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Acute Appendicitis: Modern Understanding of Pathogenesis, Diagnosis and Management in Bangladesh

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ABSTRACT

Acute appendicitis is one of the most common abdominal emergencies worldwide. The cause remains poorly understood, with few advances in the past few decades. To obtain a confident preoperative diagnosis is still a challenge, since the possibility of appendicitis must be entertained in any patient presenting with an acute abdomen. Although biomarkers and imaging are valuable adjuncts to history and examination, their limitations mean that clinical assessment is still the mainstay of diagnosis. A clinical classification is used to stratify management based on simple (non-perforated) and complex (gangrenous or perforated) inflammation, although many patients remain with an equivocal diagnosis, which is one of the most challenging dilemmas. An observed divide in disease course suggests that some cases of simple appendicitis might be self-limiting or respond to antibiotics alone, whereas another type often seems to perforate before the patient reaches hospital. Although the mortality rate is low, postoperative complications are common in complex disease. We discuss existing knowledge in pathogenesis, modern diagnosis, and evolving strategies in management that are leading to stratified care for patients.

Keywords: *Acute disease, appendicitis, epidemiology, Bangladesh*

INTRODUCTION

Acute appendicitis is one of the most common general surgical emergencies worldwide,1 with an estimated lifetime risk reported at 7-8 %. Accordingly, appendectomy is one of the most commonly performed surgical procedures and represents an important burden on modern health systems. Despite being so common, limited understanding of etiology and absence of reliable discriminators for disease severity still exist. Limited clinical research has produced uncertainty about best practice with subsequent international variation in delivery and, as a possible consequence, variation in outcome. The aim of this review is to provide a state of the art update into the current controversies in pathogenesis, diagnosis and clinical management of acute appendicitis.

EVOLVING UNDERSTANDING OF ACUTE APPENDICITIS

Epidemiology: Acute appendicitis occurs at about 90-100 cases per 100,000 inhabitants per year in the Western world. Peak incidence usually occurs in the 2nd or 3rd decade of life, and the disease is less common at both extremes of age. Most studies show a slight male predominance. Geographical differences are reported, with lifetime risks for appendicitis of 16% in South Korea.

Etiology: Direct luminal obstruction may cause appendicitis (commonly by a faecolith, lymphoid hyperplasia or impacted stool; rarely by an appendiceal or caecal tumour) but may be exceptions rather than regular occurrences. While several infectious agents are known to cause or be associated with appendicitis,

etiology is still largely unknown. 6 Recent theories evolve around genetic factors, environment and infections.

Although no defined gene has been identified, there is an almost three times increased risk of appendicitis in members of families with a positive history for appendicitis, and a twin study suggests genetic effects account for about 30% variance in risk for developing appendicitis.

Environmental factors may play a role, as studies note a predominate seasonal presentation during the summer, which has been statistically associated with higher level of ambient ground-level ozone, used as a marker of air pollution. Time-space clusters of disease presentation may further indicate an infectious etiology. Pregnant women appear to have a lower risk for appendicitis, with lowest risk in third trimester, although being a diagnostic challenge when present.

Population level data on ethnicity from the UK and USA shows that appendicitis is less common in non-white groups, albeit with little understanding of why. Ethnic minority groups are conversely at higher risk of perforation, although this might be due to unequal access to care rather than predisposition; definitive evidence is lacking.

Neurogenic appendicitis has also been suggested as a causative mechanism of pain. Characterised by excess proliferation of nerve fibres into the appendix with over-activation of neuropeptides, this poorly understood condition may be relatively common, especially in children. From a case series of 29 patients, neurogenicity was present in both inflamed and normal appendix specimens. It may theoretically provide an explanation for improvement after normal appendectomy, although evidence for this and for its general importance is limited.

