

# Does time to antibiotic initiation and surgery have an impact on acute appendicitis results?

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## ABSTRACT

**Objective.** Time to treatment initiation is a key element to be considered in infectious pathologies such as acute appendicitis (AA). There are few articles in the literature analyzing the relationship between early pre-surgical antibiotic treatment initiation and complication occurrence in AA. Our objective is to analyze such influence and the effects of late treatment initiation.

**Materials and methods.** A retrospective, observational study was carried out in children undergoing surgery for AA between 2017 and 2018. Demographic variables, time to antibiotic treatment initiation, time to surgery, and postoperative complications were analyzed.

**Results.** 592 patients with a median 12-month follow-up were included in the study. Antibiotic treatment initiation in the first 8 hours following diagnosis prevents complications [OR 0.24 (95% CI: 0.07-0.80)] and dramatically reduces the occurrence of intra-abdominal abscess from 25.0% to 5.5% ( $p=0.03$ ). Antibiotic treatment initiation in the first 4 hours following diagnosis significantly reduced wound infection rate in non-overweight patients [2.9% vs. 13.6%; OR 0.19 (95% CI: 0.045-0.793);  $p=0.042$ ]. Surgery within the first 24 hours following diagnosis reduced the proportion of advanced AA (gangrenous appendicitis and peritonitis) from 100% to 38.6% ( $p=0.023$ ).

**Conclusions.** Antibiotic treatment initiation in the first 4 hours following AA prevented the occurrence of post-surgical complications, especially in non-overweight patients. An adequate clinical approach and an early assessment by the pediatric surgeon are key to reduce the morbidity associated with AA.

**KEY WORDS:** Acute appendicitis; Appendectomy; Antibiotics; Pediatric patient; Time to treatment; Post-surgical complications.

## ¿INFLUYE EL TIEMPO HASTA EL INICIO DE LA ANTIBIOTERAPIA Y LA INTERVENCIÓN EN LOS RESULTADOS DE LA APENDICITIS AGUDA?

### RESUMEN

**Objetivo.** El tiempo hasta el inicio del tratamiento es un elemento fundamental a considerar en patologías infecciosas como la apendicitis aguda (AA). Existen escasos artículos en la literatura que analicen la relación entre el inicio precoz de la antibioterapia prequirúrgica y el desarrollo de complicaciones en la AA. Nuestro objetivo es analizar dicha influencia y el efecto de su retraso.

**Material y métodos.** Se realizó un estudio observacional retrospectivo en niños intervenidos de AA entre 2017-2018. Se analizaron variables demográficas, tiempo transcurrido hasta el inicio de la antibioterapia, tiempo hasta la cirugía y complicaciones postoperatorias.

**Resultados.** Se incluyeron 592 pacientes con mediana de seguimiento de 12 meses. El inicio de la antibioterapia en las primeras 8 horas tras el diagnóstico previene la aparición de complicaciones [OR 0,24 (IC95% 0,07-0,80)], disminuyendo significativamente el porcentaje de aparición de abscesos intraabdominales del 25,0 al 5,5% ( $p=0,03$ ). El inicio de la antibioterapia en las primeras 4 horas tras el diagnóstico disminuyó significativamente la tasa de infección de herida en pacientes sin sobrepeso [2,9 vs. 13,6%; OR 0,19 (IC95% 0,045-0,793);  $p=0,042$ ]. La intervención quirúrgica en las primeras 24 horas tras el diagnóstico disminuyó la proporción de AA evolucionada (gangrenada y peritonitis) del 100 al 38,6% ( $p=0,023$ ).

**Conclusiones.** El inicio de la antibioterapia en las primeras 4 horas tras el diagnóstico de AA previno el desarrollo de complicaciones postquirúrgicas, sobre todo en pacientes sin sobrepeso. Una orientación clínica adecuada y valoración precoz por el cirujano pediátrico son un elemento clave para disminuir la morbilidad asociada a la AA.

**PALABRAS CLAVE:** Apendicitis aguda; Apendicectomía; Antibióticos; Paciente pediátrico; Tiempo hasta el tratamiento; Complicaciones postquirúrgicas.

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## INTRODUCTION

Acute appendicitis (AA) is the most frequent surgical pathology in pediatric age, with an incidence in life of 8.6% in men, and 6.9% in women<sup>(1,2)</sup>. Incidence progres-

sively increases in the first years of age, with peak incidence occurring in the second decade<sup>(3-6)</sup>.

