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Comparison of conservative and operative treatment of uncomplicated appendicitis in the pediatric population

Компарација конзервативног и оперативног третмана акутног некомпликованог апендицитиса у педијатријској популацији

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Компарација конзервативног и оперативног третмана акутног некомпликованог апендицитиса у педијатријској популацији

SUMMARY

Introduction/Objective Studies about possibilities of conservative, i.e. non-operative management of acute uncomplicated appendicitis in adult and pediatric population have been published lately, considering benefits of preserving appendix and potential complications related to appendectomy.

Methods In this retrospective study medical data of 76 patients treated at the Institute for Child and Youth Health Care of Vojvodina in Novi Sad for acute uncomplicated appendicitis in 2015 and 2016 have been analysed, comparing length of stay, antibiotic therapy use, complications occurement, as well as the financial burden depending of the type of therapy applied.

Results During this period, 76 patients (55 operated and 21 treated conservatively) were treated for acute uncomplicated appendicitis. Conservatively treated children spent statistically significantly shorter period of time at the hospital compared to the operated ones (4.24 *vs.* 5.76 days; $p < 0.001$). Early surgical complications occurred in 10.91% operated and 9.52% non-operated children, which wasn't statistically significant difference ($p = 0.863$). The total cost of hospital stay was significantly lower in those who underwent non-operative management (10,340 RSD *vs.* 54,281 RSD; $p = 0$). The difference was significant even when analyzing costs related to rehospitalization and operative treatment of children initially treated conservatively ($p < 0.001$).

Conclusion Non-operative i.e. conservative treatment of acute uncomplicated appendicitis in the pediatric population is safe and effective compared to the operative one, and it is not associated with more frequent occurrence of early surgical complications. Total costs for the non-operative treatment are significantly lower, even considering costs related to re-hospitalization of children initially treated conservatively.

Keywords: acute uncomplicated appendicitis; conservative treatment; antibiotics; children

САЖЕТАК

Увод/Циљ У последње време објављене су студије о могућностима конзервативног тј. неоперативног лечења акутног некомпликованог апендицитиса код одраслих и деце, анализирајући бенефите презервирања апендикса и потенцијалне компликације везане за апендектомију.

Методе У овој ретроспективној студији анализирани су подаци из историја болести 76 пацијената лечених на Институту за здравствену заштиту деце и омладине Војводине у Новом Саду због акутног некомпликованог апендицитиса током 2015. и 2016. године, анализирајући дужину хоспитализације, примену антибиотске терапије, учесталост јављања раних хируршких компликација, као и трошкове лечења у зависности од врсте терапијског приступа.

Резултати Током наведеног периода укупно је лечено 76 пацијената (55 оперисаних и 21 конзервативно лечен) због некомпликованог акутног апендицитиса. Конзервативно лечена деца су краће боравила у болници (4,24 у поређењу са 5,76 дана; $p < 0.001$). Ране хируршке компликације су уочене код 10,91% оперисане и 9,52% неоперисане деце, што није статистички значајна разлика ($p = 0,863$). Трошкови хоспиталног лечења неоперисане деце били су значајно нижи (10 340 у поређењу са 54 281 динара; $p < 0.001$). Разлика у цени била је значајна чак и узевши у обзир трошкове настале услед поновне хоспитализације и оперативног лечења деце која су иницијално конзервативно лечена ($p < 0.001$).

Закључак Неоперативно тј. конзервативно лечење акутног некомпликованог апендицитиса у педијатријској популацији је безбедно и ефикасно у поређењу са оперативном лечењем и није праћено учесталијом појавом компликација. Трошкови неоперативног лечења у поређењу са оперативним знатно су нижи, чак узевши у обзир и поновне хоспитализације иницијално конзервативно лечене деце.

Кључне речи: акутни некомпликовани апендицитис; конзервативни третман; антибиотици; деца

INTRODUCTION

Acute appendicitis is the most common intra-abdominal condition in children that requires surgical intervention. It is considered to occur in approximately 4–8% of pediatric

population, with the pick incidence in the second decade of life, while it is extremely rare (incidence less than 0.5%) during the first year of life [1–4]. Appendicitis can be classified as complicated (appendicitis with generalized peritonitis or appendicitis abscess) or as an uncomplicated disease [5].