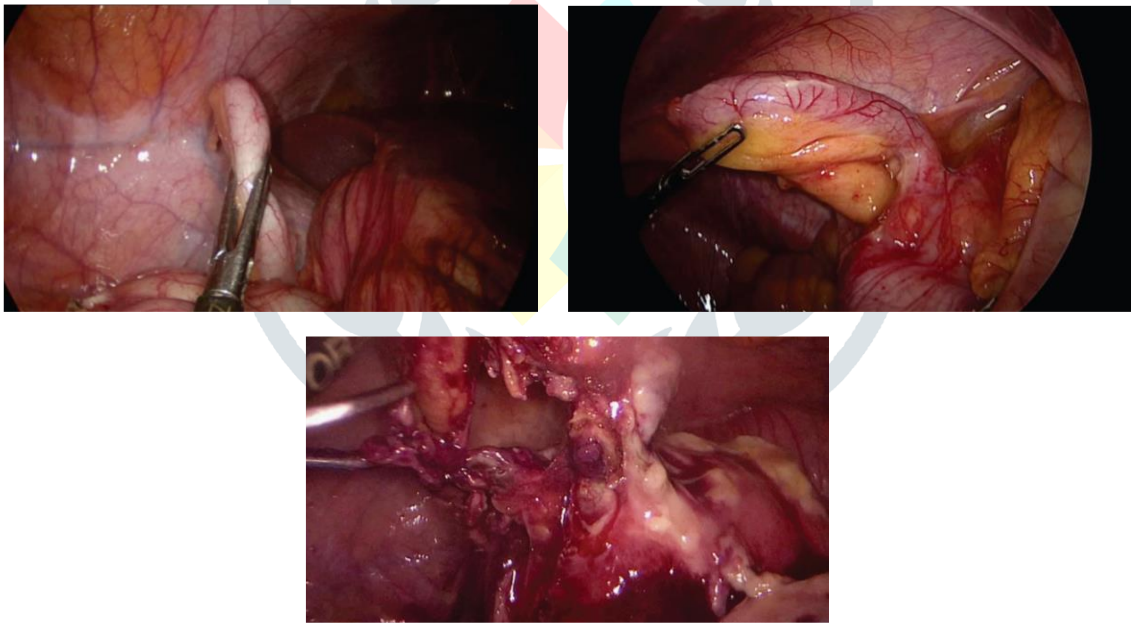


Figure 1: Macroscopic pathological features of appendicitis
(A) Macroscopically normal appendix. (B) Simple inflamed appendicitis. (C) Complex appendicitis showing perforation with pus formation.

A debated theory divides acute appendicitis into separate forms of acute inflammation processes with different fates. One is the simple inflamed appendicitis without gangrene or necrosis that does not proceed to perforation. This “reversible” form may present as phlegmonous (pus-producing), or advanced inflammation (but without gangrene or perforation) that may require surgery, or alternatively a mild inflammation who may settle spontaneously or with antibiotic therapy. In contrast, the more severe inflammatory type rapidly proceeds to gangrene and/or perforation. Data to support separate types of inflammation arises from clinical registries19 and laboratory studies. In population-based studies, the rate of non-perforated appendicitis declined in males, with even greater declines in females. However a similar decline in rate of perforated appendicitis was not seen. Although this points to disconnect between

perforated and non-perforated disease, it may also represent improved diagnosis with increased used of imaging over the period, reclassifying some previous labelled early appendicitis into other diagnoses.

Modern Diagnostic Strategies

Modern diagnosis aim to firstly confirm or eliminate a diagnosis of appendicitis, and secondly to stratify simple and complex disease when appendicitis is suspected. The optimum strategy that limits harm (e.g. radiation from imaging) whilst maintaining a high degree of accuracy has still not achieved consensus, representing the difficulty faced by patients and surgeons.

Biomarkers

Biomarkers are used to supplement history and clinical exam, especially in children, women of fertile age and the elderly where diagnosis is difficult. No inflammatory marker alone, including white blood cell (WBC) count, c-reactive protein (CRP) or other novel tests including procalcitonin, can identify appendicitis with high specificity and sensitivity. However, WBC count is obtained in virtually all patients being assessed for appendicitis, where available. A range of novel biomarkers has been suggested over the last decade, including bilirubin, but these lack external validity and repeatedly suffer from low sensitivity, meaning they are unlikely to come into clinical practice.

Clinical Decision Rules/Risk Scores

Each and every clinical sign for appendicitis alone has a poor predictive value. However, in combination the predictive ability is much stronger, although not with perfect accuracy. Consequently, a number of clinical risk scores have been developed, the purpose of the clinical scores are to identify low, intermediate or high-risk patients for appendicitis (figure 2), allowing further investigations to be stratified according to risk (figure 3).

