Analysis of a clinical guideline for treatment and early discharge in complicated acute appendicitis

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ABSTRACT

Objective. The objective of this study was to assess the results of a clinical guideline for the treatment and early discharge of patients with complicated acute appendicitis in terms of infectious complications and hospital stay.

Materials and methods. A guideline for appendicitis treatment according to severity was created. Complicated appendicitis cases were treated with ceftriaxone-metronidazole for 48h, with discharge being approved if certain clinical and blood test criteria were met. A retrospective analytical study comparing the incidence of postoperative intra-abdominal abscess (IAA) and surgical site infection (SSI) in patients under 14 years of age to whom the new guideline was applied (Group A) vs. the historical cohort (Group B, treated with gentamicin-metronidazole for 5 days) was carried out. A prospective cohort study to assess which antibiotic therapy (amoxicillin-clavulanic acid or cefuroxime-metronidazole) proved more effective in patients meeting early discharge criteria was also conducted.

Results. 205 patients under 14 years of age were included in Group A, whereas 109 patients were included in Group B. IAA was present in 14.3% of patients from Group A vs. 13.8% from Group B (p= 0.83), while SSI was present in 1.9% of patients from Group A vs. 8.25% from Group B (p= 0.008). Early discharge criteria were met by 62.7% of patients from Group A. Median hospital stay decreased from 6 to 3 days. At discharge, 57% of patients received amoxicillin-clavulanic acid, whereas 43% received cefuroxime-metronidazole, with no differences being found in terms of SSI (p= 0.24) or IAA (p= 0.12).

Conclusions. Early discharge reduces hospital stay without increasing the risk of postoperative infectious complications. Amoxicillin-clavulanic acid is a safe option for at-home oral antibiotic therapy.

KEY WORDS: Appendicitis; Pediatrics; Penicillins, Cephalosporins; Metronidazole; Guideline.

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ANÁLISIS DE UNA GUÍA CLÍNICA PARA EL TRATAMIENTO Y ALTA PRECOZ EN APENDICITIS AGUDA COMPLICADA

RESUMEN

Objetivo. El objetivo de este estudio es evaluar los resultados en términos de complicaciones infecciosas y estancia hospitalaria de la instauración de una guía clínica para el tratamiento y alta precoz en pacientes con apendicitis aguda complicada.

Material y métodos. Se elaboró una guía para el tratamiento de las apendicitis en función de su grado de severidad. Las complicadas se trataron con ceftriaxona-metronidazol durante 48 h, siendo alta si cumplen ciertos criterios clínicos y analíticos. Se realizó un estudio analítico retrospectivo comparando la incidencia de abscesos intraabdominales postquirúrgicos (AIA) e infección del sitio quirúrgico (ISQ) en pacientes menores de 14 años sometidos a la nueva guía (Grupo A), respecto a una cohorte histórica (Grupo B), en la que la pauta de tratamiento era gentamicina-metronidazol 5 días. Además, se realizó un estudio de cohortes prospectivas para evaluar qué antibioterapia (amocilina-clavulánico o cefuroxima-metronidazol) es más eficaz en los pacientes que cumplen criterios de alta precoz.

Resultados. Se incluyeron 205 pacientes menores de 14 años en el Grupo A y 109 en el Grupo B. Presentaron AIA un 14,3% en el grupo A, frente al 13,8% en el B (p= 0,83); e ISQ un 1,9% y un 8,25% respectivamente (p= 0,008). Cumplieron criterios de alta precoz el 62,7% de los pacientes del Grupo A. La mediana de estancia disminuyó a de 6 a 3 días. Al alta, el 57% recibieron amoxicilina-clavulánico y el 43% cefuroxima-metronidazol, sin hallarse diferencias en términos de ISQ (p= 0,24) ni de AIA (p= 0,12).

Conclusiones. El alta precoz disminuye la estancia hospitalaria sin aumentar el riesgo de complicaciones infecciosas postquirúrgicas. La amoxicilina-clavulánico es una opción segura para la antibioterapia oral domiciliaria.

PALABRAS CLAVE: Apendicitis; Pediatría; Penicilinas; Cefalosporinas; Metronidazol; Guía.

INTRODUCTION

The objective of this study was to assess the results in terms of infectious complications and hospital stay of applying a clinical guideline introduced in June 2018 for the treatment of acute appendicitis in our department and

Table 1. Classification and treatment according to acute appendicitis staging.

