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Antibiotics alone for uncomplicated acute appendicitis in high operative risk adult patients: analytical review of RCTs and proposal of evidence based treatment decision

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Summary. *Background:* Clinical trials have so far shown controversial results as regards the standard of care for treating uncomplicated acute appendicitis (uC-AA). High operational risk adult patients (HORAP) could represent selected patients where primary antibiotic conservative therapy (pACT or A) could be indicated. *Methods:* We carried a comprehensive search of the PubMed searching engine in the English language scientific literature from 1995 to 2015, using medical subject headings "antibiotics", "uncomplicated appendicitis", "appendicectomy", "conservative treatment", "surgery" and "randomized clinical trial". All RCTs comparing the outcomes of pACT versus primary surgical open or laparoscopic appendectomy (pSOLA or S) as primary treatment options for uC-AA were identified. Inclusion criteria for our analytical review were RCTs evaluating outcomes in terms of or related to all of the following four parameters: treatment efficacy, post therapeutic/operative complications, in hospital length of stay (LOS) and recurrence. *Results:* The conclusion of all five RCTs considered antibiotics alone in the treatment of AA as an efficient and non inferior therapeutic option respect to surgery. Primary ACT was characterised by a higher LOS, a higher rate of recurrence and a lower rate of postoperative complication than pSOLA. *Conclusions:* Based on the current body of evidence, an appropriate pACT could be a rational tailored primary treatment option for CT proven uC-AA in HORAP. Accurate diagnoses and surgical risk stratification in patients with uC-AA could aid decision making for target therapy. However, results of large sample prospective multicenter RCTs are required to routinely recommend pACT for uC-AA in the clinical practice. (www.actabiomedica.it)

Key words: antibiotics, uncomplicated appendicitis, appendicectomy, conservative treatment, surgery, randomized clinical trial

Introduction

Acute appendicitis (AA) in adult patients is the most commonly encountered cause of abdominal emergency surgery worldwide (1). Suspected (S-AA), uncomplicated (uC-AA) or complicated (C-AA) AA represent the main clinical presentations of this illness. Primary appendicectomy is without doubts the gold standard for treating complicated AA (2). The present scientific literature as regards the management of S-AA focuses on potential means of improving the diagnostic accuracy in oder to enable physicians to easily exclude, confirm or differentiate AA from other causes of acute abdomen in the right lower abdominal quadrant (3). Uncomplicated AA has been managed traditionally by early appendectomy even though the num-

ber of acute appendectomies has been decreasing over the years. Emerging literature in AA seems to favour the non operative management through primary antibiotics conservative therapy (pACT) since many patients are treated conservatively with high success rates and fewer postoperative complications than primary surgical open or laparoscopic appendectomy (pSOLA) (4). However, clinical trials have so far shown controversial results as regards the standard of care for treating uC-AA even though high operational risk patients could represent an ideal subgroup of selected patients where pACT could be indicated.

Methods

Study selection

The purpose of this review was to evaluate the outcomes of both surgical (S) and conservative antibiotics (A) management of uC-AA in order to justify our proposal of an evidence based decision making for the treatment of uC-AA in high operative risk adult patients (HORAP), that could be in line with the results of the present trend of treatment in literature, while awaiting unanimous results from large scale multi-centre RCTs. We carried a comprehensive search of the PubMed searching engine in the English language scientific literature from 1995 to 2015, using medical subject headings "antibiotics", "uncomplicated appendicitis", "appendicectomy", "conservative treatment", "surgery" and "randomized clinical trial" . All RCTs comparing the outcomes of primary conservative antibiotics therapy (pACT or A) versus primary surgical open or laparoscopic appendectomy (pSOLA or S) as primary treatment options for uC-AA from 1995-2015 were identified. Inclusion criteria for our analytical review were RCTs evaluating outcomes in terms of or related to all of the following four parameters: treatment efficacy, post operative complications, in hospital length of stay (LOS) and recurrence. Uncomplicated appendicitis was considered as cases of AA were clinical, US or CT findings excluded local peritonitis (abscess or phlegmon), with an appendix external diameter less than or equal to 10 mm. Articles published in other languages and those without free access to full text were excluded. Five RCTs were eligible for our analytical review as reported in table 1.

Definitions of outcomes analysed in the RCTs

Treatment efficacy

Treatment efficacy or success in the antibiotic treatment arm could be considered as patients who are successfully treated with antibiotics only, without developing of any post-therapeutic complications, being discharged from the hospital without the need for surgical intervention and have no recurrence of symptoms requiring appendicectomy during a minimum follow-up of one-year. Treatment efficacy or success in the surgical treatment arm could be considered as patients who are successfully treated with appendicectomy evaluated to be 100% through confirmed appendicitis at operation, in the presence of appendicitis on histology and in the absence of postoperative complications including readmissions.

