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Antibiotics versus Appendectomy for Acute Appendicitis: A Randomized Trial

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Abstract

Background: Although appendectomy is the standard treatment of Acute Appendicitis (AA), we tried to determine the role of antibiotics in the management of AA and to justify if appendectomy still remains the gold standard of care.

Methods: Randomly selected two hundred consecutive suspected AA patients, screened by Modified Alvarado Score, allocated equally in study group (with antibiotics) and control (appendectomy) group. All Pre-, per- and post-treatment clinical information's collected and recorded in a pre-designed data collection sheet and Telephone (or email) follow-ups conducted at 15 days, 1 month, 6 months, and 12 months.

Results: Antibiotics were efficacious in 67% of cases, 9 needed urgent appendectomy and 24 relapse cases at 12 months follow-up. Early postoperative complications was 25% in appendectomy group and during follow up 5% present with sub-acute intestinal obstruction.

Conclusion: Recurrent appendicitis and risk of missing serious pathology is potential drawback, but good patient selection can help overcome this and Use of antibiotics for the treatment of acute appendicitis could be a good option for treatment.

Keywords: Acute appendicitis; Antibiotic treatment; Recurrent appendicitis; Follow up; Appendectomy; Efficacy; Complications

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Introduction

Acute appendicitis still ranks as one of the most common acute surgical emergencies, which was described and systematically studied in the mid-19th century. Appendectomy has been the mainstay for the treatment for acute appendicitis since it was first reported by McBurney in 1889. Since then, many studies, articles and even books have been written upon this subject and it seems that nothing new can be added and still an ongoing debate. The role of antibiotic treatment in acute uncomplicated appendicitis may have been overlooked mainly on the basis of tradition rather than evidence, considering that other intra-abdominal inflammatory processes such as colonic diverticulitis, salphingitis, neonatal enterocolitis etc. are primarily managed non-operatively. The incidence of acute appendicitis is lowest in societies with a high dietary fiber intake, but in developing countries that are adopting a more refined western-type diet; the incidence continues to rise. There has been a dramatic reduction in the incidence of appendicitis in Western countries over the last three decades. Is there a relationship between falling incidence and increased use of antibiotics?

Traditionally, appendectomy has been the primary treatment, even in cases of unconfirmed diagnosis, given the low incidence of major complications. However, in 15% – 30% of cases the appendix is found to be free of disease upon resection [1,2]. As appendectomy is associated with surgical wound infection, intestinal obstruction due to adhesions, pneumonia, and tubal infertility in females, the possibility of using conservative treatment merits investigation. In this study we tried to find benefit using antibiotic in acute appendicitis and made a comparison with appendectomy cases.

Material and Methods

Study population

Patients (>14 years old) presented with suspected AA screened carefully by attending surgeons in Rajshahi Medical College Hospital, Rajshahi, Bangladesh from January 2013 to December 2014 was enrolled in this study. Clinical history, physical examination and laboratory blood tests (blood hemoglobin g/l and leukocyte count E9/l, Neutrophil count) as well as urine analysis, X-ray K.U.B region and U.S.G of lower abdomen was undertaken as per need. Finally by using Modified Alvarado Score total 200 Patients who were eligible for inclusion in the randomized control study invited to participate and informed about the protocol. Acute appendicitis patients with diffuse peritonitis, antibiotic (ciprofloxacin) documented allergy, Positive pregnancy test and irritable bowel disease IBD were excluded from study. After signed informed consent obtained, 100 patients were included in appendectomy group and 100 patients in antibiotic group. There is no formal ethical committee in the institute we tried to maintain all ethics of research of international standard.

Registration procedure

After signed informed consent, all patients evaluated for study enrollment are registered in participating institution using pre-designed data collection sheet.

Randomization

After confirming the diagnosis of uncomplicated AA by Modified Alvarado Score, patients were randomized by number of patient. 1st patient was allocated to antibiotics (study group), and 2nd patient to appendectomy (control group). Thus uneven no. patients remain under antibiotic therapy and even no. patients got operative treatment. The randomization was performed in 1:1 equal allocation ratio. To randomize a patient, an independent surgeon on duty worked.