Type of appendicitis	*Definition*	*Treatment*
Uncomplicated (phlegmonous)	Increased in size and erythematous	30 mg/kg **preoperative single dose of iv A/C**
Complicated (gangrenous, perforated, plastron, peritonitis)	• **Gangrenous**: grey/blackish color • **Perforated**: macroscopic perforation or extraluminal appendicolith • **Plastron** • **Peritonitis**: non- periappendicular fibrinopurulent exudate	Iv **metronidazole + ceftriaxone** for **48 hours** Treatment completed with oral **cefuroxime + metronidazole**

aimed at standardizing its management. The primary goal was to establish whether early discharge in complicated appendicitis is feasible without causing an increase in the incidence of complications.

The secondary objective was to describe which oral antibiotic therapy is the most adequate in patients with complicated appendicitis meeting early discharge criteria.

MATERIALS AND METHODS

A literature review of acute appendicitis treatment in databases such as PubMed, Embase, etc. was carried out. Acute appendicitis types were defined according to the National Surgical Quality Improvement Program (NSQIP)-Pediatric Data Definitions Committee's[1] standardized criteria, as well as those used in similar studies to differentiate uncomplicated vs. complicated appendicitis[2-5]. Depending on the type, treatment corresponding to each stage was established as featured in Table 1. In uncomplicated appendicitis (UCA) cases –those where the appendix is inflamed and erythematous, but has no gangrenous changes (phlegmonous)–, decision was made to administer only the preoperative prophylactic dose with intravenous amoxicillin-clavulanic acid (A/C). Such dose should be established once diagnosis had been achieved and repeated intraoperatively if the time from the first dose to surgery exceeded 4 hours.

In the case of complicated appendicitis (CA) –which includes both gangrenous and perforated appendicitis, plastrons, and peritonitis–, intravenous ceftriaxone and metronidazole were established as the treatment of choice, and they were administered for 48 hours at least. If patients met a series of clinical and blood test criteria, they would be discharged and complete oral treatment at home. Early discharge criteria were the following: no fever (temperature < 37.5ºC) in the last 24 hours, adequate oral tolerance, adequate oral analgesic control, < 12,000 leukocytes, and < 435,000 platelets at the blood test carried out following 48 hours[6]. If these criteria were met, the patient would be discharged and complete treatment at home with oral antibiotic therapy for 7 days. To define the most adequate therapy, decision was made to prospectively randomize the administration of A/C vs. combined cefuroxime and metronidazole.

In the case of patients who did not meet early discharge criteria, if they underwent 5 days of intravenous treatment with ceftriaxone and metronidazole with no fever or symptoms, they would be discharged without additional antibiotic treatment. However, in those presenting with fever or persistent clinical signs following 7 days with this treatment, control ultrasonography should be conducted to rule out the presence of intra-abdominal complications. If IAA was confirmed, intravenous meropenem treatment would be implemented.

In order to assess the results of such measures, the data of two cohorts was collected and compared. Group A was made up of patients under 14 years of age undergoing acute appendicitis surgery from June 2018 to June 2021, and to whom the aforementioned clinical guideline was applied. Even though Group A also consisted of UCA patients so as to describe the impact of the preoperative single prophylactic dose, the comparison of results in order to evaluate the efficacy of the short therapy and early discharge was made between both groups by including CA patients only. Group B was made up of patients under 14 years of age undergoing complicated acute appendicitis surgery from August 2013 to August 2015 –before the clinical guideline was implemented. In Group B, all CA cases were treated with intravenous gentamicin and metronidazole for 5 days at least, and a blood test that should reveal no alterations was carried out prior to discharge. Group B only consisted of CA patients, since it was the control group and the short therapy was also administered to CA patients. Patients undergoing surgery as a result of suspected appendicitis but with a normal appendix following microscopical analysis and no inflammatory signs, patients who could not be categorized as UCA or CA, and patients with unavailable clinical records due to lack of diagnostic coding in the computer system were excluded from the study.

The variables collected are featured in Table 2. With this data, a retrospective analytical study to assess the incidence of postoperative complications (SSI and IAA) was carried out by comparing CA complications and hospital

Table 2. Variables collected in the study.