The most widely used to date is the Alvarado score. Systematic review and pooled diagnostic accuracy study showed that the score has good sensitivity (especially in men) but low specificity, limiting its clinical impact and meaning few surgeons rely on it to guide management above and beyond their own clinical opinion. The predictive ability of each component of the recently derived modified Alvarado score in children is shown in supplemental table 1.25 recently the appendicitis inflammatory response score has been developed, and appears to outperform the Alvarado score in accuracy.

Transabdominal Ultrasonography

Initial reliance on ultrasound has been more recently guarded due to moderate sensitivity (86%, 95% confidence interval 0.83-0.88) and specificity (81%, 78%-84%%) shown through pooled diagnostic accuracy of 14 studies27, limiting its diagnostic ability. Due to the need for a specialist operator, it is frequently unavailable out of hours and at weekends, further limiting its usefulness. Its first line investigative role is greater in paediatric populations, who typically have thinner musculature, less abdominal fat than adults and a greater need for radiation avoidance.

Computed Tomography

In adolescent and adult patients, computed tomography has become the most accepted imaging strategy. In the USA, it is used in 86% of patients, with a sensitivity of 92.3%. This has led to a normal appendectomy rate of 6%. Uptake outside of North America is lower due to concerns over risk of radiation exposure in children and young adults, differing hospitals remuneration systems, unavailability outside of normal hours and absence of scanners in low resource hospitals.

In one RCT comparing low-dose versus standard-dose CT in 891 patients, the normal appendectomy rate was 3.5% versus 3.1% respectively, although these advanced technology scanners are not in wide scale use. For older patients at higher risk of malignancy, pre-operative CT is recommended to identify malignancy masquerading as (or, causing) appendicitis. Selective CT based on clinical risk scores is likely to target its use and justify radiation exposure.

Magnetic resonance imaging (MRI)

MRI for patients with an acute abdomen may eliminate the risks associated with radiation use in young patients. However, little is known about the exact utility and accuracy in acute abdomen. For one, there are

few units worldwide able to provide immediate access MRI at present. Second, MRI currently has no better accuracy than ultrasound in discriminating perforated appendicitis.

Diagnostic strategies in young female patients

In fertile female patients, the initial approach includes urinary pregnancy test to identify possible ectopic pregnancy and transvaginal ultrasound to identify ovarian pathology. In equivocal cases, a thorough clinical assessment (including pelvic examination) by on-call gynaecologists can differentiate alternative pathology and direct further investigations. Early laparoscopy has been suggested as a method to improve diagnosis in female patients with an equivocal diagnosis, having so far been assessed in single centre randomized trials. When compared to clinical observation and selective escalation, routine early laparoscopy increases the rate of diagnosis and may facilitate earlier discharge.

Differentiating simple from complex disease

At present, both CT and emergency MRI lack ability to discriminate between non-perforated and perforated appendicitis. This limits clinicians' ability to objectively stratify patients for short in-hospital delays prior to surgery or for selection to trials of non-operative treatment with antibiotics. Presence of an appendicolith in radiological imaging is associated with both a higher risk of antibiotic failure and recurrence, whereas the triad of CRP <60g/L, WCC<12x109 and age <60 years has been reported to predict antibiotic success.34
Treatment strategies

Non-operative management

Primary antibiotic treatment of simple inflamed appendicitis. Antibiotics have more recently been proposed as single treatment for uncomplicated appendicitis, but not without controversy. Meta-analysis of RCTs comparing antibiotics with appendectomy has shown that although antibiotic treatment alone can be successful, patients should be made aware of a failure rate at one year of around 25-30% with need for readmission or surgery (table 2). Pilot RCT suggests this strategy may also be effective in children, although similarly to adults, 38% require subsequent appendectomy during follow-up.

The RCTs have methodological limitations including different criteria for diagnosis, low inclusion rate, inadequate outcome measures and different follow-up between groups. Importantly, some studies did not confirm diagnosis with imaging, which in combination with substantial crossover between study arms, has led some surgeons to question the validity. Within the most recent meta-analysis, three studies originated from Sweden and one from France, meaning that these findings may not be automatically generalizable worldwide due to potential ethnicity and health care access issues.

Until more accurate selection criteria emerge (based on combinations of clinical risk scores and imaging) for patients or subgroups who are likely to succeed in the long term from primary antibiotic treatment, suitable patients with mild symptoms (representing mild to moderate appendicitis) should ideally be entered into randomized clinical trials, or at minimum be counseled about a 25-30% one year failure rate.