Interventions

Surgical treatment: After randomization to undergo operative treatment, open appendectomy was performed by standard technique using a McBurney right lower quadrant muscle splitting incision. Prophylactic antibiotic as a single dose of 400 mg i.g ciprofloxacin and 500 mg metronidazole i.v. was administered approximately 30 min preoperatively. The histopathological examination of the appendix performed and the histological diagnosis of acute appendicitis requires involvement of the muscularis of the appendix (transmural neutophil invasion).

Antibiotic therapy

After randomization to receive antibiotic treatment, intravenous ciprofloxacin 400 mg 12 hourly with Metronidazole 500 mg 8 hourly administered for three days. The clinical status of the antibiotic group patients re-evaluated within 12-24 hours after admission and monitored during the whole stay. If progressive infection, perforated appendicitis or peritonitis is clinically suspected, the patient underwent emergency appendectomy and the histopathological examination of the appendix performed. The three-day intravenous antibiotic treatment was followed by seven days of oral antibiotic therapy with Cipofloxacin 500 mg × 2 combined with metronidatzole 400 mg × 3 resulting in ten-day total duration of the antibiotic therapy.

Operational analysis

The primary end-point

The primary endpoint of treatment success in this trial is defined as treatment efficacy in the antibiotic treatment group as the resolution of AA with antibiotic treatment resulting in discharge from the hospital without the need for surgical intervention and no recurrent appendicitis during a minimum follow-up of one-year. Treatment efficacy in the operative treatment arm is defined as successful appendectomy evaluated to be 100%.

Secondary end-points

- Post-intervention complications
- Late recurrence of AA after conservative treatment
- Duration of hospital stay
- Sick leave

A recurrent AA will be diagnosed on a clinical basis. A patient with recurrent AA could receive 2nd time antibiotic therapy or appendectomy as per need and the recurrent AA diagnosis would be verified histopathological examination of removed appendix. For the primary study endpoint, the overall treatment efficacy will favor surgical treatment. For the secondary end-points, late recurrence of AA after one-year follow-up is naturally associated only with the antibiotic treatment arm. The outcome regarding the other secondary endpoints of overall morbidity, sick leave, treatment costs, pain scores and pain medication utilization in the antibiotic treatment arm is evaluated to be superior compared with surgical treatment. The duration of the hospital stay was most likely be similar in both treatment arms.

Follow-up

Patients outcome obtained during hospital stay (days 0,1,2) and then by a phone interview at two week, one month, six month and at one year after the intervention. During follow up additional need for sick leave, wound infections and recurrent AA, an incisional hernia with the McBurney incision for the surgery group was registered. Potential adhesion related problems such as sub acute intestinal obstruction evaluated for both groups.

Statistical analysis

Pre study estimates suggested that at least 200 allocated patients would be necessary to confirm a 10-15 per cent difference in treatment efficacy and complications between study and control patients at 80 per cent power with a 5 per cent significance level. The $\chi 2$ test was used to check for differences between proportions. Student's t test or ANOVA was used for comparisons of continuous variables between groups. P <0.050 was considered significant in two-tailed tests. SPSS® version 16.0 software was used for the statistical calculations.

Results

Study population

The total study population (200) consisted of 91 female and 109 male with age ranged from 14 to 45 years. A peak incidence of acute appendicitis was found in patients 14–30 years of age in both age groups. The mean age in appendectomy group and primarily treated antibiotic group was respectively 25.06 years and 24.63 years, on the other hand female: male ratio 1:1.3 and 1: 1.08 respectively (Figure 1).

Per operative finding of resected appendix

In appendectomy group, per operatively 69 appendixes was inflamed with fibrinous exudates and faecolith was found in only 3 appendixes. 2 perforated appendixes with faecolith in lumen were found and 4 gangrenous appendixes were found. But 25 appendixes