The role of appendix in human body is still a subject of debates. It is believed that appendix is an important part of the immune system as a "safe-house" for beneficial microbiota, and therefore is important for recolonizing the bowel after gastrointestinal infections balancing between pathogenic and commensal bacteria [1, 6]. There is also evidence that mesenchymal cells of appendix can be a source for restauration of damages in intestinal tract during a lifetime. It can be used for performing vesicostomy (Mitrofanoff procedure) or appendicostomy for anterograde enemas (Malone procedure), and in recent studies, decellularized appendix was used in a preclinical model for bladder augmentation [7].

Although operative management is a "gold standard" in treating acute appendicitis, conservative (non-operative) management for carefully selected children has been described as efficient alternative [8]. Operative approach can be open (classical) or laparoscopic.

Evidence of conservative treatment of acute appendicitis have been found in a mummy from Byzantine era. However, significant improvement has occurred with implementation of antibiotics in 20th century [9]. This management can be applied if there are no sure indications for surgery, such as the presence of peritonitis or signs of perforation. At first, these studies were conducted only in adults, but recently a larger number of studies include pediatric patients as well [8, 10, 11].

There were debates about need for interval appendectomy after successful conservative management. Recently published studies claim that considering low risk of occult appendiceal neoplasm in young individuals, interval appendectomy is recommended in patients older than 30 and with complicated forms of appendicitis [12]. Considering potential risks related to surgery and/or anesthesia as well as potential benefits of appendix preservation, it is important to analyze safety and efficiency of conservative management of acute uncomplicated appendicitis in children.

METHODS

This study included 76 children treated between January 2015 and December 2016 at the Institute for Child and Youth Health Care of Vojvodina under the diagnosis of acute

uncomplicated appendicitis. Respondents were divided into two groups: conservatively treated and operatively treated. The study was performed as a retrospective descriptive study. In the conservatively treated group were children who had clinical, radiological, and/or laboratory signs of acute appendicitis, but were not operated on during their initial hospitalization according to the clinical monitoring of the patient. Patients with similar signs and symptoms who were selected by the attending surgeon for operative treatment were in the other group.

The diagnosis was made based on the patient's history, physical examination, laboratory tests, and ultrasound findings. The ultrasound examination results were categorized depending on the findings on the appendix and surrounding structures. A negative finding was labeled as U0, unspecified as U1, a positive finding limited to the appendix as U2, while a positive finding on the appendix associated with signs of inflammation of the surrounding adipose tissue and/or the presence of free fluid in the abdomen was labeled as U3.

Children who were operated underwent either laparoscopic or open appendectomy. After hospital admission, per oral intake was paused and parenteral rehydration was initiated. 30–60 minutes preoperatively antibiotic therapy was administered and surgery was performed under general anesthesia. Each removed appendix was sent for histopathological verification. Parenteral antibiotic therapy was continued postoperatively, observing postoperative recovery. Per oral intake was paused as well in patients who were treated conservatively, followed with parenteral rehydration. If no progression of symptoms was observed during the clinical follow-up, conservative treatment was started, only with parenteral antibiotics 6–12 hours after admission. After 24 hours, if there was no progression of symptoms, oral intake was initiated. The duration of parenteral antibiotic therapy depended on the general condition of the patient, tolerance of oral intake as well as laboratory analyzes, i.e. (elevated) leukocyte values. Children from both study groups were discharged after resolution of symptoms, initiation of per oral intake and with established intestinal peristalsis, and antibiotic therapy was continued in oral form.

The consent for conducting the research was obtained by the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina in Novi Sad. Reviewing patient's medical charts, we have analyzed the occurrence of individual signs and symptoms of the disease, the presence of leukocytosis, ultrasound findings, as well duration of hospital stay, antibiotics administration, and possible complications, including appendectomies performed in initially conservatively treated patients. Also, financial burden during the patients' stay in hospital conditions was analyzed.

Recorded data were analyzed using Microsoft Office Excel 2016 and IBM SPSS 26 statistics programs. Data were described using frequencies, percentages, means and standard deviations where appropriate. Between-group differences were analyzed using the independent-samples T-test, Mann Whitney U test, and chi-square test, while correlations between variables were estimated using Pirson's (r) and Spearman's (rho) correlation coefficients. Calculated differences lower than the significance level of 0.05 were considered relevant.