Choice of antibiotic regimen

Antibiotics with aerobic and anaerobic coverage for ordinary bowel bacteria should be given, taking into account local resistance patterns and the potential for heterogeneous etiology. Antibiotics have been given intravenously for one to three days in all the referred trials; total oral therapy has not been tested. Therefore, it is reasonable to recommend at least one day of intravenous treatment and also hospital surveillance considering that rescue appendectomy has been judged necessary for 5-23% of patients. Oral antibiotics have subsequently been given for 7-10 days as part of this regimen, illustrating the potential for slower recovery in some patients, albeit whilst avoiding early surgery. The length and nature of treatment should be subject for future research.

Spontaneous resolution

Periods of active observation resulting in resolution suggest that spontaneous resolution of simple appendicitis is possible. RCTs comparing active observation with antibiotic treatment have not been made and therefore it is impossible to know whether the reported recovery rates (77-95%; table 2) after primary antibiotics represent a true treatment effect or just the natural course of simple, acute appendicitis. Safe

selection criteria for active observation alone to treat confirmed appendicitis do not exist and so it is not recommended as a current treatment strategy outside trials.

Appendiceal abscess

Pre-surgery intra-abdominal or pelvic abscess is found in 3.8% (95% CI 2.6-4.9) of patients presenting with appendicitis and should be suspected in those presenting with a palpable mass. Whilst pre-hospital delay was considered a traditional risk factor, evidence of disconnect between the strata of disease severity means that some patients may be at risk of abscess formation despite prompt treatment.21 Meta-analyses on mainly retrospective studies recommend conservative treatment consisting of antibiotics with percutaneous drainage of abscess if needed. Immediate surgery is associated with higher morbidity (pooled odds ratio 3.3, 95% CI 1.9-5.6) and risk of unnecessary ileoceacal resection; the recurrence rate is 7.4% (95% CI 3.7-11.1).

Follow-up after non-operative management

Following conservatively treated abscess, 1.2% of patients will be found to have malignancy.41 Follow-up with colonoscopy and/or CT after conservatively treated appendiceal abscess is recommended in patients aged ≥40 years, or those with symptoms or laboratory/radiologic signs that are suspicious of colonic malignancy. The rate of occult appendiceal malignancy after initial successful antibiotic treatment for simple (non-perforated) appendicitis is unknown. Long-term (beyond one year) evidence of outcome and optimum follow-up of is lacking; only one study reports a recurrence rate of 14% after two years.42 Extrapolating from abscess, patients ≥40 or those with other suspicious symptoms should be considered for further investigation to identify malignancy, which may include interval appendectomy in selected cases based on age, on-going symptoms and/or radiological findings.

OPERATIVE TREATMENT

Timing of Surgery

Outcomes in relation to timing of surgery have been controversial, especially since disease presentation may vary with time of day. Meta-analysis of 11 non-randomized studies (8858 patients) showed that short in-hospital delays of 12-24 hours in selected, stable patients were not associated with increased risk of perforation (odds ratio 0.97, 95% CI 0.78-1.19, p=0.750).43 Notably, allowing a delay or, rather, an increased observation time in patients with equivocal signs, with renewed interval clinical assessment increases diagnostic accuracy without increased risk of perforation in acute appendicitis. Delays can aid service provision, avoiding night-time operating and increasing access to daytime technological resources where available. Emergency surgery models can structurally separate elective from emergency care, reduce night-time surgery and improve emergency theatre efficiency. Planned early laparoscopy in patients with an equivocal diagnosis can improve the diagnostic rate and facilitate early discharge (without increasing the risk of complications). Ambulatory appendectomy, leading to day of surgery discharge, has been reported from single centres and is potentially attractive to improve patient satisfaction and reduce costs in patients with simple inflammation.

Surgical approach

Use of laparoscopic appendectomy depends on availability and expertise, with equivalent results achievable from urban centres in India and Africa compared to the UK and USA47. The concept of low-cost laparoscopy, using simple, inexpensive, reusable devices can lead to equivalent costs and outcomes even in complex appendicitis.

