# THE IMPORTANCE OF PERITONEAL CULTURES IN THE TREATMENT OF CHILDREN WITH RUPTURED APPENDICITIS

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**Abstract**

Introduction: The management of ruptured appendicitis in children is of great importance and still controversial. Acute appendicitis is one of the most common conditions treated by pediatric surgeons. Around 30% of the acute appendicitis treated in childhood involve a ruptured appendix. Objective: The purpose of this study was to establish if identification of both aerobic and anaerobic bacteria and their susceptibility to antibiotics, leads to better outcomes when treating perforated appendicitis. Material and Methods: This study was conducted at the Pediatric Surgery Department of Emergency Children's Hospital, Cluj Napoca, Romania. A total of 330 patients (aged 0 to 18 years) admitted between January 2007 and December 2014 were included in the study. Data collected from review of medical charts included age, gender, demographic data, and duration of hospitalization, surgical and medical treatment, initial presentation and investigations. The total number of patients was divided in two groups. Group A (153 patients) had no peritoneal fluid samples prelevated and Group B (177 patients)) in which peritoneal fluid samples were sent to the lab for determination of both aerobic and anaerobic bacteria. Results: Postoperative infective complications of group B were found in 20/177(11, 29%) patients. From a total of 24 complications we found 3 intraabdominal collections, 6 deep wound infections and 15 superficial wound infections. A significant decrease in number of complications can be noticed in group B which can result from better surgical technique but also from better antibiotic coverage. Discussion: The combination of cefuroxime/ gentamicin/ metronidazole can be appropriate until definitive culture results are done but in more severe cases of perforated appendicitis we recommend the use of a single broad-spectrum agent. This may help reduce the incidence of postoperative infectious complications associated with amoxicillin resistant E. coli in appendicitis related peritonitis. Conclusion: Based on the study results, a triple antibiotic combination of cefuroxime, gentamicin and metronidazole is reasonable empiric basis for treatment of perforated appendicitis in selected cases but when dealing with cases that have late diagnosis, are clinically and biologically impaired or show no improvement, the best option is a broad spectrum single agent, like ertapenem or piperacillin/tazobactam.

**Keywords:** antibiotic resistance, perforated appendicitis, peritonitis

## Introduction

The management of ruptured appendicitis in children is of great importance and still controversial. Acute appendicitis is one of the most common conditions treated by pediatric surgeons. Around 30% of the acute appendicitis treated in childhood involve a ruptured appendix.

The classic description of appendicitis includes the onset of periumbilical pain followed by nausea, then migration of pain to the right lower quadrant (RLQ) and finally, vomiting and fever. However, this progression of symptoms is less common in children than adults [1]. Absence of classic symptoms leads to a higher rate of appendicular perforation in children. Pathogenesis of appendicitis is still uncertain, its significance in septic complications of appendicitis is well established [2, 3]. The exact cause remains unclear, but luminal obstruction, diet, and familial factors have been suggested, and the etiology may be multifactorial in some cases [4, 5]. Some bacteria and parasites were found in histopathological evaluations of the appendices [6]. Inflammation of the appendix ranges from minor, simple acute inflammation to necrosis and perforation, but in some appendectomies patients it could be histologically classified as normal appendices.

Peritoneal cavity swab during surgical treatment of perforated appendicitis is not a routine procedure in all pediatric surgery units. Cultures from inflamed appendices usually revealed that the most common organisms are a mixture of Escherichia coli (85%), enterococci (30%), non-hemolytic streptococci, anaerobic streptococci together with clostridium welchii (30%) and bacteroides [7, 8].

Microbiological investigation of intra-abdominal infections in children has been limited [9, 10, and 11]. Historically, empirical antibiotic therapy with clindamycin or metronidazole, gentamicin, and ampicillin has been used [12, 13], but the bacteriology and antibiotic susceptibility of specific pathogens involved in peritonitis requires epidemiological monitoring.

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This comparative study analyzed the outcome in treating perforated appendicitis in two groups of patients, the first (group A), without taking peritoneal cultures and the second (group B) with peritoneal fluid samples to establish the etiology and antimicrobial susceptibility of isolates (over a 8-year period)

**Objectives**

The purpose of this study was to establish if identification of both aerobic and anaerobic bacteria and their susceptibility to antibiotics, leads to better outcomes when treating perforated appendicitis.

