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Characteristics of acute appendicitis at a tertiary hospital: analyzing the implementation of an antibiotic optimization program

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Abstract

Introduction. Acute appendicitis (AA) is the most frequent surgical pathology in pediatrics. However, publications discussing the most adequate antibiotic therapy for AA prophylaxis and treatment in children are limited.

Materials and methods. A retrospective analysis of patients under 14 years of age hospitalized as a result of AA was carried out. The periods pre- and post- implementation of an antimicrobial optimization program (AOPR) were compared. The pre-AOPR period went from September 2017 to March 2019, while the post-AOPR period went from April 2019 to September 2019.

Results. 206 patients were included, 139 in the pre-AOPR group, and 67 in the post-AOPR group. Dual therapy (ceftriaxone + metronidazole) and single therapy (cefoxitin) were more commonly used in the post-AOPR group ($p= 0.0001$), with reduced use of amoxicillin + clavulanic acid and piperacillin + tazobactam as an empirical therapy ($p= 0.0001$). To determine whether conversion to oral therapy was feasible or not, a number of clinical (no fever, sustained transit, adequate tolerance with satisfactory oral pain control) and blood test (a 20-50% CRP decrease from its highest level and a $\leq 12{,}000/mm^3$ leukocyte count) criteria were established. This allowed conversion to oral treatment to increase in the post-AOPR period ($p=0.03$). No differences in terms of hospital stay or complications were found between periods, but narrower spectrum oral antimicrobials were used earlier in the post-AOPR period.

Conclusions. Implementing an AOPR for surgical pathologies and establishing protocols adapted to the resistance and microbiological profile found at each unit is strongly recommended.

Keywords: Appendicitis; Antimicrobial optimization programs; Antibiotic prophylaxis; Drug resistance.

CARACTERÍSTICAS DE LA APENDICITIS AGUDA EN UN HOSPITAL DE TERCER NIVEL. ANÁLISIS DE LA IMPLANTACIÓN DE UN PROGRAMA DE OPTIMIZACIÓN ANTIBIÓTICA

Resumen

Introducción. La apendicitis aguda (AA) es la patología quirúrgica más frecuente en Pediatría. Las publicaciones sobre la antibioterapia más adecuada como profilaxis y tratamiento de la AA en niños son limitadas.

Material y métodos. Se realizó un análisis retrospectivo en pacientes menores de 14 años hospitalizados con AA. Se comparó el período previo a la implantación del programa de optimización del uso de los antimicrobianos (PROA), pre-PROA (septiembre 2017-marzo 2019) y posterior, post-PROA (abril 2019-septiembre 2019).

Resultados. Se incluyeron 206 pacientes: 139 del período pre-PROA y 67 post-PROA. Destacamos la mayor utilización de biterapia (ceftriaxona y metronidazol) y monoterapia (cefoxitina) en el período post-PROA ($p= 0{,}0001$), con reducción del uso de amoxicilina-clavulánico y piperacilina-tazobactam como terapia empírica ($p= 0{,}0001$). Para determinar el paso a terapia oral, se estableció el cumplimento de criterios clínicos (estado afebril, tránsito mantenido, tolerancia oral adecuada y con buen control del dolor vía oral) y analíticos (descenso de la PCR al menos un 20-50% del valor máximo y leucocitos $\leq 12.000/mm^3$). Esto permitió un incremento de la secuenciación del tratamiento oral en el período post-PROA ($p= 0{,}03$). No hubo diferencias en la estancia hospitalaria ni complicaciones entre ambos períodos, aunque se emplearon antimicrobianos de menor espectro con terapia oral de forma más precoz en la etapa post-PROA.

Conclusiones. Es recomendable la implementación del PROA en patologías quirúrgicas y elaborar protocolos adaptados al perfil microbiológico y resistencias de cada unidad.

Palabras Clave: Apendicitis; Programa de optimización de uso de antimicrobianos; Profilaxis antibiótica; Resistencia a medicamentos.