- Date of birth
- Sex
- Date of surgery
- Type of surgery: open or laparoscopic
- Appendicitis staging: uncomplicated or complicated appendicitis
- Intravenous treatment
- Oral treatment in complicated appendicitis with early discharge in Group A
- Date of discharge
- Complications: surgical site infection, intra-abdominal abscess

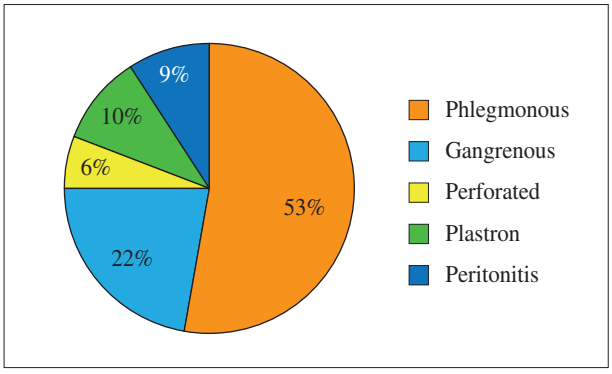

Figure 1. Percentage distribution according to appendicitis type in Group A (post-guideline).

stay between both groups. To describe which oral antibiotic treatment was the most adequate in cases meeting early discharge criteria, a prospective cohort study was conducted. Patients discharged on even days received 50mg/kg/day A/C every 8 hours, whereas patients discharged on odd days received a 15 mg/kg cefuroxime dose every 12 hours as well as a 10 mg/kg metronidazole dose every 8 hours. Oral treatment duration was 7 days from surgery. The incidence of infectious complications (SSI and IAA) in the A/C treated group vs. the cefuroxime-metronidazole treated group was collected. Variables were analyzed using the SPSS 25 statistical software. Statistical significance was established at $p< 0.05$.

This study was approved by the Hospital's Ethics Committee.

RESULTS

437 patients met inclusion criteria for Group A, but once UCA patients had been ruled out, 205 CA patients were used for the comparative study. Group B consisted of 109 patients. Mean age was similar in both groups, with 9.6 and 9.4 years, respectively. The incidence of appendicitis was slightly higher in male (65%) than in female patients (35%).

The distribution according to the type of appendicitis in Group A is featured in Figure 1. When simplifying data based on UCA or CA, UCA was present in 53.1% of cases, and CA was present in 46.9% (n= 205). Within the UCA subgroup, SSI incidence was 2.1% (n= 5), and IAA incidence was 1.3% (n= 3). Regarding CA, SSI was present in 1.9% (n= 4) of cases, and IAA was present in 9.7% (n= 20). Table 3 features a comprehensive description of SSI and IAA incidence according to CA subtype (gangrenous, perforated, plastron, or peritonitis) and whether patients were early discharged ('short therapy') or not ('long therapy'). 89.7% of gangrenous appendicitis cases were eligible for early discharge vs. 15.4% of peritonitis cases. In the case of perforated appendicitis and plastron, discharge occurred in 50% and 48.9% of cases, respectively.

CA data was compared with the incidence of the same parameters in Group B, where SSI incidence in CA was 8.25%, and IAA incidence was 13.8%. A statistically significant difference (p= 0.008) was found in terms of SSI, with SSI incidence being lower in Group A. However, no

Table 3. Results in Group A according to appendicitis subtypes regarding the administration of a short or long therapy in CA, surgical site infection (SSI), and intra-abdominal abscess (IAA).

Type of appendicitis	*Subtype*	*Therapy (%)*	*SSI (n)*	*IAA (n)*
Uncomplicated (UCA)	Phlegmonous (53.1%)	-	5	3
Complicated (CA)	Gangrenous (22.2%)	Short 87 (89.7%)	0	10
		Long 10 (10.3%)	1	0
	Perforated (5.5%)	Short 12 (50%)	0	1
		Long 12 (50%)	0	1
	Plastron (10.3%)	Short 22 (48.9%)	1	3
		Long 23 (51.1%)	0	1
	Peritonitis (8.9%)	Short 6 (15.4%)	0	0
		Long 33 (84.6%)	2	4

