatment of CA-IAIs. In complicated CA-IAIs with peritoneal involvement, source control is likely to fail; therefore, these cases should also be brought under control through appropriate antimicrobial therapy [18,25]. In our study, when the prognosis of patients with ESBL-positive agent growth was evaluated, complete recovery with source control was observed in patients who had been treated with cefazole, cefotaxime or ampicillin-sulbactam alone for the treatment of acute appendicitis.

This is because the infectious focus was eliminated and microbial contamination was prevented. Complete recovery was also seen in patients with complicated perforated appendicitis; however, those treated with ampicillin-sulbactam alone were found to have surgical site infections due to ESBL positivity. It is crucial in the empirical antibiotic approach to consider ESBL positivity in complex CA-IAIs for which full source control is not possible through surgical treatment.

In conclusion, in complicated CA-IAIs, routine intraoperative cultures should be obtained for empirical antimicrobial treatment and antibiotic susceptibility should be evaluated. The epidemiological data gathered in our study are very valuable as they determine the factor and resistance rates in CA-IAIs in our region and represent the data of Turkey. According to our results, resistant Gram-negative microorganisms are the factors that should be first considered in CA-IAIs. Ampicillin-sulbactam, ceftriaxone and cefotaxime should not be preferred in the monotherapy of complicated CA-IAIs, but they can be used in combination with aminoglycosides. Quinolones should be included in the treatment due to their low resistance rates. However, larger-scale studies with more patients are needed in this area.

Riassunto

INTRODUZIONE: In questo studio abbiamo analizzato i risultati delle colture intraoperatorie con antibiogramma in bambini operati con diagnosi di infezione intra-addominale acquisita da comunità (CA-IAIs) per determinare gli agenti microbici responsabili e la relativa sensibilità ad antibiotici.

METODO: Sono stati inclusi nello studio pazienti di età <18 anni, presentati all'ambulatorio di chirurgia pediatrica nel periodo compreso tra marzo 2017 e marzo 2018, e sottoposti ad intervento chirurgico con la diagnosi di CB-IAI. Sangue prelevato preoperatoriamente e da 1 a 10 ml di liquido peritoneale sono stati inoculati su piastre di agar sangue e agar EMB. Le sensibilità agli antibiotici dei microrganismi isolati sono state valutate in conformità alle raccomandazioni EUCAST (European Committee on Antimicrobial Susceptibility Testing)con il metodo della diffusione dei dischi.

RISULTATI: Dei 50 pazienti sottoposti all'operazione, 31 (62%) erano ragazzi e 19 (38%) ragazze. L'età media era di 10,96±4,67 anni. Lo sviluppo batterico è stato rilevato in 17 (34%) delle colture di sangue e in 38 (76%) delle colture addominali intraoperatorie. Dei ceppi isolati, 44 (80%) erano Gram-negativi e 11 (20%) erano Gram-positivi. I microrganismi più frequentemente isolati erano E.coli 52,72%, K.pneumonia 14,54%, Enterobatteri 5,45%. La resistenza alla beta-lattamasi a spettro esteso (ESBL) è stata rilevata in 12 (41,38%) dei ceppi di E.coli. Il tasso di resistenza all'ampicillina-sulbactam era del 43,2%, il tasso di resistenza al ceftriaxone e al cefotaxime era del 40,9%, mentre il tasso di resistenza alla ciprofloxacina era del 6,8%.

CONCLUSIONE: Nel nostro studio, i microrganismi gram-negativi resistenti alle GSBL nella CB-IAI sono i fattori che dovrebbero essere considerati per primi. Nel trattamento delle CB-IAI complicate, ampicillina-sulbactam e ceftriaxone e cefotaxime non dovrebbero essere preferiti in monoterapia a causa dei loro alti tassi di resistenza, ma possono essere associati con aminoglicosidi. I chinoloni possono essere inclusi nel trattamento perché i loro tassi di resistenza sono bassi. Come si può vedere, la coltura intraoperatoria di routine e la valutazione della suscettibilità antibiotica nelle CB-IAI complicate rappresentano informazioni utili per l'adozione di un trattamento empirico.

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