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INTRODUCTION

Acute appendicitis (AA) is the most frequent pediatric surgical emergency[1-4]. It presents as peritonitis in 35%

of cases, while complications as a result of abdominal abscess occur in up to 15% of AA instances[5]. Apart from the surgical approach, the rational use of antimicrobials from the moment AA is suspected is key[6]. Today, there are few randomized studies discussing the most adequate antibiotic therapy in pediatrics, which means therapeutic attitude is usually based on that used in adults[7]. This pathology can be managed in very heterogeneous ways[8,9], especially regarding the type of antimicrobials used, the time of conversion to oral treatment, and total duration[10,11]. *E. coli*, *Bacteroides fragilis*, and *S. anginosus* are the most commonly isolated germs[11,12]. Some recent protocols advocate the use of broad spectrum antibiotic therapy with carbapenem or piperacillin + tazobactam (PTZ) to deal with *Pseudomonas* and emergent multi-resistant pathogens[5,10,12].

The Antimicrobial Optimization Program (AOPR)'s team implemented a protocol of action aimed at reducing variability in the antimicrobial approach. The use and duration of antibiotic therapy were monitored and optimized through daily controls carried out by pediatric infectious disease, pediatric surgery, microbiology, and pharmacology specialists.

The main objective of this work was to review how the adequate use of antimicrobials can impact AA, selecting the most adequate type and definitive duration in our unit. AA patient characteristics and AOPR's impact on AA management were described.

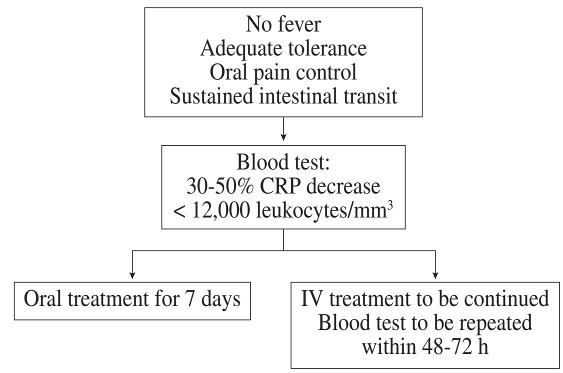
MATERIALS AND METHODS

Study design

Clinical records of AA patients under 14 years of age managed at a tertiary hospital – a reference center for pediatric surgery – from September 2017 to September 2019 were retrospectively analyzed. Two periods were established – a pre-AOPR period from September 2018 to March 2019, and a post-AOPR period from April 2019 to September 2019. Exclusion criteria included referral to other institutions, incomplete records, and/or patients receiving antibiotic therapy only, without surgical management. Adequate use of antimicrobials, peritoneal fluid (PF) culture, changes in antibiotic therapy according to the PF analyzed, blood tests as an indicative tool for intravenous (IV) into oral therapy conversion, hospital stay, and complications were compared between groups.

Adequate use of antimicrobials was defined as:

- Antibiotic therapy with single therapy (cefoxitin) or dual therapy (ceftriaxone + metronidazole) as the first choice.
- In complicated AA, conversion to oral treatment as long as clinical (adequate tolerance with satisfactory oral pain control, no fever, and sustained intestinal transit) and blood test (at least a 30-50% decrease in C-reactive protein [CRP] from its highest level and a < 12,000 mm³leukocyte count) criteria were met (Fig. 1). Blood test was performed right after the aforementioned clinical criteria had been fulfilled.
- In complicated AA, total treatment duration of 7-10 days.



IV: intravenous; CRP: C-reactive protein.

Figure 1. Conversion to oral treatment algorithm.

Demographic variables such as age, sex, and type of appendicitis according to surgical, histological, and ultrasound assessment were collected. The microbiological and blood test data analyzed included highest CRP level, leukocyte and neutrophil count, and microorganisms isolated at PF culture. Therapeutic variables included time to surgery, type of antimicrobial used, IV and oral treatment duration, and change in antibiotic therapy. Hospital stay and postoperative complications were assessed, with a subsequent follow-up of at least six months.