As a result of such a high incidence in pediatric age, AA is the most frequent urgent surgical procedure carried out by pediatric surgeons.

Without an adequate treatment, AA naturally advances to perforated appendicitis and subsequently to peritonitis, so it is considered by many authors as the most frequent cause of intra-abdominal abscess and abdominal sepsis in pediatric population<sup>(7,8)</sup>. These advanced forms are significantly associated with a longer time lapse between symptom onset, diagnosis, and adequate treatment<sup>(9)</sup>. In many cases, late diagnosis can be a result of the unspecific nature of patient symptoms, which may explain the fact that advanced AA forms tend to appear in patients under 5 years of age primarily<sup>(10)</sup>. Therefore, as it is case in most infectious pathologies, time is a key element in order to prevent progression to more severe forms, complications, and even death. As a result of such infectious nature, antibiotic treatment is a crucial element in AA management, and it can even be proposed as a single therapy, with or without subsequent surgical procedure, according to recent studies<sup>(11)</sup>.

The use and type of antibiotic treatment in AA, initiation time, and treatment duration remain controversial. The latest guides for AA management according to evidence-based recommendations advocate the use of pre-surgical broad spectrum antibiotic treatment<sup>(12)</sup>. However, in the literature, as well as in various clinical guides, pre-surgical antibiotic treatment initiation time is not explicitly established. Therefore, it can either be started at AA diagnosis and maintained until the procedure – according to the relevant pattern –, or administered only 30-60 minutes prior to the procedure. But there are no studies analyzing the effect of earlier or later antibiotic treatment initiation on child appendicitis results or complications, so no evidence-based recommendations can be proposed in this respect.

The objective of this study is to analyze the potential influence of earlier pre-surgical antibiotic treatment initiation on AA results in pediatric patients.

## MATERIALS AND METHODS

### Study design

Observational, retrospective, single-center study in pediatric patients undergoing surgery for acute appendicitis in our hospital.

Patients were divided into groups, in time slots, according to time to pre-surgical antibiotic treatment initiation and time to surgery.

In addition, patients were subsequently differentiated according to body mass index (BMI) and divided into two groups: non-overweight patients and overweight patients,

so as to analyze certain variables where overweight may be a cause of confusion.

### Patient selection

AA patients under 16 years of age undergoing open or laparoscopic appendectomy in our healthcare facility in 2017 and 2018 were included in the study.

AA patients treated with antibiotic therapy and deferred appendectomy, patients undergoing prophylactic appendectomy in the context of another surgical procedure, and patients with intercurrent pathology interfering in prognosis or post-surgical evolution were excluded.

### Study variables

The variables of interest for this study, collected from clinical record data, included:

- **Social and demographic variables:** age, sex, weight, personal history.
- **Body mass index (BMI):** codified as thin, normal weight, overweight, and obese patients according to weight and age as per BMI calculation charts. This variable was subsequently re-codified as non-overweight patients (thin and normal weight patients) and overweight patients (overweight and obese).
- **Clinical variables:** abdominal pain evolution hours.
- **Time to antibiotic treatment initiation:** time from diagnosis (established once compatible clinical, analytical, and ultrasound findings had been confirmed) to pre-surgical antibiotic treatment initiation. This variable was sub-divided into 1-hour slots (1 to 11 hours) for comparative study purposes.
- **Time to surgery:** time from diagnosis to surgery initiation. This variable was sub-divided into 1-hour slots (1 to 24 hours) for comparative study purposes.
- **Intra-operative diagnosis:** intra-operative appearance of appendicitis progression, assessed by the surgeon, and codified as incipient (catarrhal or phlegmonous appendicitis) or advanced (gangrenous appendicitis, appendicular plastron, or appendicular peritonitis).
- **Post-surgical complications:** codified as wound infection (erythema, induration, or purulent material emerging through it), surgical wound dehiscence (total or partial wound opening requiring an additional suture, tissue glue, or secondary closure), intra-abdominal abscess (intra-abdominal collection of purulent material visualized at ultrasound or CT-scan examination), paralytic ileus (absence of intestinal transit or peristalsis with no underlying medical cause), intestinal obstruction (absence of intestinal transit owing to a mechanical cause), and overall complications (including all of the above).

In all cases, intravenous amoxicillin-clavulanic acid was administered as pre-operative antibiotic treatment and maintained following the procedure only in case of advanced appendicitis.

## Statistical analysis

The variables described above were analyzed and compared using the IBM SPSS Statistics 22.0 statistical software.

