Acute appendicitis: not just a therapeutic puzzle to solve

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Abstract

Over the last 5 years, acute appendicitis (AA) is definitely drawing the scientific attention. As the timing in efficiently and promptly treating patients with AA is essential, any potential blind spot in understanding the disease should be clarified. Consequently, physicians will be able to address the patient towards the more appropriate therapeutic pathway (antibiotic or surgery) and avoid any harmful delay. Currently, neither surgery nor antibiotic seem offer a remarkable advantage to the patients therefore surgery remains the gold-standard in treating AA in accordance to the historical dogma.

Background

Over the last 5 years, acute appendicitis (AA) is definitely drawing the scientific attention. In the recent years there is a strong research interest on acute appendicitis: Figure 1 shows the rate of publication on PubMed with mesh terms of *acute appendicitis*. These numbers highlight uncertain areas in understanding the function of the appendix and its diagnosis and therapy; moreover a renewed interest is triggered by questioning the surgery as unique treatment.

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As the timing in efficiently and promptly treating patients with AA is essential, any potential blind spot in understanding the disease should be clarified. Consequently, physicians will be able to address the patient towards the more appropriate therapeutic pathway (antibiotic or surgery) and avoid any harmful delay. Clarifying the appendix function represents the mainstay of the therapeutic puzzle. Does the appendix play such a relevant role in the human physiology to prevent its removal in the most of the cases? Or does it not have any role to play, so it is better remove it in any case? Over the years the evolutionist theories have attempted to answer to these queries and suggest that it is wrongly interpreted as a vestigial organ that had lost its function in the development of lymphocyte immune responsiveness.[1]

The real appendix function has always been controversial to find out since the first published article which addressed this topic in 1904.[2] More recently, it was proposed that the appendix had a function similar to the caecum in the herbivores: that is digesting cellulose. Subsequently, over the years, the appendix has turned its function as consequence of an evolutionary mechanism which is known as exaptation (a similar mechanism is found in the ostrich wings which now work as stabilizers during the run).[3] Other theories suggest an active role into the immune system mechanism in several diseases. To date, published epidemiological articles show that the appendix removal is related to an increased risk of cardiac ischemia, type II diabetes mellitus and chronic intestinal inflammatory diseases during the three years post-appendectomy.[4,5]

From the etiopathogenetic perspective two hypotheses have been conceived about the AA. The first hypothesis depicts the AA as a progressive mechanism based on the obstruction of the appendix lumen due to fecal matter inducing the bacteria growth inside it and increasing the appendix lumen pressure causing blood vessel compression with a significant reduction in the blood supply to the appendix wall. The second hypothesis defines the AA as a perforative process that might basically have an infectious etiopathogenesis.[6]

The dogma of surgery for AA, which can lead to a 20% of negative appendectomies,[6] has been questioned during the last two decades with a growing scientific attention on medical therapy. This fact increased the need of improving the diagnosis process. The availability of imaging in a growing number of hospitals played a further important role.

A diagnostic algorithm is set for the vast majority of diseases but for the AA. In AA the decision-making is mostly based on the clinical judgment yet. However ethical, medical and legal issues related to a wrong diagnosis and potential harmful surgical treatment stimulated the researcher in developing diagnostic algorithm. Some of these are CT scan based, other on standardization of patient's complains, signs and lab test value.

Several score have been conceived over the last years in order

to facilitate the clinical judgment. Among clinical scores, that combine simplicity of computation and higher likelihood ratio (LR) or likelihood ratio, the Appendicitis Inflammatory Response Score or Appendicitis Inflammatory Response Score (AIR score) has been shown to be more accurate than the Alvarado's score.[7,8] In the AIR score the scale goes from 0 to 12. High risk patients for appendicitis range 8-12: Patients who range 5-8, remain uncertain for a diagnosis of AA and the clinical experience and imaging still play a considerable role (Table 1). Nevertheless, given the large number of clinical scores, any hospital should have its own protocol for the AA as the SIS (Surgical Infection Society) suggests.[9,10]

From the other side the surgery is superior, obviously, in avoiding the relapse of the disease but exposes to the risk of surgery with a mortality and morbidity ranging from 0.07 to 0.7%, 0.5 to 2.4%, respectively.[11-13] Moreover, due to the lack in diagnostic accuracy, the appendix removal exposes to an unuseful and harmful surgery; late occlusion from post-operative adhesion is widely described

Once the diagnosis of AA is accomplished, a further controversy arises by defining whether or not a AA is complicated; it remains controversial according to the following funding: peritoneal free fluid, perforation, abscess, diffuse or localized peritonitis. After surgery, the dilemma continues at the examination in the department of pathology. Interestingly, surgical and anatomopathological examination may remarkably disagree about appendicitis, appendix perforation and gangrenous.