RESULTS

During this period, 76 patients were treated for uncomplicated acute appendicitis at the Institute for Child and Youth Health Care of Vojvodina in Novi Sad. There were 55 children in "operative treatment" group (30 males *vs.* 25 females) and 21 children in "conservative treatment" group (14 males *vs.* 7 females). The mean age of children in "operative treatment" group was 10.88±3.801 while in "conservative treatment" group it was 11.44±3.398 ($p = 0.539$) (Table 1). In the majority of children, symptoms did not last longer than 24 hours (71.43% in the group of conservatively treated and 80% in the group of operated). In the group of conservatively treated there were no patients whose symptoms were present longer than a week, while in the group of operatively treated there were 3.64% of them. This difference wasn't statistically significant ($p = 0.465$) (Figure 1). Groups were similar considering age and gender of the patients, as well as duration of their symptoms.

In majority of patients (95.24% of conservatively treated and 83.64% of operated) leukocyte values (WBC) were above the reference values, although difference between the groups was not statistically significant ($p = 0.232$) (Table 1).

Also, in majority of children (80.95% in the group of conservatively treated and 72.73% in group of operated) ultrasound findings corresponded to U3. 9.52% of patients in "conservative treatment" group, and 7.27% of those who had been operated had a finding that corresponded to U2. 9.52% of children who were treated conservatively and 18.18% of operated children had an indeterminate finding (U1). Due to technical reasons, ultrasound diagnostics was not performed in 1.82% of children from the group of surgically treated. Difference between these groups was not statistically significant ($p = 0.72$) (Figure 2).

Hospital stay was significantly shorter in conservatively treated children (4.24 ± 1.091 *vs.* 5.76 ± 1.018 days; $p < 0.0001$) (Table 1). These children have been given parenteral

antibiotic therapy significantly shorter as well (2.86 ± 1.558 *vs.* 5.29 ± 1,536 days; $p < 0.0001$) (Table 1).

After hospital discharge, except for two of them (9.52%), all the children continued to take oral antibiotics. Conservatively treated patients have been taking oral antibiotics for an average of 6.19 ± 2.4 days, which is significantly longer ($p < 0.0001$) compared to 1.64 ± 2.256 days in the group of operated patients (Table 1).

Analyzing all the children, early surgical complications were slightly more common in the group of operated patients (in 10.91% compared to 9.52% in non-operated), but this difference was not statistically significant ($p = 0.863$). Within 10 months after successful conservative treatment, 6 patients (28.57%) came back due to abdominal pain and/or other symptoms that may have been related to appendicitis, but only in two of them (9.52%) complications really occurred, i.e. recurrence of acute appendicitis (Figure 3). These two children developed recurrent appendicitis 4 months after discharge, which was treated operatively (minimally invasive). One of them was uncomplicated and one complicated appendicitis. Also, one month after the discharge, one child underwent elective appendectomy despite the absence of symptoms, on parents' request. Postoperative complications were wound secretion, epigastric pain, obstruction, minor purulent collection in the ileocecal lodge, and the presence of an intra-abdominal abscess. No cases of ileus have been reported. Correlation analysis did not show an association between complications occurrence and the duration of taking parenteral or oral antibiotics (Table 2).

Hospital costs during conservative and operative treatment were analyzed. Due to the high cost of drugs used due to the underlying disease (coagulation disorders), the costs of treating one operated child had a value that stood out as extreme during the statistical analysis, which excluded this case from subsequent analyzes that included this variable. The costs of hospital treatment for children undergoing conservative treatment were significantly lower (10340.41 ± 3599.43 dinars (RSD) *vs.* 54281.82 ± 6242.02 RSD; $p < 0.0001$). The difference was significant even considering the costs related to a re-hospitalization for surgical treatment of children who were initially conservatively treated ($p < 0.0001$) (Table 3).

