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C-REACTIVE PROTEIN INDEPENDENTLY PREDICTS FAILURE OF ANTIBIOTIC NON-OPERATIVE MANAGEMENT OF EARLY UNCOMPLICATED ACUTE APPENDICITIS IN ADULTS.

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ABSTRACT

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KEYWORDS: Acute Appendicitis, ALVARADO score, Appendicitis Inflammatory Response (AIR) score, C-Reactive Protein, Non-Operative Management, RIPASA score.

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KEYWORDS: Acute Appendicitis, ALVARADO score, Appendicitis Inflammatory Response (AIR) score, C-Reactive Protein, Non-Operative Management, RIPASA score.

INTRODUCTION

Acute appendicitis (AA) is one of the most common abdominal emergency requiring surgery with lifetime prevalence of 7%.[1] As such it posed a great burden to modern healthcare system.[2] Majority of cases present as early uncomplicated acute appendicitis (EUAA), defined as those presenting with AA without signs of generalized peritonitis, appendicular mass/abscess or rigid abdomen, of which the latter only represents 20% of AA cases.[3] Even though appendectomy historically considered as mandatory and a preferred treatment, it is not a harmless operation especially in complicated cases.[4,5,6] Overall com-

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plication rate for open or laparoscopic has been reported as 11.1% and 8.7% respectively.[7] In addition, 3% of patients who have had appendectomy are at risk of developing adhesive small bowel obstruction (ASBO) in 10 years' time.[3] Therefore, avoiding surgery especially in patients with EUAA who otherwise would have had surgery could therefore improve overall risk benefit ratio of the treatment.[3]

There is a growing interest in non-operative management (NOM) with antibiotics for EUAA with numerous publications from observational cohort studies, randomized controlled trials and meta-analyses. Several randomized controlled trials (RCTs) and meta -analyses have reported such approach was safe and as effective as a primary treatment with significant reduction in morbidity although with considerable one-year recurrence rate of 23%.[4] In addition, latest guideline by World Society of Emergency Surgery (WSES) in 2016 has stated antibiotics non-operative management (ANOM) therapy can be successful in selected patient with EUAA who wishes to avoid surgery.[6]

However, a proportion of patients do failed ANOM therapy, for whom would later require appendectomy. By establishing variables that can predict failure of ANOM therapy, surgeons can make appropriate decisions on who would benefit from ANOM and who would need appendectomy. The primary objective of the study is to identify possible predictors for failure of ANOM in EUAA. Secondary objectives are to determine success rate of ANOM in the overall management of EUAA and its outcome with comparison to those who were diagnosed with complicated AA.

MATERIALS AND METHODS

This retrospective comparative cohort study was conducted at Kuala Krai Hospital, Kelantan, Malaysia from January until December 2016. Kuala Krai Hospital is a secondary specialist district hospital and provides care to nearly 250 000 populations. All adult patients, greater than 12 years of age, clinically suspected of having EUAA were included. Exclusion criteria were AA presenting with appendicular mass/abscess or with generalized abdominal sepsis (generalized peritonism) considered as complicated AA, recurrent AA and AA in special group such as in pregnancy. Sample size required was 62 patients based on calculation of expected success rate for ANOM of 80% (p=0.8), type 1 error of 5% and absolute error/precision of 0.1 (d=10%).[9]

Diagnosis of acute appendicitis.

We developed our local guideline for the management of AA since 2012 which is primarily based on the clinical scoring system, Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) score.[8] It was revised in 2014 and ANOM was included and considered as an option for suspected EUAA (figure 1).

Selection of initial treatment (complicated AA versus EUAA).

Recruited participants were labeled into 3 groups based on their diagnosis and treatment outcomes, and analyzed accordingly; group 1 (complicated AA), group 2a (EUAA successful on ANOM) and 2b (failed EUAA on ANOM). All suspected complicated AA cases (Group 1) were offered immediate surgery but for EUAA cases (group 2a&b), empirical antibiotics were started and admitted for active observation. Suspected complicated AA cases were those with generalized peritonitis at presentation or suspected mass or sustained SIRS (systemic inflammatory response syndrome, excluding white cell count) even after 6-12 hours of presentation. Otherwise they were considered as EUAA and were offered ANOM. Definitive diagnosis and target were made and achieved within 24 hours of admission respectively. Worsening or sustained abdominal pain or persistent SIRSs were considered as failed ANOM (Group 2b) and surgery

was offered. Otherwise, those who responded to antibiotics were later discharged home with oral antibiotics and considered as successful ANOM (Group 2a) (Figure 1).