Role of laparoscopic appendectomy in specific populations

Laparoscopy is safely performed in children and the obese with favorable outcomes and low risk profile. Its availability and use depends on expertise and access to specialist equipment and so does not need to be mandated. Appendicitis in pregnancy remains challenging due to displacement of the caecum by the growing uterus. Meta-analysis of low-grade observational evidence suggests that laparoscopic appendectomy in this group is associated with a higher rate of foetal loss compared to an open approach (3415 women, 127 events and relative risk 1.91, 95% CI 1.31-2.77). However, selection bias and confounders might have influenced these observational results; open appendectomy remains as standard. A selection of best available evidence for surgeons guiding intra-operative decision-making.

Novel surgical technologies

Single incision laparoscopic surgery (SILS) and low-cost SILS techniques (e.g. "surgical glove port", supplemental videos 1 and 2) have been recently described and may be performed with inexpensive equipment and routine instruments, leading to satisfactory functional and cosmetic results. Meta-analysis of 7 RCTs comparing SILS to conventional laparoscopy demonstrate no real differences for SILS and considerable heterogeneity exist between studies.

Natural orifice transluminal endoscopic surgery (NOTES) is a technological adaptation of laparoscopy that is available in well-funded centres. Its role and application (transvaginal approach in women; transgastric approach in both genders) is controversial and debated.

Since the role of these technologies seems to be in providing marginal gains to selected patients (which may only be neutral or at best improved cosmetic outcome at the cost of longer operative times and higher post-operative pain), widespread adoption seems unlikely in light of raised cost and increased procedural complexity.

Administration of pre-operative and duration of post-operative antibiotics

Pre-operative prophylactic antibiotics should be started well before skin incision commences (>60 minutes) and may be initiated as soon as the patient is scheduled for surgery. Broad coverage of gram-negatives is warranted based on studies on microbiology cultures. Metronidazole given intravenously is usually well tolerated, and given alone or in combinations in most studies. Piperacillin/ tazobactam are also adequate, in particular if perforation or complex disease is suspected on pre-operative diagnosis. Meta-analysis of randomized trials comparing prophylactic pre-operative antibiotics to placebo showed significant reduction of wound infection with either single agent (11 studies, 2191 patients, OR 0.34, 95% CI 0.25-0.45) or multiple agents (2 studies, 215 patients, OR 0.14, 95% CI 0.05-0.39).

Administration of post-operative antibiotics is stratified by disease severity. Routine post-operative antibiotics following surgery for simple inflamed appendicitis are not recommended. Currently, 3-5 days of post-operative intravenous antibiotics are recommended for complex, perforated appendicitis. Adjusted observational data suggests that three days post-operative antibiotic duration is as effective as 5 days. Shorter duration of antibiotics based on cessation following resolution of bedside clinical parameters (core temperature <38 degrees C for 24 hours, tolerated two consecutive meals, mobilizing independently, requiring only oral analgesia) may be equally as efficacious, as proven in pediatric populations. Patients should be informed about a continued risk of post-operative abscess formation in perforated appendicitis.

Table 1: Clinical trials comparing primary antibiotic treatment vs. surgery for acute appendicitis

	Study design	Patients (n)	Antibiotic treated patients (n)	Age (years)/ gender	Diagnosis	Antibiotic regimen (days)	Recovery rate (%)	1-year failure (%)	1-year efficacy** (%)
Eriksson 1995[37]	RCT	40	20	≥18	US	iv 2 oral 8	95	37	60
Styrud 2006[38]	RCT multicentre	252	128	18-50 male	clinical	iv 2 oral 10	88	14	76
Hansson 2009[39]	RCT multicentre	369	119	≥18	clinical (+US/CT)*	iv 1 oral 9	91	14	78
Vons 2011[40]	RCT multicentre	239	120	≥18	CT	iv 2 oral 8	88	25	68
Svensson 2014[36]	RCT	50	24	5-15	US (+CT)*	Iv 2 oral 8	92	5	62
Turhan 2009[73]	Prospective interventional	290	107	≥16	US or CT	iv 3 oral 7	82	10	74
Hansson 2012[74]	Prospective interventional	558	442	≥16	clinical (+US/CT)*	iv 1 oral 9	77	11	69
Di Saverio 2014[42]	Prospective interventional	159	159	≥14	clinical (+US/CT)*	total 5-7	88	13	77
APPAC study (on-going; NCT01022567)	RCT multicentre (Estimated completion 2025)	600	-	-	-	-	-	-	-

CT = computer tomography
US = ultrasound
IV = intravenous
* If judged clinically necessary
** Overall efficacy at one year including recurrence