DISCUSSION

Suspected acute appendicitis is the most common surgical reason for visiting the emergency department in pediatric population. The clinical picture is primarily characterized

by acute abdominal pain. Distinguishing acute appendicitis from other conditions that manifest with acute abdominal pain can sometimes very difficult in childhood, both due to difficult examination and communication with the patient, and due to the fact that the manifestation of this disease in childhood can be very different. In our study, during the observed period, 76 patients were treated for acute uncomplicated appendicitis. Patients included in the study were approximately 11years old, similar with reported in literature pick incidence during the first two decades of life [1, 2, 13]. Compared to children of preschool age or younger, school-age children are usually able to express their symptoms in an appropriate way, which might be the reason why majority of our patients referred to the emergency department within 24 hours after symptoms onset. Delay in presenting to the emergency department has been shown to harm the success of conservative treatment [14].

One of the most commonly used laboratory parameters when considering the diagnosis of acute appendicitis is the number of leukocytes. Some authors state that the number of neutrophils is a far more sensitive parameter and that neutrophil to lymphocyte ratio can be a useful predictor of complicated appendicitis forms [15, 16]. A significant percentage of our subjects (83.64–95.24%) had leukocyte values greater than 10×10^9/L, which is consistent with the diagnosis. Considering the fact that neutrophils and lymphocytes were not determined in majority of our patients, in this study we did not analyze neutrophil count and lymphocyte to neutrophil ratio, but it remains as an interesting idea for future researches. The number of neutrophils is not routinely determined in most laboratories. In this regard, Kalan et al. Modified the most commonly used Alvarado score by excluding neutrophilia as one of the score parameters, and thus adapted it to the pediatric population [17].

Frequent use of ultrasound imaging in diagnosis of acute appendicitis can be explained due to its high sensitivity and specificity, as well as its harmlessness [18]. Ultrasound sensitivity in the diagnosis of acute uncomplicated appendicitis is estimated at 62–100%, and specificity 79.1–96.8% [18, 19]. Although the specificity of computed tomography (CT) in the diagnosis of acute appendicitis is considered to be 100%, and the sensitivity is about 90%. it is known that the CT method is more harmful due to the high dose of ionizing radiation. In addition, ultrasound diagnostics is far more accessible. In a recently published study by a group of Turkish authors, CT showed greater sensitivity and specificity in relation to ultrasound, although it did not lead to a reduction in the number of negative appendectomies in children [20]. However, optimizing ultrasound diagnostic quality resulted in 67% decreased utilizing of CT imaging in patients with suspected acute appendicitis, and consequently in significant

decreases in hospital costs [21]. In the study of Binkowitz et al. [22], where ultrasound diagnostics was analyzed and compared with operative and histological findings, the categorization of ultrasound findings was performed. Ultrasound findings indicating acute uncomplicated appendicitis with signs of inflammation of the surrounding adipose tissue or presence of free fluid in the abdomen were most commonly observed in this study, in 72.73–80.95% of children. In addition, less than 10% of children had signs limited to the appendix, which indicate its inflammation, such as an increase in the diameter of the appendix above 6 mm, an increase in the thickness of its wall, incompressibility, and the possible presence of an appendicolith. There were also several cases in which the finding could not be determined with certainty, because the appendix was not visualized. In reported literature, in approximately 10% of cases, appendix can't be visualized, and possible reasons for this are abdominal wall tension, obesity, air or fecal superposition, or atypical position of the appendix [19, 23, 24]. There were no patients in this study that underwent CT scans.

Analyzing hospital stay, patients included in our study who were treated with antibiotics only had significantly shorter hospital stay compared to the operated ones (approximately 4 compared to 6 days). This finding is consistent with several reported studies in the pediatric population, but some studies reported shorter hospital stays for conservatively treated compared to the operated adult patients with acute uncomplicated appendicitis, but not for children treated for the same condition. Also, there are studies which find no significant difference between these two therapeutic modalities [14, 25]. The length of hospital stays of patients operated on for acute appendicitis is significantly longer in our study possibly due to the different protocols considering the length of hospital stay after appendectomy in our hospital, which differs from studies published in the world [26, 27, 28].

The majority of published studies describe conservative treatment using parenteral antibiotic therapy for at least 48–72 hours, and until accessing clinical improvement. Therapy is then continued with enteral antibiotics for up to a total of 10 days [28]. A similar protocol was applied to our patients, and it was determined that the operated children received parenteral antibiotics significantly longer compared to the non-operated ones. On the other hand, children treated conservatively were taking enteral antibiotics significantly longer after discharge from the hospital compared to those who underwent appendectomy. In this study, no differences were analyzed concerning the choice or number of antibiotics, which is certainly material for some future research.