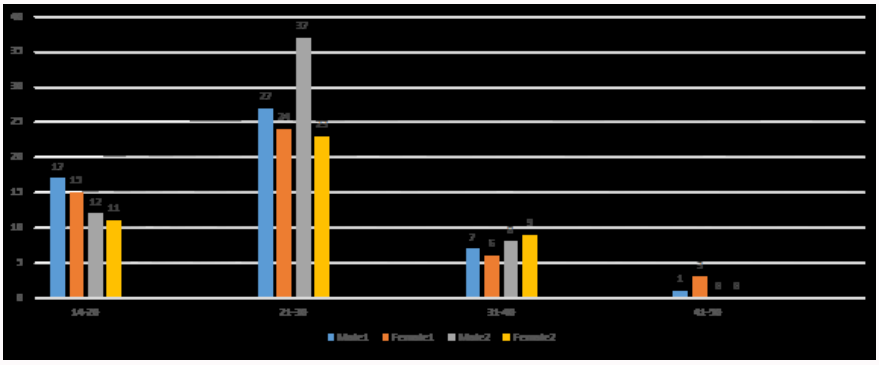

Figure 1: Age distribution of the patients (both groups) n = 100 + 100 (age in years).

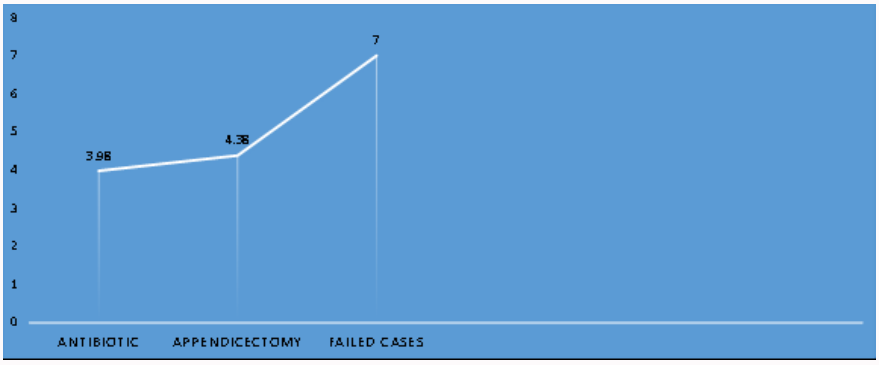

Figure 2: Duration of Hospital Stay in different groups in days.

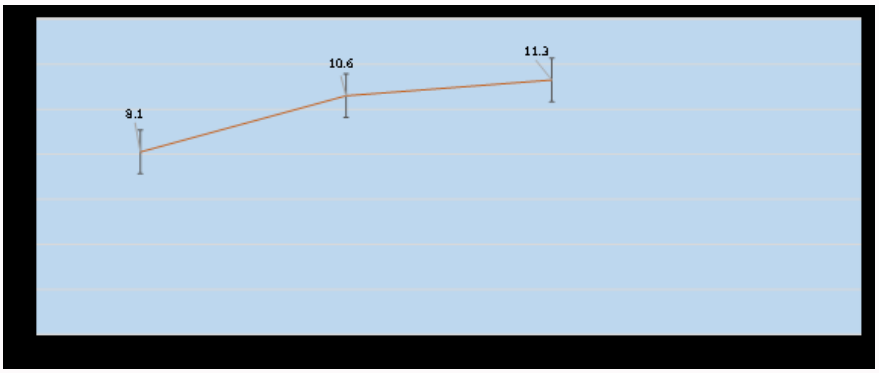

Figure 3: Return to normal activity in days.

were apparently looking normal. Those patients who underwent appendectomy after failure of antibiotic therapy, preoperatively 4 appendixes were highly inflamed and 5 was gangrenous appendix. During follow up period two (2) patients underwent appendectomy due to recurrent appendicitis.

Complications during hospital stay

In Antibiotic group thirteen (13) patients developed complications nine (9) underwent appendectomy during antibiotic therapy, three (3) patients develop appendicular lump, one (1) patient suffered from appendix abscess. Twenty five (25) patients developed complications after primary appendectomy treatment which is described in Table 2.

Complications during follow-up period

This study design resulted 100 antibiotic treated patients, with a primary recovery rate of 91% (91 in 100) and a 12 months recurrence rate of 24% (Figure 2-5). In appendectomy group during follow up five (5) patients later present with recurrent subacute intestinal obstruction and improved by conservative treatment. Among these 5 patients 4 were with normal appendix according to histopathological report.

Duration of hospital stay

Mean duration of hospital stay in conservative group was 3.97 days while in operative group was 4.24 days. Those who underwent appendectomy during antibiotic treatment stay in hospital for a median of 7 days (Figure 2). So according to t-test and ANOVA test there is significant difference in duration of hospital stay between appendectomy group and those who underwent appendectomy due to development of localized peritonitis after antibiotic therapy (Table 1 and 2) but Post Hoc test shows no significant difference in between groups.