Intra-operative grading of severity of acute appendicitis.

For patients who underwent surgery, intra-operative grading of AA was based on World Society of Emergency Surgery (WSES) grading system. Grade 0; normal looking appendix, Grade 1; inflamed appendix (hyperemia and oedema and/or fibrinous exudates), grade 2; presence of necrosis, grade 3; inflammatory mass (phlegmon or abscess) and grade 4; perforated appendicitis with diffuse peritonitis. Grades 0 and 1 were considered as EUAA whereas Grade 2-4 were considered as complicated AA.

Predictive variables of failure of antibiotic NOM

Other than demographic data, parameters analyzed were neutrophil lymphocyte ratio (NLR), C-reactive protein (CRP) and three clinical appendicitis scores; RIPASA[8], Alvarado[9,10] and Appendicitis Inflammatory Response score (AIR).[11] All the blood tests were taken only at the time of admission. The frequency of advanced imaging such as ultrasound or CT scan used was also determined. Morbidity was defined as all complications developed other than Clavien-Dindo type 1 and mortality as in-hospital death.[12]

Statistical analysis

Clinical data were recorded and analyzed using SPSS version 18. Independent student t-test and Pearson Chi square was used for quantitative and qualitative data respectively. A value of $p < 0.05$ was considered as statistically significant. Parameters with $p<0.25$ were subsequently included in multivariate analysis using logistic regression model. Subsequent analysis was done to determine AUROC (Area Under the Receiver Operating Characteristic curve) followed by sensitivity analysis. Complicated AA (Group 1) was included for comparison with EUAA group (Group 2a&b) but predictive variables analysis was only carried out on Group 2 EUAA cases.

RESULTS

One hundred and twelve patients (n=112) were identified within the study period suspected of having AA. Eighteen cases were excluded (recurrent appendicitis; n=12, appendicular mass; n=4, acute appendicitis in pregnancy; n=1 and TB gut; n=1). Of remaining 94 patients, 29 patients (30%) were diagnosed as complicated AA and almost all (n=26, 90%) were operated (group 1). Three cases were not operated due to patient refusal (n=1) and poor general medical status (n=2). All three cases were successfully treated with antibiotics. Sixty-five patients (70%) were labeled as EUAA and were managed primarily with antibiotics (ANOM). Following active observation for 24 hours, 16 patients (24.6%) failed ANOM based on our criteria (group 2b) and was operated on. The remaining 49 patients (76%) were successfully managed with ANOM and discharged (group 2a). Negative appendectomy rate (NAR) in our study was 4% (n=3).

Demographics and clinical variables of complicated AA and EUAA are shown in table 1. There was no significant difference in mean age, NLR and Alvarado score between the two groups. Significant differences were noted for CRP level (129.1 vs 59.9 mg/L; p=0.0001), RIPASA score (10.2 vs 8.9; p=0.002) and AIR score (8.4 vs 6.9; p=0.0001) between the groups on univariate analysis. The use of advanced imaging, either ultrasound or CT scan was similar (p=0.098) and at very low rates. Forty percent of complicated AA cases had either ultrasound or CT and only 10% received pre-operative CT scan. Similarly, majority of EUAA cases received no imaging at all (77%). Majority of cases in both groups 1 and 2b requiring surgery were performed via open