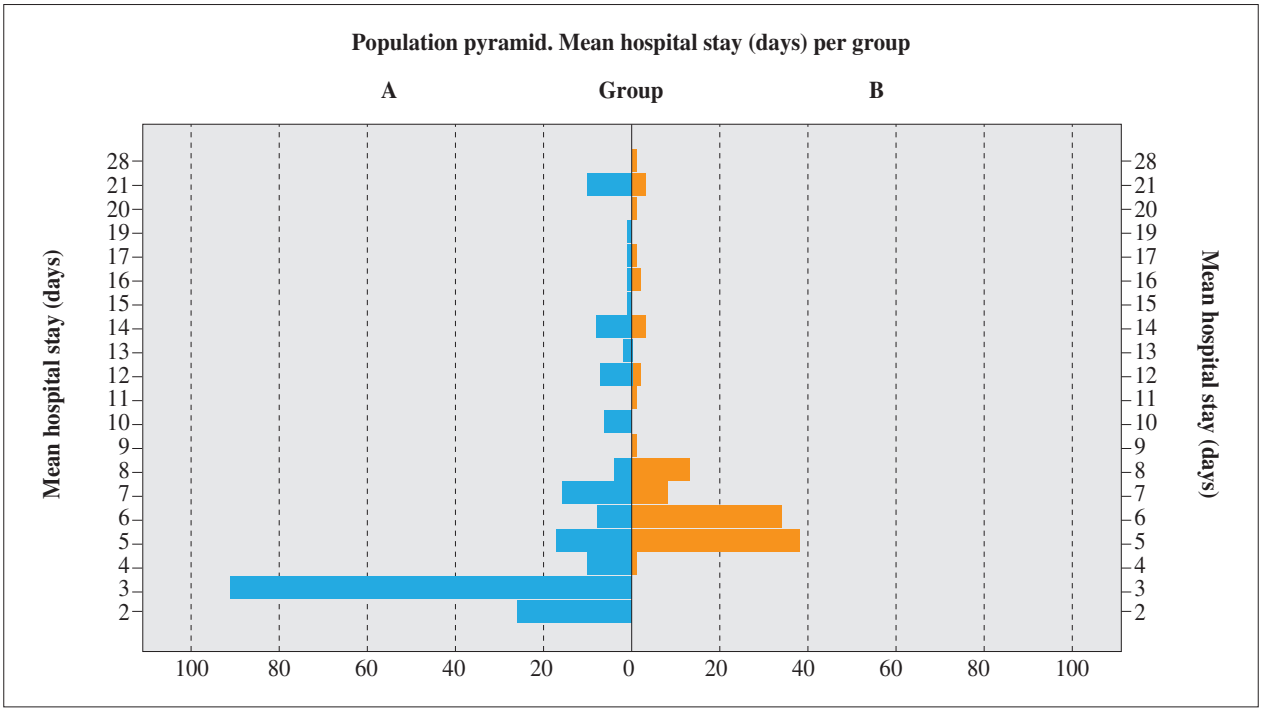

Figure 2. Patient distribution according to mean hospital stay (days) in Group A (*left*) vs. Group B (*right*).

statistically significant differences (p= 0.83) were noted in terms of IAA.

Hospital stay was similar, with 5.7 days for CA in Group A vs. 6 days in Group B. However, median hospital stay was 3 days in Group A vs. 6 days in Group B. Group-based hospital stay distribution is featured in Figure 2. Of the total of CA patients from Group A, 62.7% (n= 127) met early discharge criteria. Mean hospital stay in these patients was 2.4 days.

Regarding the oral antibiotic therapy used in CA patients meeting early discharge criteria, 57% (n= 72) received A/C, whereas 43% (n= 55) received metronidazole-cefuroxime. However, no significant differences in terms of SSI (p= 0.24) or IAA (p= 0.12) were found according to the type of oral antibiotic used. When asked at the postoperative check-up, some patients expressed their subjective dislike towards cefuroxime as a result of its bad taste.

DISCUSSION

Antibiotic therapy for the treatment of appendicitis has evolved in the last decades. In terms of UCA, the administration of a single preoperative or intraoperative dose has been demonstrated to be sufficient[7]. This is also supported by this study, where the incidence of infectious complications was extremely low (SSI: 0.02%; IAA: 0.01%).

Regarding CA, triple intravenous antibiotic therapy –up to two weeks with ampicillin, gentamicin, and clindamycin– used to be administered to reduce the risk of IAA complications[8]. However, treatment has evolved towards intravenous antibiotic therapy simplification and reduction in time. The first changes started with the decrease in treatment duration, as demonstrated by the randomized prospective study carried out by Rice et al.[9] in 2001, which revealed no differences in terms of complications between the intravenous administration of the triple therapy for 10 days and a short 3-5-day oral therapy completed at home. This was also the case with the comparative study conducted by Adibe et al.[10], which came to the same conclusions. Some articles, such as the one describing the protocol by Desai et al.[8] to establish the adequate timing for switching into oral therapy, are based on clinical criteria –adequate oral tolerance, good analgesic control, and no fever– and the absence of leukocytosis. However, some authors do not consider blood test parameters. This is the case with Willis et al.[11], who administer piperacillin-tazobactam for 7 days followed by oral ciprofloxacin + metronidazole for another 7 days, irrespective of leukocytosis. For the creation of our guideline, clinical criteria including tolerance, absence of fever, and adequate analgesic control, as well as normal leukocyte and platelet count, were established. Platelets were selected instead of other markers such as C-reactive protein (CRP) based on Fanjul et al.'s study[6], which found CRP to have a low diagnostic usefulness vs. platelet count < 435,000.