Figure 1: Panel title: Macroscopic pathological features of appendicitis

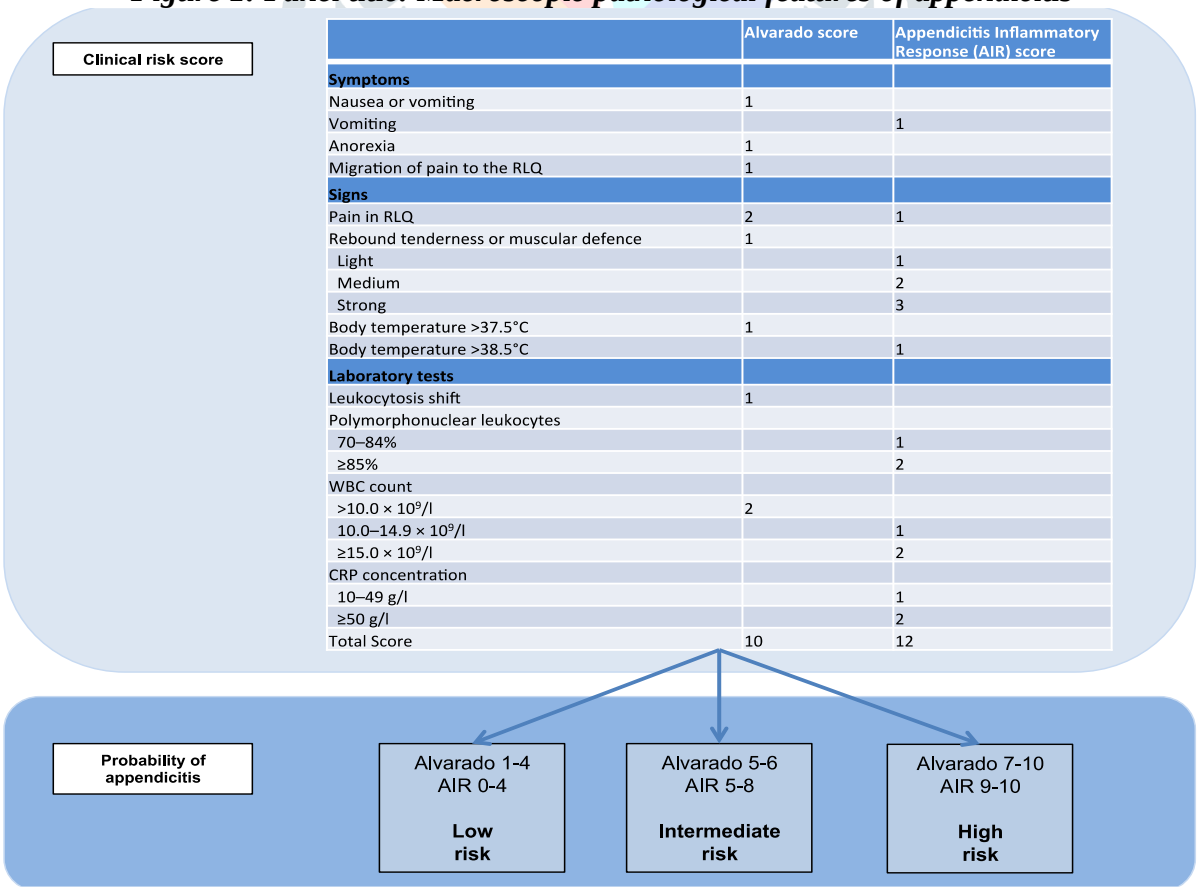
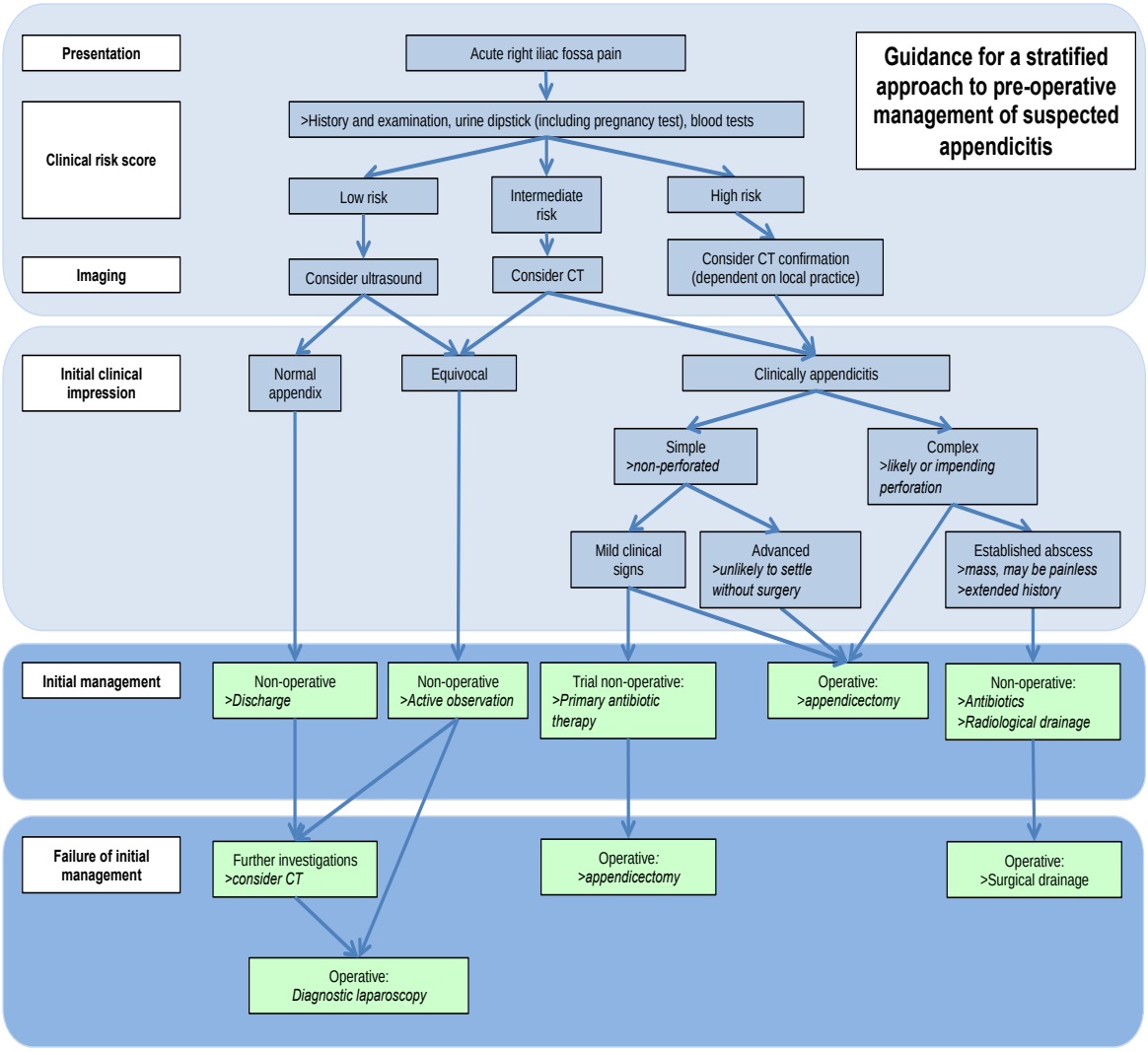