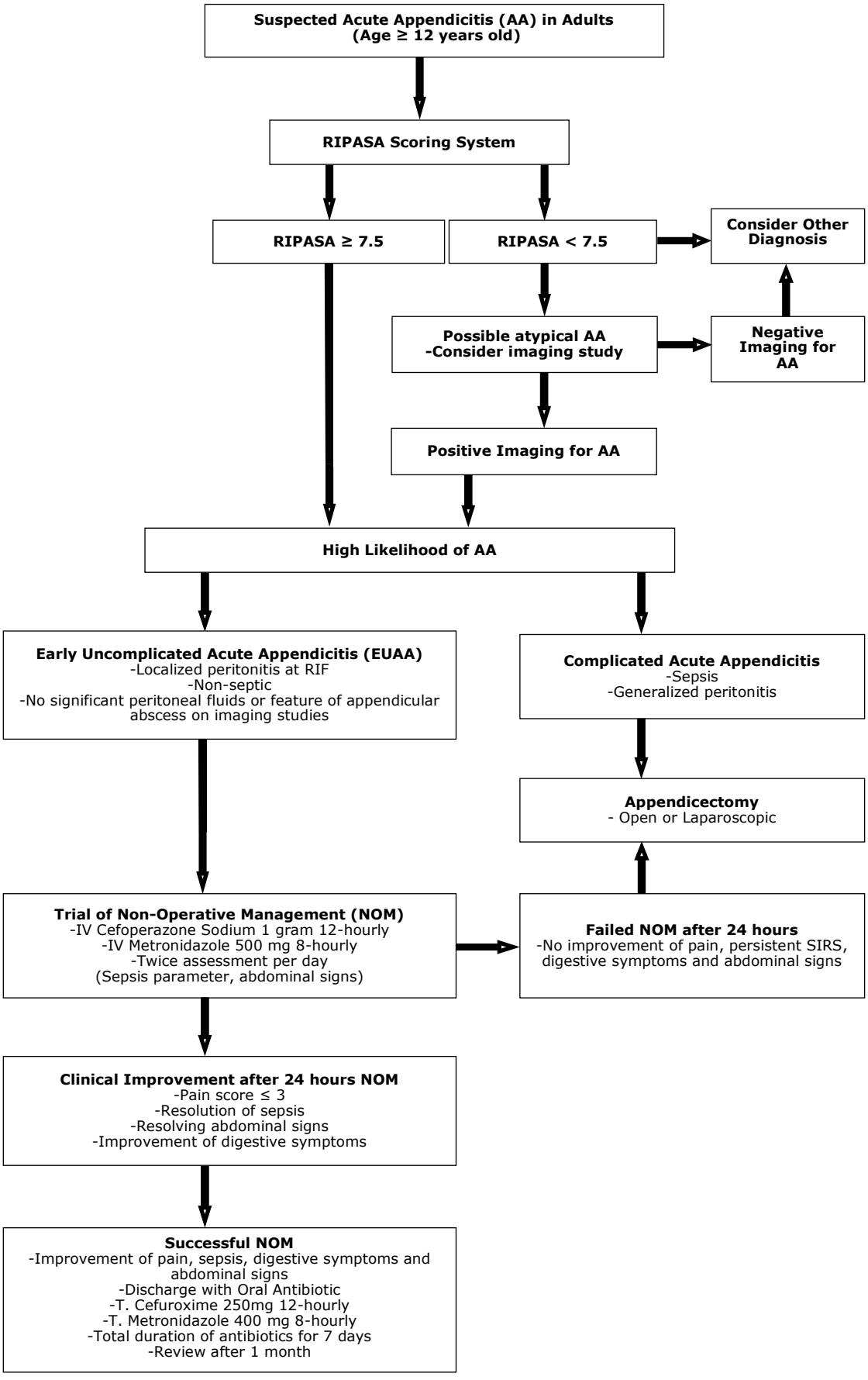


Figure 1: Diagnostic algorithm for suspected acute appendicitis at Kuala Krai Hospital.

Table 1: Demographics and Clinical features for all cases.

Variables		COMPLICATED AA (n=29) (Group 1)	EUAA (n=65) (Group 2a + 2b)	*p* Value
Age (year)		27.6 (13.2)	23.8 (9.77)	0.129
Gender	**Male**	14	48	0.016
	Female	15	17	
Blood investigations	**NLR**	10.8 (6.86)	8.3 (6.48)	0.095
	CRP	129.1 (53.61)	59.9 (57.46)	0.0001*
Duration of pain/ (hours)	**<12H**	0	9	0.004 *
	12-24H	4	27	
	24-48H	7	9	
	>48H	18	20	
Clinical Prediction Rules	**RIPASA score**	10.2 (1.64)	8.93 (1.72)	0.002 *
	ALVARADO score	7.5 (1.64)	7.1 (1.73)	0.28
	AIR score	8.4 (1.68)	6.9 (1.55)	0.0001*
Imaging	**No imaging done**	18	50	0.098
	USG	8	14	
	USG and CT	1	1	
	CT only	2	0	
Operative approach	**Open**	20	12	0.869
	Laparoscopic appendectomy	2	2	
	Laparoscopic converted open	4	2	
	Laparotomy	0	0	
Intraoperative diagnosis	**Grade 0**	2	1	0.019 *
	Grade 1	6	8	
	Grade 2	3	5	
	Grade 3	3	2	
	Grade 4	12	0	
Morbidity	**No**	22	65	0.0001*
	Yes (See footnote)	7	0	
Mortality	**No**	28	65	0.123
	Yes	1	0	
Total stay in days		5.5 (6.13)	2.5 (1.29)	0.0001*