This confusion results in a deep inhomogeneity in the treatment. The randomized trials are based on subjective assessment, randomization limits, lack of parameters used for imaging, inhomogeneous antibiotic treatment, different primary target for the two cohorts of patients and small sample size. Further, meta-analyses disagree in their conclusions despite the fact they mostly analyze the same studies.[14-21]

The real benefit and limits of both surgical and antibiotic therapy have to be established.

For instance, the wide antibiotic failure range (5-47%) highlights the bias in clinically defining the patient healed. Interestingly, this may be due to subjective evaluations, incorrect antibiotic prescription, *etc*. This suggests to minimize the bias throughout further well designed studies, applying strict criteria at the decisional knots. Nowadays, the recurrence of AA within one year after an effective antibiotic treatment is around 15%.[14,18,22-25]

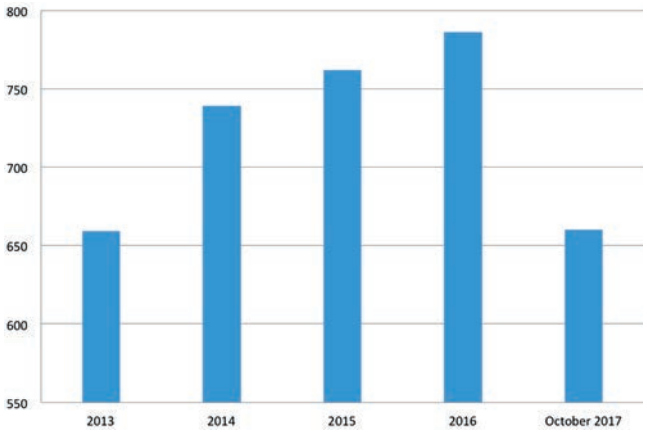

Figure 1. Trend of published articles on the acute appendicitis over the last five years.

In summary, neither antibiotic nor surgery can currently be considered as the proper treatment for AA as long as we will not be able to objectively define the clinical presentation (type of complicated acute appendicitis *vs* no complicated) the diagnosis, the antibiotic failure and to standardize the pathological findings. Due to these grey areas surgery remains the gold standard in treating AA in accordance to historical dogma.

Conclusions

Many issues about the physiology, diagnosis and treatment of the AA remain unsolved because of the shortage of papers addressing properly the grey areas over this pathway even though a multitude of published articles in literature.[26] It would be appropriate to implement the research in order to completely unearth the appendix function, which is the core of the pathology. Once we understand its function the decision-making becomes definitely clear in order to tailor the therapeutic pathway for each patient and it would decrease the appendectomy rate. Meanwhile, the clinical judgment should be accompanied to clinical scores (*e.g*. AIR score), which appear to be useful tools to facilitate clinical evaluation. Besides, the standardization of the abdominal ultrasound might be associated to clinical scores and cynical judgment. Conversely, routinely abdominal CT scan appears to be unrealistic in most parts of the world for a number of reasons such as availability, costs, patient exposure to radiation. Consequently, the increase diagnostic accuracy rate should allow us to define in which patient the antibiotic therapy has a more relevant chance of success.

Table 1. Appendicitis Inflammatory Response (AIR) score and its interpretation.

Symptoms	Score
Migration of pain to the right lower quadrant	
No	0 pt
Yes	1 pt
Vomiting	
No	0 pt
Yes	1 pt
Rebound tenderness or muscular defense	
No	0 pt
Yes	1 pt
Body temperature >38.5°	
No	0 pt
Yes	1 pt
Laboratory tests	
White blood cell count	
10.0-14.9 (10^9xL)	1 pt
>15 (10^9xL)	2 pts
Polymorphonuclear leucocytes	
70-84.9%	1 pt
>85%	2 pts
C-reactive protein concentration	
10-49 g/L	1 pt
>15 g/L	2 pts
Total score	

AIR score 0-4: low risk of acute appendicitis; follow-up in outpatient department is advised; AIR score 5-8: intermediate risk of acute appendicitis; hospitalization and monitoring according to clinical judgment and imaging, diagnostic laparoscopy might be considered; AIR score 9-12: high risk of acute appendicitis; surgery is recommended.

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