Post-therapeutic or post-operative complications

Posts therapeutic complications in the antibiotics group include perforated/gangrenous appendicitis or peritonitis (in patients who fail antibiotic treatment and have appendectomy subsequently), death, dairrhea, Clostridiun difficile infection, intra-abdominal abscess and allergic reaction arising during treatment period. Post-operative complications in patients undergoing surgery include, both major complications like small bowel obstruction, intra-abdominal abscess, wound ruptures, postoperative cardiac problems, incisional hernias, death; and minor complications like diarrhea, superficial wound infections, abdominal or incisional discomfort and fungal infection at one year.

Recurrence

Recurrence in the appendicectomy arm is considered as appendicitis of the appendix stump within 1 year from surgery while for those subjected to antibiotic treatment, recurrence is considered as patients who have suspected or proven appendicitis within one year from a successful antibiotic therapy.

Table 1 - Summary of the outcomes of randomized controlled trials comparing antibiotics and surgery in the treatment of appendicitis

Author (Year) Country	N	A/S	OUTCOME								LE	Conclusion
			Efficacy: N (%)		Complications: N (%)		Mean LOS (SD)		Recurrence (%)			
			A	S	A	S	A	S	A	S		
Eriksson (1995) Sweden	40	20/20	13 (65)	17 (85)	1 (5)	3 (15)	3.1 (0.3)	3.4 (1.9)	7 (36.8)	0	3	Antibiotic treatment in patients with acute appendicitis was as effective as surgery
Styrud (2006) Sweden	252	128/124	97 (76)	120 (96)	16 (12.5)	23 (19)	3 (1.4)	2.6 (1.2)	17 (15)	0	3	Acute non-perforated appendicitis can be treated successfully with antibiotics
Hansson (2009) Sweden	369	202/167	83 (41)	142 (85)	53 (26)	58 (35)	3 (0.1)	3 (0.3)	14 (13.2)	0	3	Antibiotic treatment appears to be a safe first-line therapy in unselected patients with acute appendicitis
Malik (2009) India	80	40/40	34 (85)	40 (100)	0 (0)	3 (7.5)	2.3 (0.3)	1.2 (2.1)	4 (10.5)	0	3	Our conclusion is that antibiotic treatment in the patients with acute appendicitis is quite effective, and these patients may not need surgery.
Vons (2011) France	239	120/119	81 (67)	119 (100)	14 (12)	24 (20)	3.96 (4.87)	3.04 (1.5)	44 (37)	0	3	Amoxicillin plus clavulanic acid was not non-inferior to emergency appendicectomy for treatment of acute appendicitis
TOT o Mean	980	427/553	308 (66.8)	438 (93.2)	84 (11)	111 (19,3)	3.1	2.6	11.2	0		

A: Antibiotic arm, S: Surgery arm, LOS: Length Of Stay, SD: Standard Deviation, LE: Level of Evidence

Length of Stay

The hospital length of stay (LOS) for the antibiotic group is defined as the number of days of inpatient admission for patients who are treated with antibiotics following admission and discharged with oral antibiotics. In the operative arm, it is defined as the number of days of inpatient admission for patients who undergo appendicectomy and are discharged with follow-up.

Summarised characteristics of the RCTs

Eriksson et al. (5)

Eriksson et al. conducted a monocenter RCT assessing the effect of antibiotics as the only treatment in acute appendicitis in 40 adult patients with history and clinical signs of acute appendicitis, positive findings at ultrasonography, and raised levels of inflammatory markers (CRP or WBC). In this study, 20 patients randomized in the antibiotics arm received antibiotics intravenously for 2 days followed by oral treatment for 8 days and 20 patients considered as controls were randomized to surgery. All patients treated conservatively were discharged within 2 days, except one who required surgery after 12 h because of peritonitis secondary to perforated appendicitis. Seven patients were readmitted within 1 year as a result of recurrent appendicitis and underwent surgery, when appendicitis was confirmed. They concluded that antibiotic treatment in patients with acute appendicitis was as effective as surgery. The patients in the antibiotic treatment arm had less pain and required less analgesia, but the recurrence rate was high. This study may be classified as level-3 evidence.

Styrud et al. (6)

Styrud and colleagues performed a prospective multicenter RCT between March 1996 and June 1999 conducted in 6 hospitals in Sweden to assess antibiotic treatment versus surgery in the treatment of acute appendicitis in 252 male adult patients. A blinded random assignment method was used. The primary outcome measures were not specifically reported but appeared to include complications and number of sick days over the 1 year of follow-up. No *P* values were provided. They concluded that antibiotic treatment for acute appendicitis was sufficient in most patients. The study may be classified as level-3 evidence.