Footnote: Morbidities included Post-operative ileus (n=3), Early adhesive small bowel obstruction (n=1), Residual abscess (n=2), Deep surgical site infection (n=1). NLR: neutrophil lymphocytes ratio; CRP: C-reactive protein.

methods (78%). Seventy percent of presumed complicated AA cases preoperatively were correctly diagnosed as evidenced by WSES grade 2, 3 and 4 intra-operatively. Excluding six cases of inflamed appendicitis and two cases of normal appendix, our true rate of complicated appendicitis was 21% (20 patients). Patients with complicated AA had longer in-hospital stay compared to EUAA cases (5.5 vs 2.5 days; p=0.0001). There were no morbidities or mortality in EUAA cases but seven cases (7.4 %) developed post-operative complications in the complicated AA group. The post-operative complications were post-operative ileus (n=3), early adhesive small bowel obstruction (n=1), residual abscess (n=2), deep surgical site infection (n=1).

Table 2 showed the comparison of pre-operative variables between EUAA Group 2a (Successful cases; n=49) and EUAA Group 2b (Failed cases; n=16). Based on univariate analysis, only two significant pre-operative variables were identified. CRP level was significantly higher in EUAA Group 2b than EUAA Group 2a (108.9 vs 44.5 mg/L; p=0.0001). EUAA Group 2a had much shorter duration of

Table 2: Clinical Variables of Success and Failure in antibiotic Non-Operative Management Groups.

Variables		EUAA SUCCESS (n=49) (Group 2a)	EUAA FAILURE (n= 16) (Group 2b)	*p* Value
Age (year)		24.3 (8.83)	22.4(12.45)	0.5
Gender	**Male**	37	11	0.5
	Female	12	5	
Blood investigations	**NLR**	8.9 (7.11)	6.7 (3.75)	0.246
	CRP	44.5 (40.83)	108.9 (75.23)	0.0001*
Duration of pain/ (hours)	**<12H**	9	0	0.003
	12-24H	23	3	
	24-48H	7	2	
	>48H	10	11	
Clinical Prediction Rules	**RIPASA score**	8.7 (1.67)	9.5 (1.83)	0.136
	ALVARADO score	7.0 (1.56)	7.4 (2.19)	0.43
	AIR score	6.8 (1.52)	7.2 (1.65)	0.336
Imaging	**No imaging done**	41	10	0.221
	USG	7	6	
	USG and CT	1	0	
	CT only	0	0	
Total stay in days		2.2 (0.88)	3.6 (1.75)	0.0001*

NLR: neutrophil lymphocytes ratio; CRP: C-reactive protein.

pain (p=0.003). Sixty-five percent of patients from EUAA Group 2a presented with duration of pain of less than 24 hours, as compared to only 18% in EUAA Group 2b. As expected, total in-hospital stay was significantly lower in EUAA Group 2a compared to EUAA Group 2b (2.2 vs 3.6 days respectively; p =0.0001).

In multivariate logistic regression analysis, only CRP remains an independent predictor for failure of ANOM in EUAA cases (adjusted OR of 1.02, CI 1.007 – 1.032, p=0.002) (table 3). The AUROC for CRP was 0.775 (95% CI; 0.613-0.937, p=0.004: Figure 2). CRP ≥ 18 mg/L can predict failure for ANOM with sensitivity of 100%, specificity of 40%, positive predictive value of 34.3% and negative predictive value of 99% (Table 4).

Table 3: Stepwise Multivariate Analysis for EUAA Group (Group 2a: Success and Group 2b: Failure Group).