**Materials and Methods**

This study was conducted at the Pediatric Surgery Department of Emergency Children's Hospital, Cluj Napoca, Romania. A total of 330 patients (aged 0 to 18 years) admitted between January 2007 and December 2014 were included in the study. Data collected from review of medical charts included age, gender, demographic data, and duration of hospitalization, surgical and medical treatment, initial presentation and investigations. The children diagnosed with acute appendicitis, gangrenous appendicitis and appendicular mass were excluded. The diagnosis of appendicular perforation was considered by clinical evaluation, blood tests, and ultrasonography and was confirmed at laparotomy. The study included 141 (42.72%) females and 189(57.27%) males. (Fig. 1)

The surgical approach to control the source of infection was appendectomy and irrigation in 107(32, 42%) patients and appendectomy, irrigation and drainage in 223(67.57%) patients. (Fig.2).117(35.45%) cases were considered generalized peritonitis and 213(64.54%) were considered localized peritonitis (Fig.3).

The age of the children included in the study ranged from 3 days to 18 years (median age was 9).The median hospital stay was 7 days (the minimum hospital stay was 3 days and the maximum 26 days).

The total number of patients was divided in two groups. Group A (153 patients) had no peritoneal fluid samples prelevated and Group B (177 patients)) in which peritoneal fluid samples were sent to the lab for determination of both aerobic and anaerobic bacteria.

Peritoneal fluid specimens in the group B were sent directly to the laboratory or kept at 4 °C until the next day if they were collected after hours. For aerobic culture, the fluid specimens were inoculated onto Columbia blood agar and MacConkey agar without salt. The plates were incubated at 37 °C in air atmosphere and were examined 24 and 48 h after incubation. For anaerobic culture, the fluid specimens were plated onto Columbia blood agar, neomycin blood agar, and nalidixic acid agar and each plated agar further impregnated with metronidazole discs so as to guide sensitivity analysis. All plates were incubated in an anaerobic gas jar with O2 levels<1 % and CO2 levels between 9 and 13 % and examined for growth at 24, 48, 96 and 120 h after incubation. All aerobic isolates were fully identified. Specimens with anaerobic isolates having more than one anaerobe identified were classified as mixed anaerobe. Sensitivity analysis was conducted with the aid of a rapid and automated VITEC-2 compact system (Biomerieux, France). [14]

Data recorded included: demographic data, microbiological data (peritoneal fluid specimens and susceptibility to antibiotics), antibiotic management (initial therapy, changes in therapy, and duration of treatment) and outcomes. Infectious complications were defined as those occurring within 30 days of surgery and included intra-abdominal abscess and wound infection. The intra-abdominal abscesses were confirmed by imaging and microbiological samples. Wound infection was confirmed clinically and by microbiological samples.

Adequate empirical antibiotic treatment was defined as resolution of disease with initial antibiotic treatment after primary surgery. Empirical antibiotic treatment was inadequate if the infection was no resolving and additional antibiotics were commenced postoperatively based on intraperitoneal fluid culture results [14].

**Results**

The group A, which was studied retrospectively, included 68 females(44,44%) and 85males(55,55%).The surgical treatment was appendectomy and irrigation in 42 patients(27,45%) and appendectomy , irrigation and drainage in 111 patients(72,54%). 51(33,33%) patients had generalized peritonitis and 102(66,66%) had localized peritonitis.

There was no consensus regarding the antibiotic treatment for perforated appendicitis, as a result there is a lot of variation in the medical approach. The most used antibiotics depending on the surgeon options and the intraoperative findings, were the associations of ampicillin/gentamicin and metronidazole, cefuroxime/ gentamicin and metronidazole and piperacillin-tazobactam as a single agent (Fig.4).