Statistical analysis

A descriptive analysis of the variables was first carried out. Quantitative variables were expressed as central tendency and dispersion measures (mean, standard deviation, median, and range) according to distribution. Qualitative variables were expressed as frequency and percentage. A bivariate analysis was performed in order to assess potential associations between variables. Independence between qualitative variables was assessed using the Chi-squared test whenever possible, and Fisher's exact test in all other cases.

Regarding the comparison of the two means, Student's t-test was used in the case of quantitative variables following a normal distribution, and Mann-Withney-Wilcoxon U test was used in the case of quantitative variables not following a normal distribution. The analysis was carried out using the Stata 15.0 statistical software. Statistical significance was established at 95% ($p < 0.05$) in all cases.

Table 1. Demographic data and general characteristics of patients with acute appendicitis.

	Phlegmonous AA *n= 126*	*Complicated AA* *n= 43*	*Abdominal abscess* *n= 37*
Sex (M/F ratio)	2.6	1.5	0.95
Age (years)	9.4 (3-14)	8 (2-13)	8.7 (2-13)
Ultrasonography*	114 (90.5%)	26 (60.5%)	9 (24.3%)
Maximum CRP (mg/l)	31 (0-192)	126 (4-438)	140 (6-430)
Maximum leukocyte count (/mm^3)	17,186 (2,000-30,280)	17,890 (10,170-36,000)	18,863 (10,540-28,660)
Maximum neutrophil count (/mm^3)	13,719 (1,690-25,200)	14,512 (6,860-32,760)	15,561 (4,000-25,190)
Time to surgery (days)	1.2 (1-3)	1.2 (1-5)	1.3 (1-6)
Peritoneal culture	8 (6.0%)	19 (45.0%)	21 (57.0%)
Microorganisms isolated**			
Bacteroides	1 (12.5%)	12 (63.1%)	9 (42.8%)
E. coli	0	7 (36.8%)	13 (61.9%)
S. anginosus	0	4 (21.0%)	2 (9.5%)
Pseudomonas	0	3 (15.7%)	2 (9.5%)
E. faecalis	0	2 (10.5%)	0
Others	1 (12.5%)	2 (10.5%)	2 (9.5%)
Control blood test	15 (12.0%)	31 (72.0%)	33 (89.0%)

Data are expressed as median (min-max) and n (%).
AA: acute appendicitis; M: male; CRP: C-reactive protein; F: female.
**Diagnostic correlation between pre-surgery ultrasonography and surgical or histological type of AA.*
***Of the total of non-sterile cultures (n= 35).*

RESULTS

General characteristics of AA. Descriptive analysis

During the study period, 219 cases of AA were diagnosed, with 13 patients being excluded – 11 as a result of having incomplete records, and 2 who were referred to other healthcare facilities. Of the 206 patients included, 126 (61.1%) had phlegmonous AA, 43 (20.9%) had complicated AA (gangrenous appendicitis, focal peritonitis, generalized peritonitis, or appendicular plastron), and 37 (18.0%) had abdominal abscess. An ultrasonography was performed prior to surgery in 203 (98.5%) patients. Age was 9 (2-14) years old, with patients being mostly male (n= 135, 65.5%). Blood test results were 70.4 (0-438) mg/l maximum CRP, 17,640 (2,000-36,000) /mm^3 leukocyte count, and 14,225 (1,690-32,760) /mm^3 neutrophil count. The antimicrobials used were amoxicillin + clavulanic acid (A/C) in 87 (43.5%) patients, and cefoxitin in 44 (22.0%) patients. Culture samples were taken in 48 (23.4%) cases. The most frequently isolated microorganisms were *Bacteroides fragilis* (n= 22, 45.8%) and *E.coli* (n= 20, 41.6%). Of the total of AA patients, 46 (23.0%) required change in antibiotic therapy while in hospital, and 6 (2.9%) patients had antibiotic therapy adjusted according to culture results. Control blood test and conversion to oral treatment were performed in 79 (38.3%) patients. Oral antibiotic therapy was pursued at home in 71 cases, with A/C being the most commonly used antimicrobial (70.0%, n= 51). Hospital stay was 4.6 (1-22) days. Regarding complications, 7 (3.4 %) patients had postoperative abscess, and 1 (0.5%) case had surgical wound infection (SWI). Patient characteristics according to the type of AA are featured in Table 1 and Table 2.