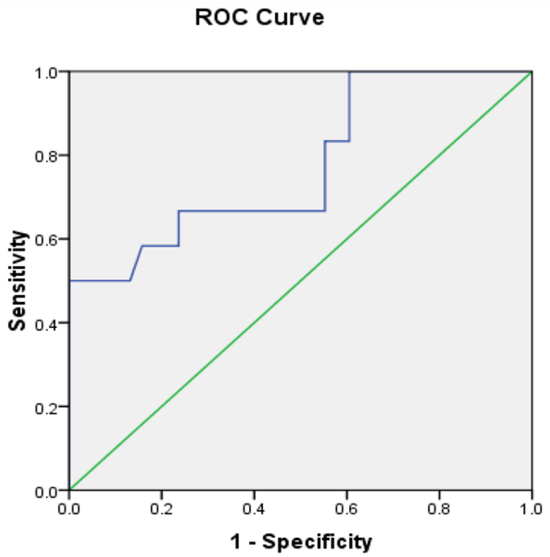
Variable	Adjusted	95% CI	*p* Value
CRP	1.02	1.007-1.032	0.002

CRP: C-reactive Protein

DISCUSSION

Recent few RCTs and meta-analyses have demonstrated the feasibility and safety of ANOM therapy in EUAA. Significant reduction in complication (31% relative risk reduction) with major cost saving are the additional benefits of ANOM. [13, 14, 15, 16.]

This study has identified several important findings. CRP is the only significant predictor that can objectively predict failure of primary ANOM therapy in EUAA group with satisfactory AUROC (0.77). Our success rate of ANOM (75%) was comparable to other published series; ranges from 70 to 90%. [1, 2, 4] In addition, diagnosis and severity of AA can be satisfactorily predicted using RIPASA score and resolution of SIRS within 24 hours of admission. We have demonstrated that our local algorithm based on RIPASA score and SIRS parameter is safe, effective and likely to be cost efficient. We have managed to reduce our NAR to 4% (3/94) even with limited usage of advanced imaging. We had neither major morbidity nor high rate of complicated AA for crossover patient in the EUAA group.



Diagonal segments are produced by ties.

Test Result Variable(s) Predicted probability				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.775	.083	.004	.613	.937

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 2: Area under operating curve (AUROC) for the use of CRP as a predictor for failure of non-operative antibiotics management of uncomplicated acute appendicitis.

Clinical scoring systems are well established tools for diagnosis of AA. Among all published scoring such Alvarado[9, 10], AIR[11] and RIPASA[8], the latter was used for few established reasons. [17, 18, 19] The former two clinical scores were designed and validated in non-Asian population. Studies have shown that performance of clinical prediction rules are usually less effective when applied outside original study population.[19] Khan et al have demonstrated low sensitivity (59%) and specificity (23%) of Alvarado in Asian population with NAR of 15.6%.[20] RIPASA score which was designed in Brunei has an excellent sensitivity (97.5%) and specificity (81.8%) with positive predictive value of 86.5%. It performs better than Alvarado and AIR score and suits well to our population.[8] It is interesting to note that, none of current available clinical scores such as RIPASA, Alvarado or AIR can predict failure of ANOM (p=0.136, p=0.43, p=0.336 respectively).

The rate of crossover to surgery within 48 hours of ANOM have been reported to be as high as 53%.[21] Therefore, it is imperative to identify this group of patients earlier to avoid potential morbidity. Furthermore our study has revealed that those who failed had significantly longer hospital stay (3.6 vs 2.2 days, p=0.0001). Unfortunately relevant data are scarce. A recent study by Vons et al also recognized a similar observation with regard to appendicolith.[3] Unfortunately, CT scan is not a routine investigation for AA in most hospital worldwide especially in developing country. Result of our study confirmed the role of CRP as a significant predictor and it is readily available and cheap. A triad of CRP < 60 g/L and TWBC < 12 000 and age < 60 years old predict antibiotic success in another study by Hansson et al.[2] Most prior series on CRP have demonstrated its role in predicting late or complicated appendicitis, CRP > 10 mg/L has sensitivities of 65-85% and specificities of 59-73%.[22, 23, 24] Shindoh et al also proved that, CRP > 5 mg/dL with additional CT findings could identify complicated appendicitis with

Table 4: Sensitivity analyses for each CRP level in predicting failure of non-operative antibiotics management of uncomplicated acute appendicitis.