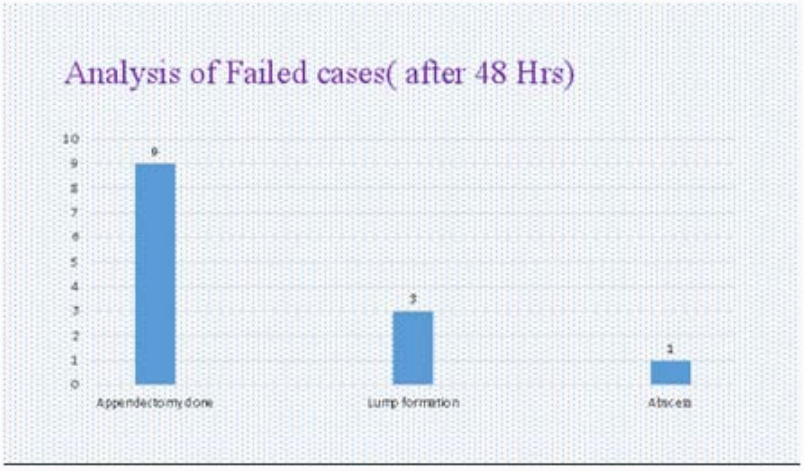

Figure 4: Analysis of failed cases.

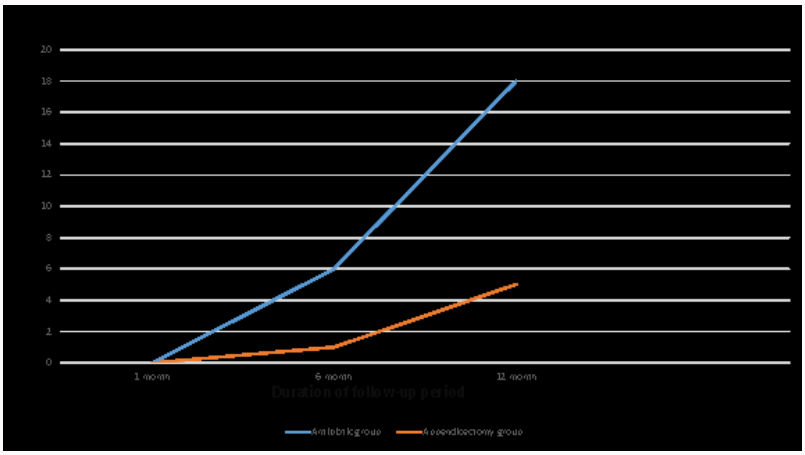

Figure 5: Shows result of follow up after treatment.

Return to normal activity

Those improve by antibiotic therapy (91 patients) return to normal activity within mean duration of 8.1648 days. Mean duration of return to normal activity was respectively 10.8367 and 11.333 in appendectomy group (100 patients) and appendectomy done after failure of antibiotic group (9 patients).

Incidence rates of negative appendectomy

There was highest percentage of negative appendectomy was found in the second and third decade and mostly among female (8).

Discussion

Main findings

In this RCT according to definition of operational analysis treatment efficacy in antibiotic group was 67% and in appendectomy group it is 100%. But rate of complication in appendectomy group (30%) was comparable to failure of antibiotic therapy (33%). Rate of negative appendectomy in appendectomy group and antibiotic group was respectively 12% and 1%.

Strengths and limitations

This RCT was under direct supervision of few competent surgeons, so less chance of diagnostic dilemma and no chance of delay to take operative decision if antibiotic treatment failed. In the meantime follow up was ensured by using mobile reminder system. There are several important limitations. The number of population in this RCT was small and during subsequent follow up complications were noted from verbal interview of the patients. Only in few cases, patients could submit hospital document of their complications.

Comparison with previous study

The first prospective randomized controlled pilot study comparing antibiotic treatment with appendectomy was published in 19951 with 40 adult patients and promising results. Only one of twenty patients (5%) who received antibiotic therapy did not recover on this treatment (iv cefotaxime 2 g x 2 and tinidazole 800 mg x 1 for 2 days followed by oral ofloxacin 200 mg x 2 and tinidazole 500 mg x 2 for 8 days) and required surgery. Seven patients (37%) experienced recurrent appendicitis within one year. The authors concluded that antibiotic therapy was as effective as surgery, but with high recurrence rate.