First, a descriptive analysis of the sample was carried out. To study associations with quantitative variables, non-parametric tests (Mann-Whitney's U test) were used, since none of the variables followed a normal distribution. To analyze qualitative variables, the Chi-square test and Fisher's exact test were used, as required.

Results with a  $p < 0.05$  value were considered statistically significant. All intervals were calculated with a 95% confidence.

## RESULTS

592 patients undergoing surgery for AA were included in the study. A descriptive study of the main variables of interest was carried out and featured in Table 1.

Median patient follow-up was 12 months (1-24 months).

### Time to pre-surgical antibiotic treatment initiation and postoperative complications

Patients were divided into groups according to the number of hours from diagnosis to pre-surgical antibiotic treatment initiation. No significant differences in the proportion of the various acute appendicitis degrees (catarrhal, phlegmonous, gangrenous, peritonitis, and appendicular plastron) were noted in any of the groups studied.

Appendectomy's overall complications tended to increase with time from diagnosis to pre-surgical antibiotic treatment initiation, with a complication rate of 11% in those cases where antibiotic treatment had been initiated in the first hours, and an increased complication rate of up to 19% in those cases where antibiotic treatment had not been initiated before 8 hours, as it can be noted in Figure 1.

After comparing the proportion of appendectomy-related complications according to time slots, a significant reduction in complications, both overall complications (10.9% vs. 33.3%;  $p=0.037$ ) and intra-abdominal abscess (5.5% vs. 25%;  $p=0.029$ ), was only observed in those patients where pre-surgical antibiotic treatment had been initiated in the first 8 hours following diagnosis, as compared to those patients where pre-surgical antibiotic treatment had been initiated after the first 8 hours following diagnosis (Fig. 2). Odds Ratio (OR) for overall complication occurrence was 0.24 (95% CI: 0.07-0.80), and 0.17 (95% CI: 0.04-0.68) for intra-abdominal abscess occurrence. No significant differences were found in the percentage of surgical wound infection, dehiscence, paralytic ileus, or intestinal obstruction. No significant differences were noted in complication occurrence in the remaining time slots analyzed.

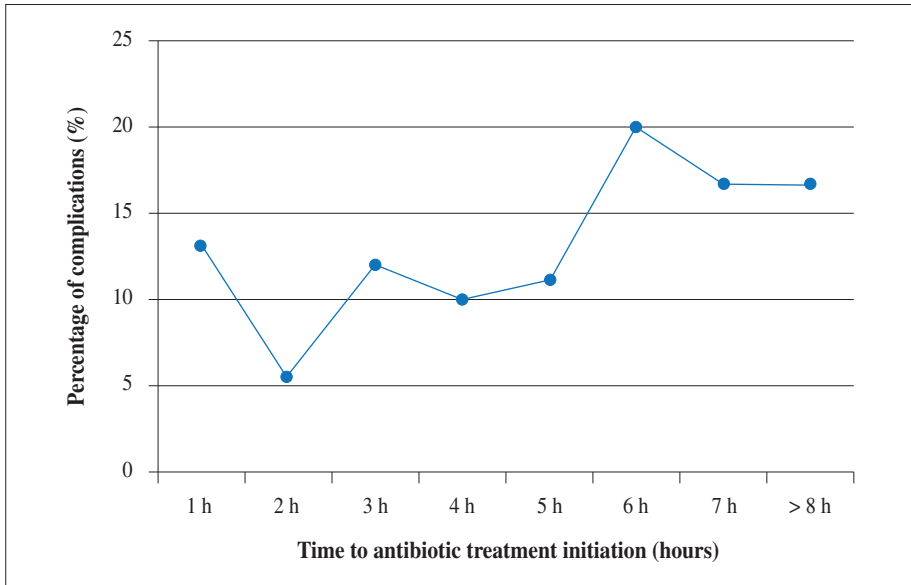
**Table 1. Descriptive analysis of the sample.**