CRP level (mg/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value
≥ 18	100.0	39.5	34.3	100	0.009
≥ 20	83.3	44.7	32.3	89.5	0.081
≥ 25	66.7	44.7	27.6	81	0.485

PPV: positive predictive value; NPV: negative predictive value.

much higher sensitivity (89%) and specificity (68%).[25] Based on our current data, we believe patients in the EUAA Group 2b with CRP ≥ 18 mg/L in our series (n=7) that were initially labeled as EUAA, probably should have been better and correctly labelled as complicated AA. However, none of them had generalized appendicitis or significant morbidity postoperatively.

ANOM has to be considered in all EUAA cases for few established reasons. Since majority of AA occur in young healthy patients, treatment plan has to be decided based on long-term outcome. Complication rate following surgery and risk of failure of ANOM has to be established or audited. Decision analysis made from patients' perspective revealed, if overall complication is < 11% and risk of failure > 40.3% then surgery will undoubtedly be a better option.[26] Well known morbidities which potentially avoidable are reduction in NAR as demonstrated by our study and adhesion related small bowel obstruction (ASBO). In a recent large population -based study in Italy, 1.3% of their patients were readmitted for ASBO after a median of 11 months following appendectomy and 60% of them required surgery.[4] Wu et al and a recent NOTA study (Non-Operative Treatment for Acute appendicitis study) also concluded ANOM had positive impact on patients, OT utilization as well as health care cost.[5, 27] To date, one Cochrane review, 8 meta-analyses, 5 systematic reviews and 7 RCTs have been published and most concluded that majority of patients with EUAA can be treated with ANOM therapy with good outcomes. What remains controversial is its long-term efficacy, which ranges between 60% - 90.8%. [28]

We have demonstrated that 75% of EUAA cases can be successfully managed with ANOM despite the limited usage of advanced imaging with negligible morbidities. In addition, those who crossover, only 43% of them had complicated AA but none had generalized peritonitis. This is in accordance to previous meta-analysis which revealed no risk of perforation or severe peritonitis even when operation was delayed by initial antibiotics approach.[1] In contrast, a latest systematic review by Podda et al revealed the opposite, significantly higher rate of complicated AA with peritonitis during surgery in antibiotics than operated group (19.9% vs 8.5%).[24] Further studies are obviously warranted. NAR has fallen in the past decade in countries with early access to CT scan and diagnostic laparoscopy as in USA (6%) and Switzerland (6.1%)[2, 23] Interestingly our study reported NAR of only 4% despite the limited usage of CT scan or laparoscopy.

The main drawback of ANOM is recurrence but there is currently no accepted guideline set up yet regarding its definitive management.[26] It annual rate ranges between 13.8 – 27%. [2, 6, 13, 28] The recurrence are typically milder and those requiring surgery often did not experience significant complications.[1] Based on available data, we can assume our recurrence rate was around 11% as only 12 cases (12/112) were managed in 2016.

There are few limitations from our study being retrospective in nature. We could have missed few patients even though two independent medical officers have gone through annual admission and operative data. All of our suspected cases were not confirmed to have appendicitis as only 46% of them underwent surgery. Despite that, our mean score for either RIPASA (9.5) or AIR (7.6) was much higher unlike in NOTA study (mean AIR; 4.9) which also use clinical rather than radiological diagnosis.

CONCLUSION

The current management of AA is not "one size fits all" thus not all degrees of AA requires an appendectomy. A shared decision

making together with the patient must be done with informed consent for each approach. ANOM should be considered in all patient with EUAA especially those with CRP < 18 mg/L and active observation can possibly be extended to 48 hours in order to reduce crossover or failure rate (high negative predictive value; 99%). Those with CRP ≥ 18 mg/L should be consented for appendicectomy as they are likely to fail ANOM. Our local management algorithm based on RIPASA score appears safe and potentially cost effective especially in rural hospital. CRP, which is cheap and readily available, could be utilized to predict the failure of ANOM for EUAA.

DISCLOSURE

All authors have contributed to the manuscript equally. None of the authors have direct or financial conflicts of interest with this paper and material contained herein.

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