A decade later another prospective multicenter randomized controlled trial was presented by Styrud et al. [2] 252 male patients between 18-50 years old with clinically assumed appendicitis, CRP >10mg/l and without suspicion of perforation were included. The antibiotic recovery rate was 88% and the recurrence rate within one year was 14%. This was compared with a complication rate of 14% in the surgery group. The antibiotic regimen was the same as in

Table 1: Duration of hospital stay (Post Hoc test).

(I) Management approach of the patient	(J) Management of the patient	Mean difference (I-J)	Standard error	Sig.	95% Confidence interval for mean	
					Lower bound	Upper bound
Antibiotic therapy	Appendicectomy	0.402	0.299	0.349	1.09	0.28
	Appendicectomy after failure of antibiotic therapy	3.022	0.699	0	4.67	1.37
Primary Appendicetomy	Antibiotic therapy	0.402	0.29	0.349	0.28	1.09
	Appendicectomy after failure of antibiotic therapy	2.62	0.696	0.001	4.26	0.98
Appendicectomy after failure antibiotic therapy	Antibiotic therapy	3.022	0.699	0	1.37	4.67
	Primary Appendicectomy	2.62	0.696	0.001	0.98	4.26

Table 2: Outcome of Appendicectomy.

Outcome	frequency	Percentage (%)
Pelvic abscess	4	4%
Paralytic ileus	6	6%
Post-operative wound infection	12	22.0%
Faecal fistula	1	1%
Recurrent Sub acute intestinal obstruction	5	5.0%
Negative appendectomy	12	12%
Resp Tract Infection	2	2.0%

the pilot study from 1995 unpublished data, presented at a surgical symposium 2007, and showed a recurrence rate of 24% after 5-year follow-up [3]. During the completion of this study, antibiotic treatment of acute appendicitis has become in focus [4-7] and several other studies, meta-analyses and systematic reviews on the subject have been published. The RCTs have had similar antibiotic recovery rates around 90% and similar 1-year recurrence rates around 10%-15% (with some exceptions) [1,2,8,9].The conclusions of the meta-analyses and systematic reviews have been inconsistent and have varied from stating that antibiotics may be used only for selected patients with uncomplicated appendicitis with appendectomy remaining the gold standard [10-12] to a much more positive attitude towards antibiotic therapy incurring fewer complications compared to surgery [13-15]. Acute appendicitis successfully treated by antibiotics still remains a potential source of recurrent appendicitis. On the other hand, post-operative wound infections and post appendectomy bowel obstruction, even after 30 years from appendectomy, have been described. Any abdominal operation can result in adhesions, which may cause intestinal obstruction later in life. But Negative appendectomy appears at least as dangerous as perforated appendicitis concerning both small bowel obstruction and mortality [16]. Overall complication rate after appendectomy is hard to specify because definitions and reporting of complications are inconsistent, but a complication rate of 10% - 20% in large randomized trials has been shown [17-19]. In this study during follow up in control group five (5) patients later present with recurrent subacute intestinal obstruction and improved by conservative treatment. Among these 5 patients 4 were with normal appendix according to histopathological report. Our RCT showed a recurrence rate of 24% and 22 of those patients ask to be treated conservatively a second time and two needed appendectomy. The incidence of perforation was not found among patients with recurrence, and it may be that antibiotic treatment could have been used second time. First-year recurrence rate of AA successful treated by antibiotic ranges between 10 and 15%. So our RCT result is comparable with other RCT. Higher percentages have been reported in the previous study of Eriksson and in a recent prospective study by Vons et al. [9] (36.8% and 26% respectively). Due to the rate of recurrence, according to the Ansaloni meta-analysis, the clinical effectiveness favors surgery. Surgery can treat acute appendicitis in 100% of cases with the mortality and morbidity rate already described. Recurrence of appendicitis after appendectomy is quite impossible. The diagnosis of acute appendicitis is often difficult to make and remains largely a clinical one. Diagnostic uncertainty may lead to a delay in treatment or negative surgical exploration, both adding to the morbidity associated with this condition. The exact mechanisms leading to AA are still obscure but enteric bacteria (both aerobic and anaerobic bacteria) probably play a more important role. Whereas obstruction plays of minor importance, although it could be one of the contributing factors for perforation. If infection were the prevailing etiology of acute appendicitis, it would be logical to treat it with antibiotics rather than appendectomy. Thus, antibiotics offer the opportunity to treat AA even when surgical resources are not easily available such as in developing countries. There are several different types of antibiotics, and combinations of antibiotics, that can be used in the treatment of appendicitis. Considering the treatment cost and efficacy metronidazole and ciprofloxacin may be the best option given the coverage of aerobic gram-positive and gram-negative bacteria. So we have chosen this regimen of antibiotic in our study. We did not analyse the hospital costs in between two groups but significant difference in hospital costs was reported by Hansson et al. [20] with a reduction in expenses of 25-50% in the antibiotic group compared to surgery. The antibiotic approach offers the opportunity to avoid aboard Soviet ships treated at sea. In the latter Gurin et al. [21] by reviewing the conservative treatment outcomes in 252 patients with AA on vessels of the Kalingrad fishing industry from 1975 to 1987, reported a recovery rate of 84.1% with the only use of antibiotics. Thus, antibiotics offer the opportunity to treat AA even when surgical resources are not easily available such as in developing countries. Now question arise what is the best option? Probably there is no right answer to this dilemma.. Eight meta-analyses and reviews, including a Cochrane report, of the RCTs comparing antibiotics with surgery have been published during recent years [15,22,23], but the conclusions in these summaries have not been unanimous. Some authors stated that antibiotics might be safely used in selected patients with uncomplicated appendicitis leading to overall reduced complication rate, but the reports emphasized that appendectomy should remain the gold standard treatment. Others pointed out that antibiotic treatment incur fewer and less severe complications than surgery and could be regarded an alternative treatment in a majority of patients when such patients are willing to accept a risk of either initial treatment failure or later recurrence. The American College of Surgeons, [24] the Society for Surgery of the Alimentary Tract, [25] and the World Society of Emergency Surgery [26] all describe