<i>Qualitative variables</i>	<i>Frequency</i>	<i>Percentage (%)</i>
<b>Sex (n=592)</b>		
Female	227	38.3
Male	365	61.7
<b>Body mass index (n=403)</b>		
Thin	23	5.7
Normal weight	283	70.2
Overweight	67	16.7
Obese	30	7.4
<b>Intra-operative diagnosis (n=592)</b>		
Catarrhal	9	1.5
Phlegmonous	353	59.6
Gangrenous	151	25.5
Peritonitis	68	11.5
Appendicular plastron	11	1.9
<b>Surgical technique (n=592)</b>		
Open	434	73.3
Laparoscopic	158	26.7
<b>Complications (n=592)</b>		
Overall	60	10.1
Wound infection	26	4.4
Wound dehiscence	16	2.7
Intra-abdominal abscess	31	5.3
Paralytic ileus	5	0.8
Intestinal obstruction	4	0.7
<i>Quantitative variables</i>	<i>Mean</i>	<i>Standard deviation</i>
<b>Age (years)</b>	9.9	3.3
<b>Progression time (hours)</b>	27.7	26.1
<b>Time to antibiotic treatment (minutes)</b>	95.9	116.5
<b>Time to surgery (minutes)</b>	351.71	330.7

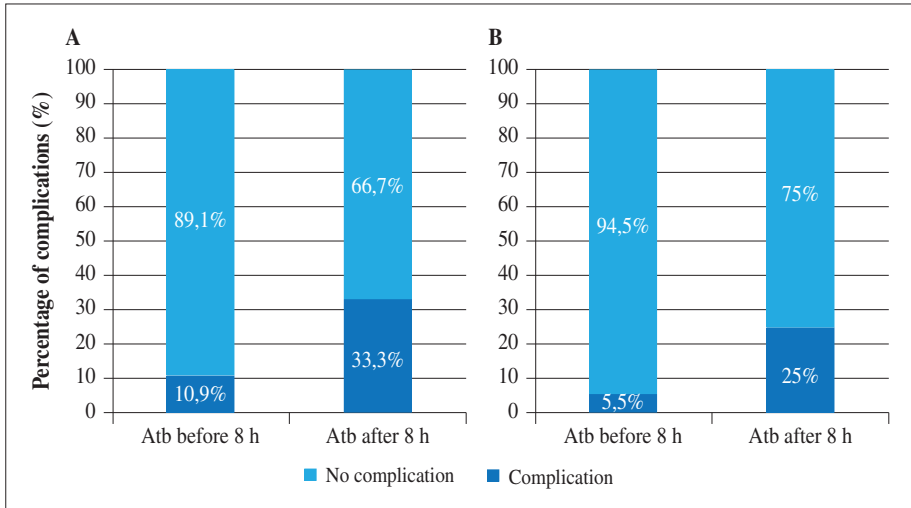
When stratifying patients in groups according to BMI, the administration of pre-surgical antibiotic treatment in non-overweight patients within 4 hours following diagnosis significantly reduced the proportion of surgical wound infection (2.9% vs. 13.6%;  $p=0.042$ ), with an OR of 0.19 (95% CI: 0.05-0.79), with no differences found in surgical wound dehiscence (Fig. 3).

### Time to surgery and acute appendicitis progression degree

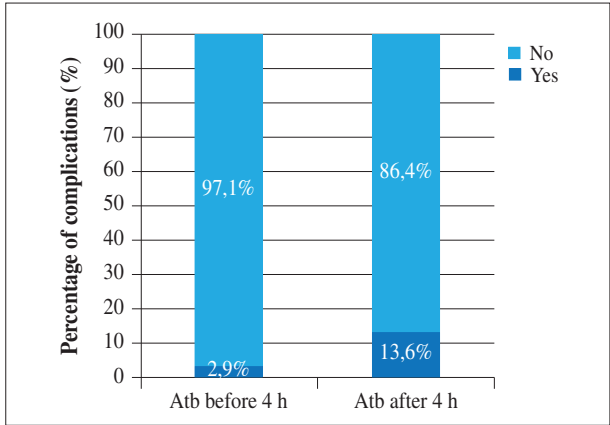
Similarly, after analyzing patients divided into groups according to time from diagnosis to surgery – either open or laparoscopic –, surgery carried out at least 24 hours following diagnosis was associated with a significant increase in the proportion of advanced appendicitis as compared to those patients where surgery was performed within the first 24 hours following diagnosis (38.6% vs. 100%;  $p=0.023$ ), as demonstrated in Figure 4.



**Figure 1.** Appendectomy overall complications according to time to pre-surgical antibiotic treatment.



**Figure 2.** Overall complications (A) and intra-abdominal abscess (B) according to time to antibiotic treatment (Atb), before and after 8 hours.