In our study, the success rate in the operated children is 100%, because only children whose clinical diagnosis of acute uncomplicated appendicitis was confirmed intraoperatively and histopathologically were selected as patients in the control group. The success rate of the initial conservative treatment was also 100%. Considering that this was a retrospective study, the conservative treatment group selected patients with signs and symptoms of acute appendicitis who were not operated on during their initial hospitalization according to the clinical monitoring of the patient. It is possible that the patient selection process in some future studies could be different. For example, a prospective study with more detailed clinical, laboratory, and radiological assessment could allow us to determine patients that are safe to be treated conservatively. The percentage of complications observed in our patients was approximately 10% in each of the groups. As complications of the operation, we noticed wound secretion, epigastric pain, obstipation, a small purulent collection in the ileocecal region, and the presence of small amount of free intra-abdominal fluid. There were no cases of ileus reported. All postoperative complications were successfully treated conservatively. There were no complications during conservative antibiotic therapy. After initially successful conservative treatment, during a follow-up period of 10 months, six children (28.57%) were brought back to the surgeon suspected for recurrent appendicitis. Four of them did not have recurrent appendicitis, but two children (9.52%) did develop the disease again. One of these children again had uncomplicated appendicitis, while the other one was complicated. Both of these were recorded as complication of conservative treatment, underwent laparoscopic surgery and recovered without further complications. During the follow-up period, another child underwent surgery, also laparoscopically. This child was asymptomatic, but the surgery was performed at the request of the parents one month after the successful conservative treatment. So, after all, success rate of conservative management decreased to 90.48% after 10 months. The percentage of recurrent appendicitis that was surgically treated recorded in this study is slightly below the literature estimate of 16–21% [8, 14].

Complications were not associated with duration of parenteral nor enteral antibiotics. For future research, it could be interesting to analyze its correlation with the type of antibiotic that were used as well as with combinations of antibiotics. It is reported in literature that larger outer appendical diameter and higher values of WBC were risk-factors for recurrent appendicitis after initially successful conservative treatment, as well as that older children have grater chances of developing recurrent disease compared to the younger ones [29]. As previously reported, delay in presenting to the emergency department has been shown to harm

the success of conservative treatment [14]. All these statements could be an inspiration for our future researches.

Considering the financial aspect of treatment, appendectomy is such a frequently performed operation that no matter how insignificant its monetary value may be, it cannot be completely neglected due to the significant burden on the health system. Conservative treatment compared to operative one is reported significantly cheaper by most authors, especially keeping in mind the growing popularity of laparoscopic compared to open (classical) surgery. Certain studies reported significantly lower costs of conservative treatment during initial hospitalization, but due to the high percentage of recurrent appendicitis with consequent appendectomies, this difference was lost during the follow-up period [30]. Our study showed that conservative treatment was significantly cheaper than surgery. The difference was significant even with re-hospitalizations due to appendectomies performed during the follow-up period, including appendectomy performed on a child without recurrent appendicitis.

Based on all the above, we came to the conclusion that conservative treatment of acute uncomplicated appendicitis in the pediatric population is not insufficient compared to surgery. Moreover, in certain aspects it proved to be better. Of course, the research had its limitations. The study was designed as a retrospective, analyzed sample was relatively small, but in terms of demographic characteristics of the respondents quite representative. It predominantly included children in the years when acute appendicitis is the most common, which is good on the one hand, but on the other hand it does not provide enough data on the applicability and safety of this therapeutic approach in children under 5 years of age. Also, the follow-up period was shorter compared to most studies published so far.

For our future researches, it would be useful to construct a prospective study, expand the research in terms of increasing the number of subjects, extending the follow-up period, more detailed analysis of the type and amount of antibiotics used, as well as attempts to determine factors that could predict complications of acute uncomplicated appendicitis in both, operatively and conservatively treated children.

CONCLUSION

Conservative treatment of acute uncomplicated appendicitis in the pediatric population is legitimate and not insufficient compared to surgery. Moreover, in certain aspects such as shorter hospital stays and lower financial burden, it seems to be superior. However, considering

the limitations of our study, for our future research we should consider expanding the sample size and try to determine factors that could predict the safety of both, conservatively and operatively treated children.