The age in group A was from 2 months to 18 years old with a median of 9, 5.The hospital stay ranged from 4 days to 26 days with a median of 8 days. Postoperative infective complications were found in 37/153(24.18%) patients. There were 49 infective complications (15 intra-abdominal collections, 13 deep wound infections and 21 superficial wound infection) Fig.5. The complications occurred more frequent in patients treated with ampicillin, gentamicin, metronidazole association.13 (8.49%) patients required change in antimicrobial therapy before clinical improvement and prolonged duration of hospital stay. Treatment failure was considered to be caused by inadequate antibiotic treatment or source control.

The patients in group B were studied prospectively whit the purpose of using the best suited antibiotics and avoiding the abuse of medication, but also getting the best antibiotic coverage depending on the peritoneal fluid bacteriology. This group included 73 females (41.24%) and 104 males (58.75%). Appendectomy and irrigation was done in 75(42.37%) patients while appendectomy, irrigation and drainage was performed in 102 patients (57.62%).66 (37.28%) patients had generalized peritonitis and 111(62.71%) had localized peritonitis.

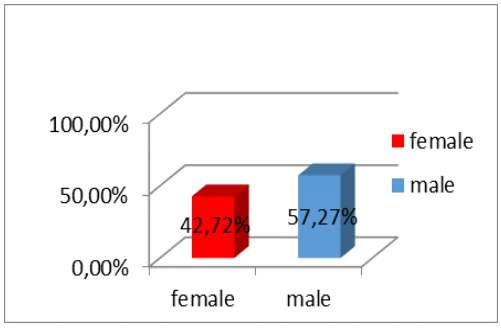


**Fig. 1.** Sex ratio

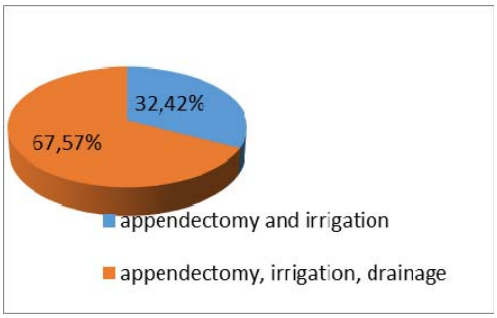


**Fig. 2.** Surgical approach

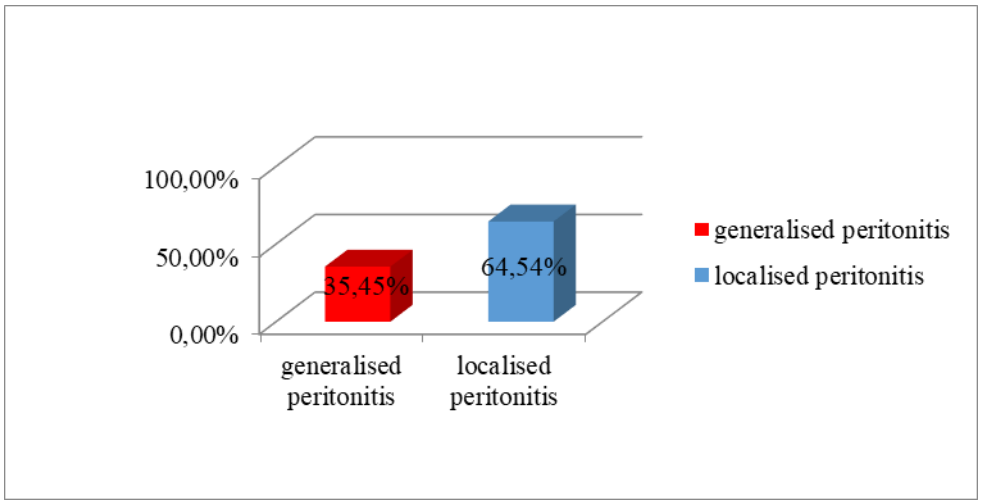


**Fig. 3.** Percentage of localised vs. generalised peritonitis

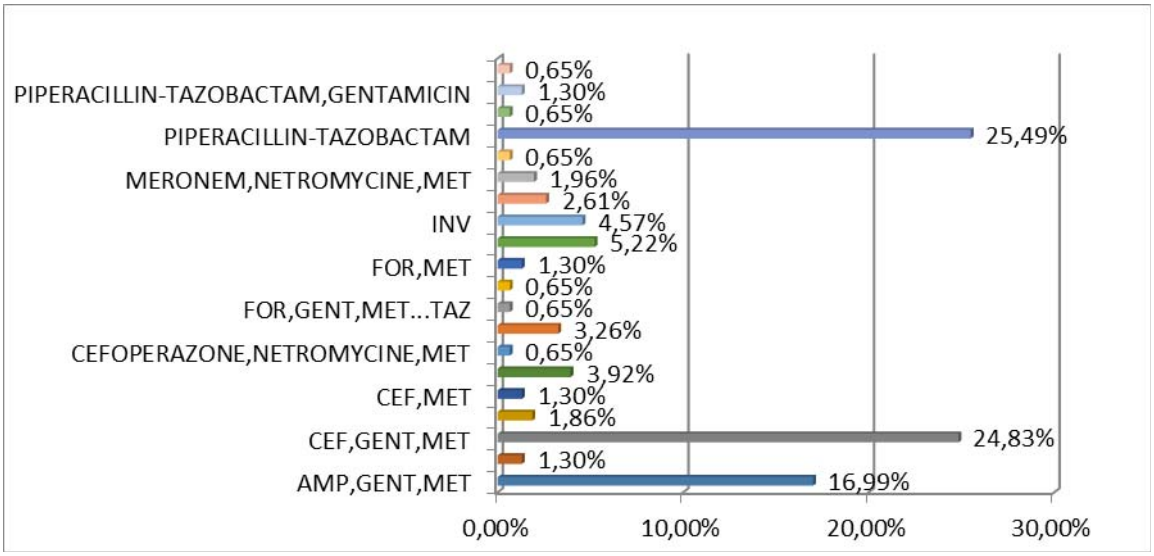


**Fig.4.** Antibiotic treatment for perforated appendicitis, retrospective group

We can easily observe that the sex ratio remained closed as values, but drainage was less used as surgical approach in group B despite the increase in generalized peritonitis proportion, which is statistically important (two tailed Z-test , p=0,0047).

The age of the patients ranged from 6 months to 18 years with a median of 10.The median hospital stay was 6(3 to 17 days).The antibiotic treatment was decided depending on biological status, paraclinical findings and intraoperative aspect (Fig. 5).