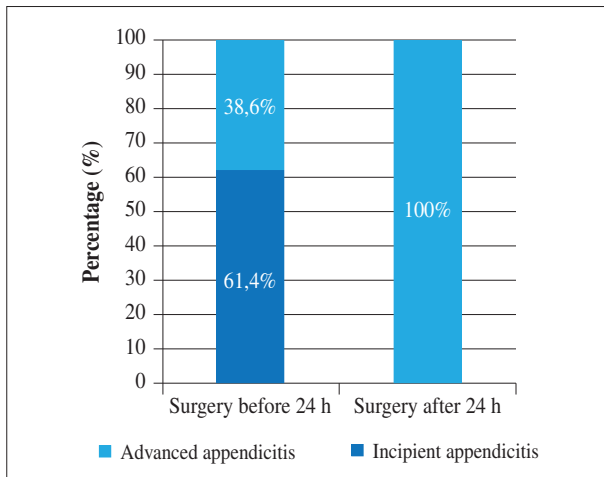
**Figure 3.** Surgical wound infection according to time to antibiotic treatment (Atb), before and after 4 hours.

No significant differences were found in the proportion of advanced appendicitis in the remaining time slots analyzed.

**DISCUSSION**

As demonstrated by our study results, late pre-surgical antibiotic treatment initiation following AA diagnosis seems to be a risk factor in the occurrence of postoperative complications such as intra-abdominal abscess. This is, to our knowledge, one of the first studies analyzing these aspects. Time should be considered as a negative factor when it comes to establishing an adequate diagnosis and treatment for AA.

In addition, late pre-surgical antibiotic treatment initiation has also been associated with an increase in other



**Figure 4.** Percentage of advanced appendicitis according to time to surgery.

complications such as surgical wound infection, especially in those patients without other risks factors typically considered so in the adult age, such as overweight and obesity<sup>(13)</sup>. Therefore, it could be inferred that an increase in BMI could be a risk factor for surgical site infection in pediatric population. Further studies should be carried out to clarify this.

Moreover, our study demonstrates that postponing surgery up to 24 hours following AA diagnosis seems to be a safe approach – provided that antibiotic treatment is initiated early –, since this time lapse is not associated with a higher risk of advanced appendicitis. These findings are consistent with those from other studies published up until now, such as those by Serres et al.<sup>(14)</sup>, Cameron et al.<sup>(15)</sup>, and Pérez-Martínez et al.<sup>(16)</sup>, which demonstrated that such delay was not associated with increased postoperative complications. It should be noted that, given our hospital's characteristics – many patients are referred to it from nearby healthcare facilities –, in some cases, the delay in surgery was partly due to the time required for the patient to get to our hospital for assessment purposes.

In order to issue evidence-based recommendations regarding AA treatment, the use of antibiotics, and other management aspects, numerous systematic reviews have been published in the literature. One of the most recent ones is that from the American Pediatric Surgical Association, which advocates the use of pre-surgical antibiotic treatment for acute appendicitis, both perforated and non-perforated. This recommendation has a grade A evidence<sup>(12,17)</sup>.

In spite of the evidence attached to these recommendations, there is still lack of consensus regarding various aspects related to AA management. This can be noted in the 2017 survey by the European Pediatric Surgeon's Association, which included questions on these aspects.

It showed a great array of opinions and acute appendicitis management techniques, which demonstrates to what extent every surgeon applies their own *medical lex artis* to their clinical activity. Indeed, up to 36% of surgeons replied they do not use pre-surgical antibiotic treatment in non-perforated AA<sup>(18)</sup>, which contradicts the latest evidence observed and seemingly represents a risk for increased postoperative complications, according to our study results.

The fact that acute appendicitis is one of the most frequently treated pathologies by pediatric surgeons in their daily activity, and that adequate treatment dramatically reduces potentially severe complications, highlights the need to standardize, improve and optimize treatment as much as possible following a series of recommendations which should be based on the scientific evidence published.

Therefore, in light of our study limitations, further studies should be carried out to analyze these aspects in depth and draw conclusions which help us improve treatment for these patients.

#### Study limitations

The main limitation is the retrospective nature of the study, which prevents patients from being randomized or allocated to a specific intervention group.

#### CONCLUSIONS

Early pre-surgical antibiotic treatment initiation following diagnosis seems to be a protective factor against acute appendicitis complications, allowing surgery to be safely postponed within the first 24 hours following diagnosis. Therefore, pediatric surgeons should be involved in the early diagnosis of potentially surgical abdominal pain, which should be a key management factor of acute appendicitis in the Emergency Room.

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