Conflict of interest: None declared.

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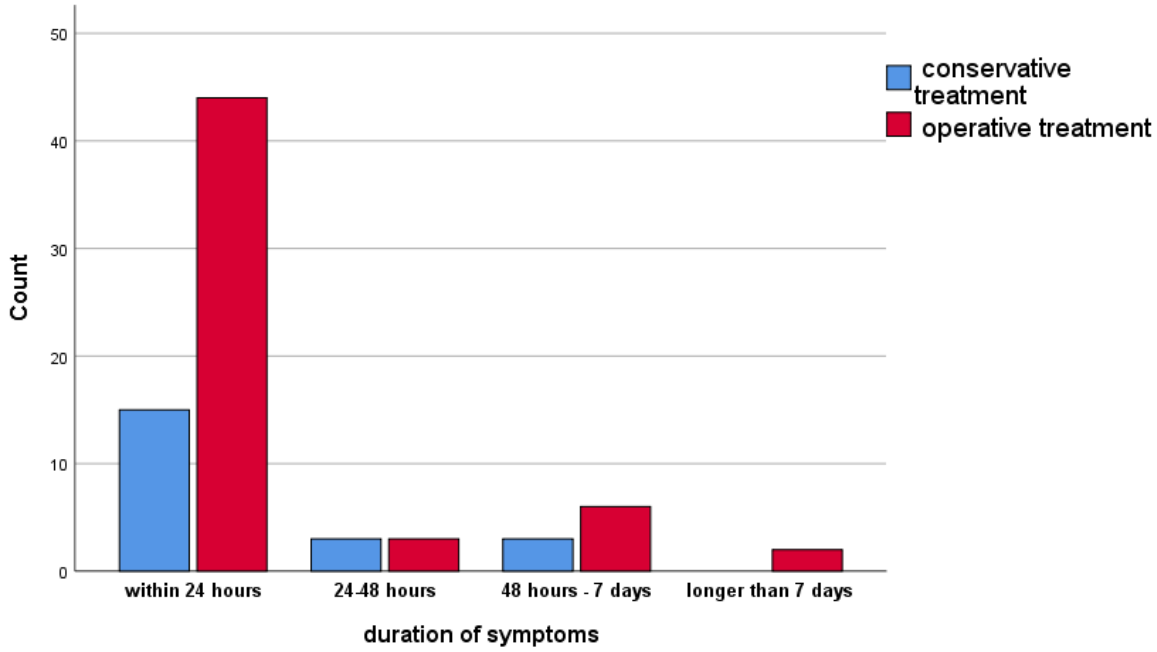

Figure 1. Duration of symptoms before hospitalization

Table 1. Differences in age of patients, laboratory parameters (leukocytes – WBC), hospital stay, and duration of antibiotic therapy

Parameters		Mean	Std. deviation	p
Age (years)	conservative treatment	11.44	3.398	0.539
	operative treatment	10.88	3.801	
WBC (10×10^9/l)	conservative treatment	16.438	3.7048	0.232
	operative treatment	15.005	4.9417	
Hospital stay (days)	conservative treatment	4.24	1.091	**0.0000**
	operative treatment	5.76	1.018	
Parenteral antibiotic therapy (days)	conservative treatment	2.86	1.558	**0.0000**
	operative treatment	5.29	1.536	
Enteral antibiotic therapy (days)	conservative treatment	6.19	2.4	**0.0000**
	operative treatment	1.64	2.256	