Postoperative infective complications were found in 20/177(11.29%) patients. From a total of 24 complications we found 3 intraabdominal collections, 6 deep wound infections and 15 superficial wound infections. A significant decrease in number of complications can be noticed in group B which can result from better surgical technique but also from better antibiotic coverage.

A total of 177 specimens were obtained from 177 children operated. From 361 isolates, 252 were aerobes and 109 were anaerobes. Anaerobes were less isolated probably because of technical difficulties. Single isolates were identified in 73/177patients (41.24%) and multiple isolate were identified in 104 patients (58.75%).The predominant aerobic bacteria was Escherichia coli and was found in 135/177(76.27%).101(57.06%) E coli isolates were resistant to ampicillin and 14(7.90%) of isolates were resistant to amocillin-clavulanate. Pseudomonas aeruginosa was found in 25/177 patients (14.12%), followed by Streptococcus, Klebsiella and Staphylococcus.The most encountered anaerobes were Bacteroides spp. followed by Peptostreptococcus and Clostridium perfringens (Table 1). In 13 out of 20 patients with no clinical improvement the antibiotic treatment was switched from cefuroxime/ gentamicin/ metronidazole to piperacillin/ tazobactam or ertapenem, after receiving the lab results, which led to prolonged hospital stay.

Antibiotic susceptibility pattern for aerobic and anaerobic bacteria which were isolated from peritoneal fluid specimens is presented in table 2.

**Discussion**

In our study the most encountered aerobic bacteria was E. coli while Bacteroides was the most frequent anaerobe, similar to previous reports [9, 15, 16, 17, 18]. Despite the increased number of generalized peritonitis in group B and the decreased percentage of children in which peritoneal drainage was used, the results were better regarding postoperative infectious complications. (24,18% in group A vs. 11,29%in group B).We assumed that this is a consequence of changing the standard treatment by eliminating the ampicillin and using more piperacillin/tazobactam and ertapenem, especially in children with delayed diagnosis and altered biological status. Better surgical technique (a more careful inspection and cleansing of peritoneal cavity) may also contribute to better results.