Figure 3: Flowchart illustrating guidance for a stratified approach to pre-operative management of suspected appendicitis



Definition of Appendicitis

***Phlegmonous appendicitis*.** Inflammation with transmural infiltration of neutrophil granulocytes. Micro-abscesses, oedema or vascular thrombi may, or may not, be present. Transmural necrosis or perforation is not present.

***Gangrenous appendicitis*.** Inflammation with transmural infiltration of neutrophil granulocytes and transmural necrosis of the appendiceal wall. No signs of perforation are detected at surgical removal.

***Perforated appendicitis*.** Macroscopic findings of perforation at operation and transmural inflammation at histopathological examination.

***Appendiceal abscess*.** A collection of pus surrounding a perforated appendix found during operation, or as indicated by diagnostic imaging in non-operated patients.

***Non-perforated appendicitis*.** Phlegmonous or gangrenous appendicitis.

***Advanced appendicitis*.** Gangrenous or perforated appendicitis or appendiceal abscess.

***Antibiotic treated appendicitis*.** Non-operated appendicitis that was verified by unequivocal signs of appendicitis at diagnostic imaging and treated with antibiotics.

***Non-treated appendicitis*.** Unequivocal findings of appendicitis at diagnostic imaging in a patient who received no surgical or antibiotic treatment.