appendectomy (either laparoscopic or open) as the treatment of choice for appendicitis. Regarding an antibiotics-first strategy, the American College of Surgeons patient information guide indicates that it "may be effective, but there is a higher chance of re occurrence [26]; the Society for Surgery of the Alimentary Tract patient care guidelines suggest that it is "not a widely accepted treatment" [27]; and the World Society of Emergency Surgery states that "this conservative approach features high rates of recurrence and is therefore inferior to the traditional appendectomy. Non-operative antibiotic treatment may be used as an alternative treatment for specific patients for whom surgery is contraindicated".

However, experience in Europe suggests that an antibiotics-first strategy is an alternative that warrants consideration, particularly in a patient who has had prior surgical complications and has a strong preference for avoiding appendectomy. European have also shown that as many as half the patients so treated will have early treatment failures, and all have a risk of recurrent appendicitis that may ultimately require appendectomy [27]. It is recommended that although appendectomy remains the recommended treatment for appendicitis, clinicians should inform appropriate patients about the evidence related to an antibiotics-first strategy, as well as the uncertainties.

However, the question whether primary antibiotic treatment of acute appendicitis is inferior, equal or superior to appendectomy is highly debated, although we believe they should be regarded complementary.

Conclusions

Appendectomy can be universally considered a "mile stone" in modern medicine. The comparison of surgery and antibiotic therapy is still an ongoing debate. Should we compare the rate of early failure in the antibiotic therapy with the rate of white appendicitis? Or should we compare the recurrence rate of antibiotic treated appendicitis within 30-days and long-time morbidity of surgery? In order to reduce the rate of "white appendicitis" and misdiagnosis there is the need to improve the diagnostic power. Therefore, we suggest adopting at least a single institutional clinical diagnostic tool and algorithm. The comparison of antibiotic and surgery needs a homogenous and more objective patient selection and guidelines. Some advantages and some disadvantages are intrinsic in both the treatment choice and cannot be compared. On the other hand, outpatient antibiotic treatment cannot be proposed as a clinical standard practice. High risk patients should be treated by antibiotics whilst surgery is to be considered mandatory after conservative treatment failure.

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