Isolation of E. coli resistant to ampicillin and amoxicillin–clavulanate may be associated with post-operative peritonitis [16].Appropriate initial antimicrobial therapy may predict successful treatment of peritonitis [19].The presence of resistant bacteroides and the isolation of P. aeruginosa in peritoneal specimens may be associated with post-appendectomy surgical infections in the absence of appropriate primary antibiotics [20, 21]. Although enterococci are frequently isolated as part of a polymicrobial intra-abdominal infection, their role as pathogens and the need for antibiotic coverage specifically toward this organism remains unclear in a review of several trials [22].

When looking at table 2 we found it justified to reduce the antibiotic regimens and to lean towards single regimen broad-spectrum antibiotic when treating perforated appendicitis in children. According to the Surgical Infection Society, monotherapy with broad-spectrum agents in perforated appendicitis is equally effective, possibly even more cost-effective. In addition, a retrospective study demonstrated that single broad-spectrum antibiotic in the treatment of PA used with increasing frequency might offer improvements in terms of length of stay, pharmacy charges and hospital charges[23].This is supported by the 13 children that improved only after changing the antimicrobial therapy from cefuroxime/ gentamicin/ metronidazole to ertapenem or piperacillin/tazobactam.

Medical studies illustrated that single-agent therapy with Carbapenems (Imipenem, Ertapenem) or penicillin plus a beta lactamase inhibitor (Ticarcillin-Clavulanic acid) were at least as effective as combination therapies [24, 25, 26]. These drugs have single or double daily dose administration schedule and are generally better tolerated by children. The median length of hospital stay was 8 days in group A and 6 days in group B which also suggests that the treatment was more efficient in group B. Routine use of peritoneal culture has been described as redundant [27], cost ineffective [28], and without any clinical advantage [29] or value [30].It has also been noted that culture results do not result in significant changes in antimicrobial management when empiric broad-spectrum antibiotics are utilized [31]. However, routine use of routine cultures may be useful epidemiologically, as it could allow early recognition of changing susceptibility patterns among intra-abdominal pathogens. This could potentially ensure use of the most appropriate empiric antimicrobial regimen, not only for those children with healthcare-associated intra-abdominal infections, but potentially even for those with community-acquired intraabdominal infections [7].

Krobot et al. [32], in a multicenter study of 162 patients with perforated appendicitis, found that appropriateness of initial parenteral antibiotic therapy was a predictor of clinical success and length of stay. Similarly, they demonstrated a high risk of postoperative infections in patients with inadequate empirical treatment.

Knowing the microbial and antibiotic resistance profile is critical in an attempt to provide the best empirical antibiotic treatment for secondary peritonitis arising from appendicitis in children [16]. There is no single empirical antibiotic known to reduce post-appendectomy infectious complications in patients with complicated appendicitis [9, 13, 32, 33].