OBJECTIVES OF THE STUDY

The objectives of the study are as follows:

1. To assess the construct and validate a diagnostic appendicitis score.

2. To evaluate new inflammatory markers for inclusion in the score
3. To explore the effect of implementing a structured management algorithm for patients with suspected appendicitis.
4. To compare the outcome of management with routine diagnostic imaging versus observation and selective imaging in equivocal cases.

METHODOLOGY OF THE STUDY

In a broader sense of the term, methodology considers all techniques, strategies, approaches to be applied at every phases of conducting the research, especially, in collecting, processing and analyzing information. Methodological consideration also involves the reliability and validity of techniques and findings. Documentary analysis has used for the study. Data are facts, figures and other relevant materials, past and present, serving as the bases for study and analysis.

Study Design: It was descriptive study. A descriptive, cross sectional study was conduct to achieve the objectives of the study.

Study Population: The study population was focused on people who are 18-40 years of age. The study populations was those entire participant, who are comes for appendicitis treatment on Dinajpur Medical College & Hospital, Dinajpur; Nurses of Dinajpur Medical College & Hospital, Dinajpur and willing to participate this program.

Study Area: The study was conduct in Dinajpur Medical College & Hospital, Dinajpur.

Sampling Method and Technique: The study population was 300 respondents in Dinajpur Medical College & Hospital, Dinajpur. 300 respondents were selected through purposive sampling.

Data Collection Procedure: Data was collected from primary Sources. The data was collected purposively selected respondent for mentally ill patients. The secondary data collection method has focused on extensive literature review covering relevant national-level studies and reports. Websites of relevant organizations was analytically surfed through. Besides, newspapers, conference proceedings, working papers, Journals, Articles, Term paper, Research Report, and other sources of information will be also explored to the optimum level. All the data obtained from secondary sources was analyzed and eventually a conclusion is drawn resulting in incorporating our ideas and experiences.

Data Collection Tools: Questionnaires was used as a form of collecting data. Data was collected through appropriate questionnaire which was prepared for the study. Closed-ended questions were used in the questionnaire. A questionnaire in English was developed and finalized through pre-test and used for data collection.

Development of Questionnaire: Before preparation of questionnaire, secondary have been reviewed and drafted the initiation questionnaire. Later on after field test it has been finalized.

Methods of Data Collection: Data was collected through interview method, i.e. Interviewers collect data from the respondents through face to face interview.

Quality control method: Data quality controlled was through tools verification (compare to standard tools) questionnaire, check editing, data entry, entry and minimizing response errors through prove question. Here, we use the data collected from dependable sources. Supervisor was checked our filed work for quality.

Data Processing and Data Analysis: The data analysis stage was really an attempt to answer the relevant research questions by examining and assessing the collected information to identify patterns and meanings. The gathered data will be interpreted and analyzed. After entire collecting data, it was s computerized using suitable data entry software, such a SPSS; MS. Excel etc Data was analyzed by using SPSS software. Statistical analysis was performed by using SPSS (Statistical Package for Social Sciences) for windows version 16.

CONCLUSION

In conclusion, the complications and adverse outcomes of appendicitis are higher among Bangladeshi population. The number of cases treated in this study was found to face these crises due to misdiagnosis and delayed referral, which caused life-threatening complications. If acute appendicitis is diagnosed early and surgical management conducted, then usually outcomes have minimum difficulties. In Bangladeshi populations, disease presentation is late and is associated with a high perforation rate, translating into increased morbidity and even mortality. Once acute appendicitis is diagnosed, expedient surgery and appropriate peri-operative antibiotics can minimize morbidity and mortality. Caregivers should be suspicious of appendicitis and present patients with abdominal pain to the hospital early. Physicians in primary/secondary level healthcare centers should prioritize appendicitis and refer patients before surgical consultation. Early and accurate management can reduce the burden of the disease.

RECOMMENDATION

- In addition to early and accurate diagnosis of disease, evaluation of the condition, and setting a plan for proper management, the following recommendations should be considered.
- Diagnosis of the disease should be based mainly on the history, with examination and USG being used to exclude other differential diagnoses and to evaluate the condition.
- Early diagnosis and prompt treatment are necessary for patients with suspected appendicitis to avoid morbidity and mortality.
- Patients with complicated appendicitis should be strictly monitored and managed accordingly in the postoperative period to avoid complications.

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