Comparison of the pre-AOPR period with the post-AOPR period

139 pre-AOPR patients and 67 post-AOPR patients were included. In the pre-AOPR group, 87 (62.6%) patients were diagnosed with phlegmonous AA, 28 (20.1%) with complicated AA, and 24 (17.3%) with abscess. Distribution was similar in the post-AOPR group, with 39 (58.2%) phlegmonous AA cases, 15 (22.3%) complicated AA cases, and 13 (19.5%) abscess cases. Regarding the type of antimicrobial used, A/C and PTZ were less frequently used in the post-AOPR group, while ceftriaxone + metronidazole and cefoxitin were more frequently used (Table 3). Peritoneal cultures were equivalent in both groups: 28/139 (20.0%) vs. 20/67 (29.8%) (p= 0.10), with antimicrobial treatment being changed according to culture results in 1/26 (3.8%) pre-AOPR patients, and in 5/16 (31.0%) post-AOPR patients as a result of unfavorable clinical progression (p= 0.04). The proportion of control blood tests was similar in both periods: 53/139 (38.1%) vs. 26/65 (40.0%) (p= 0.79). In terms of conversion to oral treatment, this occurred in 21/48 (43.7%) pre-AOPR patients and in 17/24

Table 2. Treatment and prognosis of patients with acute appendicitis.

	Phlegmonous AA n=126	*Complicated AA n=43*	*Abdominal abscess n=37*
ATBs			
Cefoxitin	33 (27.5%)	6 (13.9%)	5 (13.5%)
C+M	4 (3.3%)	16 (37.2%)	14 (37.8%)
A/C	71 (59.1%)	7 (16.2%)	9 (24.3%)
PTZ	0	8 (18.6%)	6 (16.2%)
Cefazolin	1(0.8%)	0	0
Others	11(9.1%)	6 (13.9%)	3 (8.1%)
ATB change	10 (8.0%)	15 (36.0%)	21 (57.0%)
Cefoxitin	2 (20.0%)	0	0
C+M	3 (30.0%)	6 (40.0%)	10 (47.6%)
A/C	2 (20.0%)	1 (6.7%)	0
PTZ	0	4 (26.6%)	9 (42.8%)
Meropenem	0	1 (6.7%)	1 (4.8%)
Others	3 (30.0%)	3 (2.0%)	1 (4.8%)
Oral ATBs	14 (11.1%)	27 (62.7%)	30
A/C	12 (86.0%)	19 (70.4%)	20 (67.0%)
Ciprofloxacin + M	0	5 (18.5%)	4 (13.0%)
Others	2 (14.0%)	3 (11.1%)	6 (20.0%)
Oral ATB duration (days)	5.4 (4-10)	6.4 (1-15)	5.9 (1-11)
Total ATB duration (days)	2 (1-12)	10 (1-23)	12.2 (5-28)
Hospital stay (days)	2.9 (1-8)	6.6 (2-19)	8.1 (4-22)
Complications	3 (2.4%)	2 (4.6%)	2 (5.4%)
Abscess	2 (1.6%)	2 (4.6%)	2 (5.4%)
Others	1 (0.8%)	0	0

Data are expressed as median (min-max) and n (%). AA: acute appendicitis; A/C: amoxicillin + clavulanic acid; ATB: antibiotic; C+M: ceftriaxone + metronidazole; M: metronidazole; PTZ: piperacillin + tazobactam.

Table 3. Comparison of the pre-AOPR group with the post-AOPR group regarding the use of baseline antibiotic therapy.

	Pre-AOPR n=133	*Post-AOPR n=67*	*p*
Cefoxitin	13 (9.7%)	31 (46.3%)	0.0001
C+M	16 (12.0%)	18 (26.9%)	0.115
A/C	76 (57.1%)	11 (16.4%)	0.0001
PTZ	13 (9.7%)	1 (1.5%)	0.002
Cefazolin	0	1 (1.5%)	0.009
Others	15 (11.3%)	5 (7.5%)	0.001

Data are expressed as n (%). A/C = amoxicillin + clavulanic acid; C+M = ceftriaxone + metronidazole; PTZ = piperacillin + tazobactam.