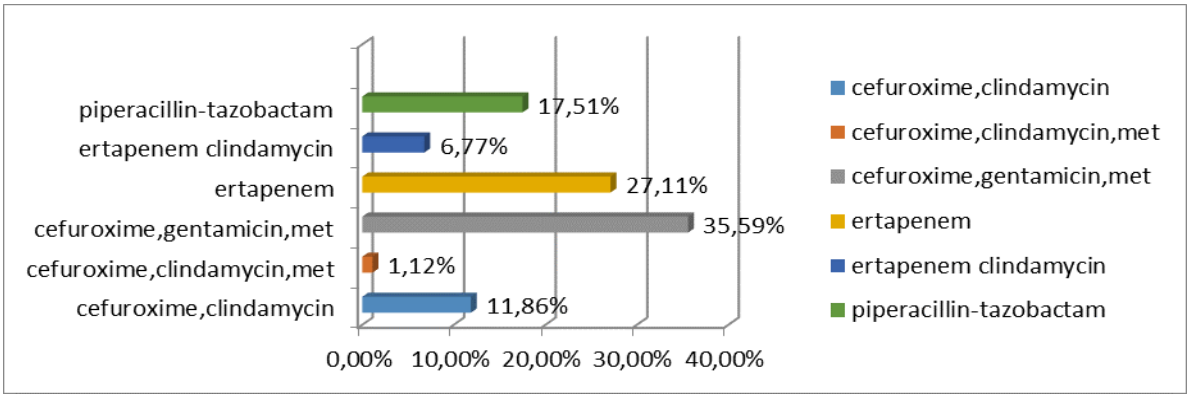


**Fig.5.** Antibiotic treatment for perforated appendicitis, prospective group

| **Bacterial species** | Total(361) |
|---|---|
| **Anaerobes** | |
| *Bacteroides spp.* | 90 |
| *Fusobacterium spp.* | 2 |
| *Clostridium perfringens* | 6 |
| *Peptococcus spp.* | 3 |
| *Peptostreptococcus spp.* | 8 |
| Total | 109 |
| **Aerobes** | |
| *Escherichia coli* | 135 |
| *Klebsiella pneumoniae* | 12 |
| *Enterobacter* | 8 |
| *Proteus spp.* | 2 |
| *Pseudomonas spp.* | 25 |
| *Streptococcus spp.* | 60 |
| *Staphylococcus spp.* | 10 |
| *Total* | 252 |

**Table 1.** Bacterial spectrum

| **Antibiotics** | Susceptible (%) | Resistance (%) |
|---|---|---|
| **Aerobic isolates** | | |
| *Ampicilin* | 19% | 81% |
| *Amocillin-clavulanate* | 46% | 54% |
| *Piperacillin-tazobactam* | 95% | 5% |
| *Gentamicin* | 65% | 35% |
| *Amikacin* | 84% | 16% |
| *Cefuroxime* | 85% | 15% |
| *Ceftriaxone* | 85% | 15% |
| *Ertapenem* | 100% | Zero |
| *Clindamicyn* | 90% | 10% |
| *Vancomycin* | 90% | 10% |
| **Anaerobic isolates** | | |
| *Carbenicillin* | 90% | 10% |
| *Cefoxitin* | 60% | 40% |
| *Cefuroxime* | 65% | 35% |
| *Clindamycin* | 70% | 30% |
| *Chloramphenicol* | 100 | Zero |
| *Metronidazole* | 83% | 17% |
| *Tetracycline* | 35% | 65% |

**Table 2. Antibiotic susceptibility pattern**

Despite the changes of antimicrobial therapy and the better results in group B, other factors such as attention to basic infection control strategies, the surgeon's experience and technique, the duration of the procedure, hospital and operating room environment, instrument sterilization techniques, preoperative preparation and management of any underlying medical condition of the patient should also be considered[33].

All the studies that focused on the use of intraperitoneal fluid cultures were open, non-randomized, and retrospective with incompletely matched control groups, non-standardized swab collection techniques, and consequently lacked power to inform surgical practice. They concluded that an appropriately powered randomized, blinded, prospective, controlled clinical trial is needed to test for absolute efficacy in the use of peritoneal cultures in patient man- agreement.

The combination of cefuroxime/ gentamicin/ metronidazole can be appropriate until definitive culture results are done but in more severe cases of perforated appendicitis we recommend the use of a single broad-spectrum agent. This may help reduce the incidence of postoperative infectious complications associated with amoxicillin resistant E. coli in appendicitis related peritonitis.

**Conclusions**

Although, only 13 of the patients had changes in the antimicrobial regimens after peritoneal cultures results, taking peritoneal fluid samples for microbiological tests proves to be of great importance. Perforation of the appendix inevitably leads to significant bacterial contamination and morbidity. E.coli and mixed anaerobes are the predominant organisms involved in the resulting peritonitis. No single antimicrobial treatment is effective and antibiotic resistance is common. Inadequate initial empirical antibiotic and amoxicillin–clavulanate resistant E. coli as well as resistant Bacteroides and Pseudomonas may contribute to increased postoperative infectious complications. Based on the study results, a triple antibiotic combination of cefuroxime, gentamicin and metronidazole is reasonable empiric basis for treatment of perforated appendicitis in selected cases but when dealing with cases that have late diagnosis, are clinically and biologically impaired or show no improvement, the best option is a broad spectrum single agent, like ertapenem or piperacillin/tazobactam.

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