Subsequently, therapies have evolved towards the simplification of antibiotic treatment per se. The Amer-

ican Pediatric Surgical Association guidelines establish piperacillin-tazobactam as the treatment of choice from the beginning[12]. However, other alternatives accepted include cefoxitin, ceftriaxone + metronidazole, cefotetan, and ciprofloxacin + metronidazole. Some studies such as Guillet-Caruba et al.'s[13] and St Peter et al.'s[14] advocate the use of metronidazole combined with a third-generation cephalosporin such as ceftriaxone[15]. In an attempt to initiate treatment with a lower-spectrum therapy but without compromising adequate covering, our guideline starts with ceftriaxone + metronidazole, with piperacillin-tazobactam and meropenem being left for complications. Based on studies such as Van Rossem et al.'s[16] –which prospectively compared the administration of intravenous treatment for 3 vs. 5 days, with no differences being found–, we decided to administer intravenous treatment for 48 hours at least.

Similarly to the aforementioned studies, we found no differences in terms of postoperative IAA incidence. However, differences were found regarding SSI incidence, which was higher in Group B, before the clinical guideline had been implemented. This could be interpreted as a coincidence resulting from the fact Group B had fewer patients or ceftriaxone + metronidazole covering is better than metronidazole + gentamicin covering, which was previously used. Be that as it may, the new therapy with early discharge did not increase the incidence of infectious complications.

Regarding hospital stay, contrarily to the other studies reviewed, no significant differences were found in our study overall. However, when analyzing median treatment duration, it decreased from 6 to 3 days following the guideline's implementation. In addition, as it can be noted in Figure 2, hospital stay was sharply reduced, since mean hospital stay in patients meeting early discharge criteria was 2.4 days, and this group represented 62.7% of the total CAs. Even though overall stay was similar, two thirds of the patients were discharged in less than 72 hours, which means a significant decrease in hospital stay vs. the pre-guideline group, where minimum hospital stay was 5 days for all patients. Not only does this represent a clear benefit for the patient, but it also allows hospital costs to be reduced. The lack of statistically significant differences was probably due to the fact patients with IAA as a postoperative complication required long treatments with intravenous meropenem, thus increasing overall mean hospital stay. Unsurprisingly, most of the patients meeting early discharge criteria were gangrenous appendicitis patients, who met the established criteria in up to 89.7% of cases. However, only 15.9% of peritonitis patients were eligible for early discharge. This comes as no surprise since these patients typically have a slower progression in terms of oral tolerance and analgesic control. In spite of that, none of the peritonitis patients who were early discharged had infectious complications. 50% of the IAAs in the CA cases from Group A occurred in gangrenous appendicitis patients who were early discharged. However, the latter are more frequent among CAs, and overall, they did not increase the incidence of complications.

Regarding the analysis of the type of oral therapy following discharge, multiple options were found in the literature. Some authors advocate the use of various antibiotic treatments combined, such as metronidazole with A/C[9] or with ciprofloxacin[11], whereas others opt for a single treatment with antibiotics such as ciprofloxacin[11]. In this study, the use of metronidazole with cefuroxime vs. l single use of A/C was prospectively compared, with no significant differences being found in terms of complication incidence. Therefore, considering that using a single antibiotic is more convenient, A/C seems a better option, even though both are valid. Indeed, recent studies such as Gordon et al.'s[17] from 2020 and Ketha et al.'s[18] from 2021 posit that if the patient meets the clinical criteria established for discharge and there is no leukocytosis, it is safe not to administer additional oral antibiotic treatments at home.

In conclusion, in UCA cases, the preoperative prophylactic dose is sufficient to prevent the risk of SSI and IAA. In CA cases, establishing a clinical guideline that unifies treatment and sets early discharge criteria allows hospital stay to be reduced in selected patients, without increasing the risk of infectious complications. Regarding at-home oral antibiotic therapy in early discharged CA patients, A/C is more convenient and equally effective as combined cefuroxime and metronidazole.