(70.8%) post-AOPR patients (p= 0.03). A/C and ciprofloxacin + metronidazole were the oral medications selected in both periods. Hospital stay was 4.82 (1-22) days and 4.32 (1-14) days, respectively (p= 0.14). Total antibiotic therapy duration was similar in both periods, but in the post-AOPR group, oral antibiotic therapy duration was shorter – 5.1 (1-11) days vs. 6.27 (1-15) days; p= 0.03. In addition, once duration, dosage, and type of antimicrobial had been optimized, the number of complications was similar in both groups – 5 (3.6%) vs. 2 (3.0%) (p= 0.19).

DISCUSSION

This study demonstrates the impact of AOPR on the management of AA. The combination of a specific protocol, patient follow-up, and daily intervention has allowed for a more rational use of antibiotic therapy without increasing complications or hospital stay. Privileging the use of ceftriaxone + metronidazole or cefoxitin over PTZ has implied a return to an adequate spectrum in our environment, with a better control of multi-resistant germs.

Shorter oral antibiotic therapy patterns have been used, with no increase in adverse events. One of the objectives of the AOPR is to improve clinical results by regulating antimicrobial prescription, with an established therapy in terms of medication type and dosage. The AOPR is aimed at reducing hospitalization and treatment duration without increasing readmissions, undesired effects, emergence of multi-resistant germs, or mortality[13-14].

The therapeutic approach currently in use in many units is conservative, with early antibiotic therapy and deferred appendectomy even in perforation cases[15,16]. Certain cases of local infection such as appendicular plastron are treated with antibiotic therapy only[12]. This management has been called into question as compared to early appendectomy, since it is associated with a greater number of intra-abdominal complications and the need for longer antibiotic therapy[17]. Anyway, according to a meta-analysis consisting of 20 studies carried out in 3,600 patients, the sporadic use of antimicrobials does not cause morbidity to increase, even if the patient ends up requiring surgery[7]. These results should be read with caution, since pediatric studies are limited. However, the therapeutic role antibiotic therapy plays in this pathology is undeniable, which means optimization proves essential[7].

There is no consensus as to whether peritoneal culture is required or not[1,12]. The Infectious Diseases Society of America (IDSA)'s consensus guidelines recommend peritoneal culture is carried out in perforation cases if the local germ resistance pattern exceeds 10-20%[12], or in previously treated cases as a result of multi-resistant pathogen risk. The Surgical Society Infection (SIS)'s guidelines advocate the use of peritoneal culture in nosocomial abdominal infections[18], since it proves useful when it comes to guiding treatment in patients with comorbidities[18] or unfavorable progression[10-12]. Other authors[1] suggest it should be systematically performed given the risk of colonization by community-acquired broad-spectrum beta-lactamase germs. Since AOPR was implemented at our institution, culture has been carried out in all cases, with treatment being changed according to microbiological results only if clinical response is inadequate[11,18].