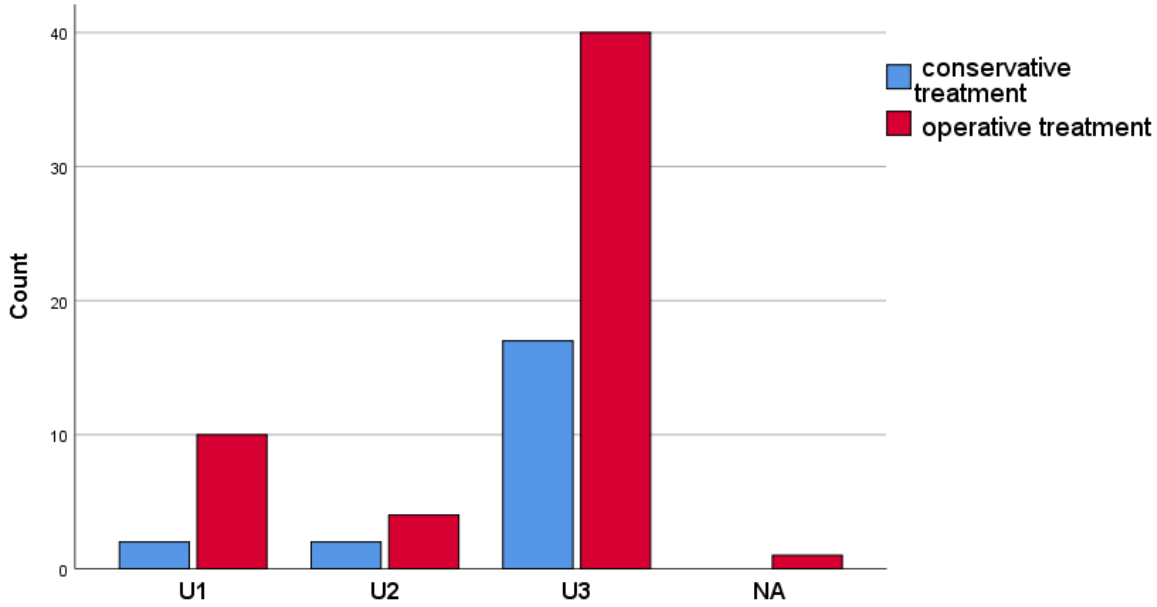

Figure 2. Ultrasound findings;

U1 – unspecified; U2 – a positive finding limited to the appendix; U3 – a positive finding on the appendix associated with signs of inflammation of the surrounding adipose tissue and/or the presence of free fluid in the abdomen; NA – ultrasound not performed

Table 2. Correlations between complications occurrence and duration of antibiotic therapy

Parameter				Parenteral antibiotic therapy	Enteral antibiotic therapy
conservative treatment	Spearman's rho	complications	Correlation coefficient	-0.384	0.274
			Sig. (2-tailed)	0.086	0.230
operative treatment			Correlation coefficient	-0.186	-0.051
			Sig. (2-tailed)	0.173	0.709

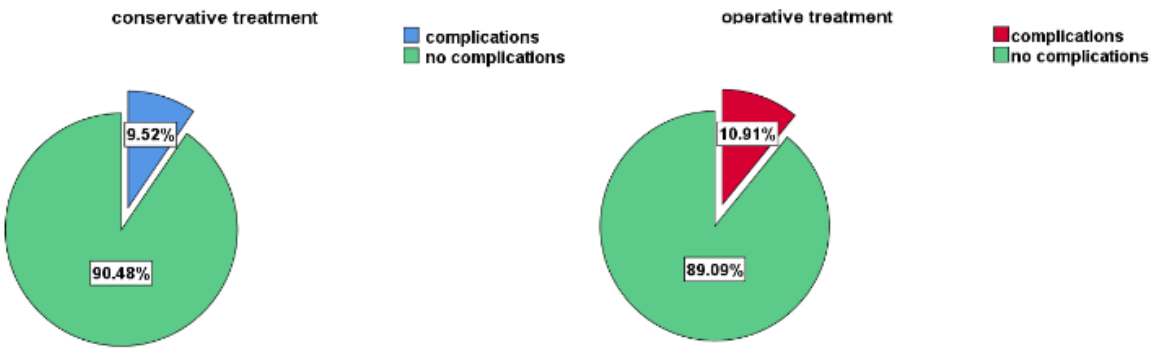

Figure 3. Rate of complications

Table 3. Hospital costs (including re-hospitalization in conservatively treated patients)

Parameter			Mean	Std. Deviation	p
hospital costs (RSD)	1st hospitalization	conservative treatment	10340.41	3599.43	**0.0000**
		operative treatment	54281.82	6242.02	
	2nd hospitalization	conservative treatment	20845.56	28533.75	**0.0000**
		operative treatment	54281.82	6242.02	