REFERENCES

1. Cameron DB, Melvin P, Graham DA, Glass CC, Serres SK, Kronman MP, et al. Extended versus narrow-spectrum antibiotics in the management of uncomplicated appendicitis in children: A propensity-matched comparative effectiveness study. Ann Surg. 2018; 268(1): 186-92.
2. Boomer LA, Cooper JN, Anandalwar S, Fallon SC, Ostlie D, Leys CM, et al. Delaying appendectomy does not lead to higher rates of surgical site infections: A multi-institutional analysis of children with appendicitis. Ann Surg. 2016; 264(1): 164-8.
3. Kessler U, Mosbahi S, Walker B, Hau EM, Cotton M, Peiry B et al. Conservative treatment versus surgery for uncomplicated appendicitis in children: a systematic review and meta-analysis. Arch Dis Child. 2017; 102(12): 1118-24.
4. Huang L, Yin Y, Yang L, Wang C, Li Y, Zhou Z. Comparison of antibiotic therapy and appendectomy for acute uncomplicated appendicitis in children: A meta-analysis. JAMA Pediatr. 2017; 171(5): 426-34.
5. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: The APPAC randomized clinical trial. JAMA. 2015; 313(23): 2340-8.
6. Fanjul M, Pérez L, Cerdá J, Zornoza M, Rojo R, Simal I et al. Protocolo de alta precoz tras apendicectomía en niños. Cir Pediatr. 2015; 28(4): 177-83.

7. Cairo SB, Raval MV, Browne M, Meyers H, Rothstein DH. Association of same-day discharge with hospital readmission after appendicectomy in peadiatric patients. JAMA Surg. 2017; 152(12): 1106.
8. Desai AA, Alemayehu H, Holcomb GW, St Peter SD. Safety of a new protocol decreasing antibiotic utilization after laparoscopic appendectomy for perforated appendicitis in children: a prospective observational study. J Pediatr Surg. 2015; 50: 912-4.
9. Rice HE, Brown RL, Gollin G, Caty MG, Gilbert J, Skinner MA, et al. Results of a pilot trial comparing prolonged intravenous antibiotics with sequential intravenous/oral antibiotics for children with perforated appendicitis. Arch Surg. 2001; 136(12): 1391-5.
10. Adibe OO, Barnaby K, Dobies J, Comerford M, Drill A, Walker N, et al. Postoperative antibiotic therapy for children with perforated appendicitis: long course of intravenous antibiotics versus early conversion to an oral regimen. Am J Surg. 2008; 195(2): 141-3.
11. Willis ZI, Duggan EM, Bucher BT, Pietsch JB, Milovancev M, Wharton W, et al. Effect of a clinical practice guideline for pediatric complicated appendicitis. JAMA Surg. 2016; 151(5): e160194.
12. Lee SL, Islam S, Cassidy LD, Abdullah F, Arca MJ. Antibiotics and appendicitis in the pediatric population: an American Surgical Association outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2010; 45(11): 2181.
13. Guillet-Caruba C, Cheikhelard A, Guillet M, Bille E, Descamps P, Yin L et al. Bacteriologic epidemiology and empirical treatment of pediatric complicated appendicitis. Diagn Microbiol Infect Dis. 2011; 69: 376-81
14. St Peter SD, Little DC, Calkins CM, Murphy JP, Andrews WS, Holcomb GW, et al. A simple and more cost-effective antibiotic regimen for perforated appendicitis. J Pediatr Surg. 2006; 41: 1020-4.
15. Rentea RM, St Peter SD. Pediatric appendicitis. Surg Clin North Am. 2017; 97(1): 93-112.
16. Van Rossem CC, Schreinemacher MH, van Geloven AA, Bemelman WA. Appendicitis Collaborative Study Group. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. JAMA Surg. 2016; 151(4): 323-9.
17. Gordon AJ, Choi JH, Ginsburg H, Kuenzler K, Fisher J, Tomita S. Oral antibiotics and abscess formation after appendectomy for perforated appendicitis in children. J Surg Res. 2020; 256: 56-60.
18. Ketha B, Stephenson KJ, Dassinger MS 3rd, Smith SD, Burford JM. Eliminating use of home oral antibiotics in pediatric complicated appendicitis. J Surg Res. 2021; 263: 151-4.