In case of suspected intra-abdominal infection, antimicrobial treatment should be initiated as soon as possible so that adequate concentrations are reached at surgery[12]. At our institution, single or multiple doses are recommended, with a new dose being administered one hour before the procedure if two antimicrobial half-lives have gone by[2,17]. One dose is equally effective as multiple doses in preventing SWI in simple AA[2]. Antimicrobial patterns are highly variable. However, the treatment of choice should be a broad-spectrum one covering aerobic and anaerobic gram-positive and enteric gram-negative pathogens[9,12]. Antimicrobials with resistance rates higher than 10-20% should be avoided[12]. Management heterogeneity was demonstrated in a survey carried out among 169 pediatric surgeons from 42 nations at the European Congress of Pediatric Surgery. According to this sample, 59% of pediatric surgeons used single therapy (penicillin or cephalosporin); 34% used dual therapy (beta-lactamase antibiotics + metronidazole), and 7% used triple therapy (penicillin + aminoglycosides + metronidazole). In complicated AA cases, the most commonly used agents were metronidazole, cefoxitin, A/C, and PTZ[4]. Differences in local microbiological profiles could be accountable for therapeutic diversity and the lack of consensus among institutions. Since 2009, certain units have proposed dual therapy with ceftriaxone + metronidazole instead of triple therapy with gentamicin + ampicillin + clindamycin or metronidazole in complicated cases[3,9]. A study of 49 pediatric patients carried out in Israel[3] compared both dosage regimens, with no differences being found in terms of postoperative complications. This new pattern represents a cost-effectiveness improvement, with reduced toxicity and less need for gentamicin level monitoring. Today, single therapy with cefoxitin or dual therapy with ceftriaxone + metronidazole are recommended by the IDSA's and the SIS' guidelines as the empirical treatment of choice[12,18]. A/C is not the first choice treatment in our environment as a result of *E.coli* resistance rates exceeding 20%[7,12]. Empirical covering of *Pseudomonas* remains an issue of discussion, since they have been isolated in up to 15% of AA instances in pediatric studies, and results are inconclusive[5]. Some authors[10] propose PTZ as an empirical therapy in perforated AA with early appendectomy, and then oral therapy with ciprofloxacin + metronidazole in case pain is under control, tolerance is adequate, there is no fever[12], and abdominal exploration is normal[10,18]. Another study[6] compared dual therapy (metronidazole + gentamicin) with ertapenem, and revealed better results in terms of hospital stay and fever duration, but with significant methodological limitations[6]. According to some studies, the postoperative complications of dual therapy with ceftriaxone + metronidazole are the same as those found with antipseudomonal treatmen[t(5)]. In addition, certain healthcare facilities empirically treat complicated AA with PTZ as a result of the high prevalence *E. faecalis* has[11]. According to the IDSA's guidelines, *Enterococcus* empirical covering is not required for community-acquired abdominal infections. In fact, the inadequate use of broader-spectrum antimicrobials should be avoided in order to prevent toxicity and generation of secondary resistance[12]. In our environment, no multi-resistant germs were isolated, and *Pseudomonas* and *Enterococcus* were rarely detected. Furthermore, most patients have not received previous antimicrobial treatment and do not have multi-resistance risk factors, which means widespread empirical covering is not required[5].

Today, neither IV treatment duration nor conversion to oral treatment are standardized in complicated AA, which means each case should be considered separately[12,18]. According to some guidelines, antibiotic therapy should be used for 4 to 7 days following surgery[18]. Most protocols establish the same clinical criteria for conversion to oral treatment: no fever, adequate tolerance, and satisfactory oral pain control[4,8,18]. Some studies suggest patients with leukocytosis at discharge should receive oral antibiotic therapy for an extra 7 days. Otherwise, treatment should be discontinued, which has not been associated with an increase in complications[8]. Other authors consider 5 days of IV therapy will suffice as long as clinical signs and blood test levels are adequately controlled[18], with no further complications[9]. Conversion to oral treatment is performed with second- or third-generation cephalosporin + metronidazole or A/C[19]. Quinolones are indicated for the treatment of *Pseudomonas*, *Enterobacter*, *Serratia,* and *Citrobacter*[12]. The implementation of this type of conversion to oral treatment protocols has allowed for shorter hospital stays[10]. Even though our results cannot be compared with those from other studies, the application of a therapeutic algorithm has caused hospital stay and oral antibiotic therapy duration to decrease. Similarly, the type of antimicrobial to be used was standardized, with no increase in complications.

One of the main limitations of this work lies in the fact it was a single-center study, with a small sample size and a low prevalence of multi-resistant germs.

The > 50% reduction in A/C and PTZ use and the acceleration of conversion to oral therapy revealed by this work demonstrate how important it is to implement an AOPR for AA. Even though evidence is inconclusive when it comes to establishing the most adequate treatment – most likely as a result of microbiological variability among units –, local protocols and cross-disciplinary cooperation are key to improve surgical results. In spite of the use of narrower-spectrum antimicrobials and the increase in conversion to oral treatment, no differences were found in terms of hospital stay or complications in the post-AOPR group.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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