Hansson et al. (7)

Hansson and colleagues carried a multicenter RCT between May 2006 and September 2007 to assess the use of antibiotic therapy versus appendectomy as the primary treatment of AA. 369 patients over 18 years of age admitted during this time period were included. 202 patients with an uneven date of birth were assigned to antibiotic treatment and 167 patients with an even date of birth were assigned to surgical treatment. There was a clear bias toward surgical intervention as patients with more severe conditions potentially received surgery. 2 of the patients who proceeded to surgery were found to have malignancies and underwent hemicolectomies. The authors determined a treatment efficacy of 90.8% for antibiotic therapy and 89.2% for surgical treatment; however, they also demonstrated that the overall incidence of major complications was 3 times higher in patients who underwent surgery compared with those treated with antibiotics ($p<0.05$). This study may be classified as level-3 evidence.

Malik et al. (8)

Malik and Bari performed a monocenter RCT between August 2003 and July 2005 to assess the role of antibiotics as the sole treatment for appendicitis in 80 patients. The random assignment method, exclusion criteria and criteria for assessing primary outcome were not clearly explained. Four patients (10%) who were treated initially with antibiotics had recurrent appendicitis and proceeded to surgery. The authors concluded that within their locality antibiotic treatment appeared to be a viable alternative to surgery. They accepted the limitations of their study. This study may be classified as level-3 evidence.

Vons et al. (9)

Vons e colleagues performed a non inferiority multicenter RCT to assess the efficacy of amoxicillin

plus clavulanic acid by comparison with emergency appendicectomy for treatment of 243 patients with CT proven uncomplicated acute appendicitis. A computer-generated randomization sequence was used to allocate patients randomly in a 1:1 ratio to receive amoxicillin plus clavulanic acid (3 g per day) for 8-15 days or emergency appendicectomy. The primary endpoint was occurrence of post intervention peritonitis within 30 days of treatment initiation. In the appendicectomy group, despite CT-scan assessment, 21 (18%) of 119 patients were unexpectedly identified at surgery to have complicated appendicitis with peritonitis. In the antibiotic group, 14 (12%) of 120 underwent an appendicectomy during the first 30 days and 30 (29%) of 102 underwent appendicectomy between 1 month and 1 year, 26 of whom had acute appendicitis. They concluded that Amoxicillin plus clavulanic acid was not inferior to emergency appendicectomy for treatment of acute appendicitis. This study may be classified as level-3 evidence.

Results

Analyses of the RCTS

The four selected outcomes for each randomised controlled trial is summarised in table 1, in line with other published reviews or meta-analyses (10-12). Considering that the high selection bias, the heterogeneity of the patients, the heterogeneity in the definitions of the outcome parameters in the various CRTs, the cross-over from pACT to pSOLA arm in some RCTs and the use of different antibiotics regimes in the five RCTs reviewed, could influence the validity of statistical analyses, we limited the interpretations of our results on an evidence based criteria as all RCTs considered for this analytical review could be classified as level-3 evidence.

A total of 980 patients were assessed in all five RCTs. 427 (43%) patients received antibiotic therapy while the remaining 553 (57%) patients underwent surgery. Mean outcome in the antibiotics versus surgical group in terms of treatment efficacy, post therapeutic/postoperative complications, in hospital length of stay in days and recurrence were respectively 66.8%/93.2%, 11%/19%, 3.1/2.6, 11.2%/0%. The conclusion of all authors considered antibiotic alone in the treatment of AA as an efficient and non inferior therapeutic option respect to surgery. However, pACT was characterised by a higher LOS and a higher rate of recurrence than pSOLA while pSOLA had a higher rate of postoperative complications (19%) respect to pACT (11%).

However, as shown in table 2, the heterogeneity and bias of the RCTs included makes the attempt to cumulative analysis inappropriate. In fact, patients in our RCTs were of different geographical origins, hence not representative of a homogeneous worldwide distribution. Age group ranged from 17-75 years and was different in all RCTs. One RCT included only male patients. The diagnoses of u-AA in the various RCTs was reached using different clinical, laboratory or imaging procedures. High risk of bais was also associated to the absence of blinding in the randomization of four ot the five RCTs. The conservative treatment methods varied greatly within the five studies in terms of antibiotic regimen, dose and the duration of treatment; while in the surgical arm, patients underwent both open and laparoscopic appendicectomy. The follow-up interval differed in all five trials.

Main characteristics and limitations of the RCTs

Eriksson et al in their RCT, presented a very small population with only 20 patients recruited per arm. One patient in the antibiotic group underwent surgery and the recurrence rate in the antibiotic arm was very high (36.8%).

Styrud and colleagues in their prospective multi-centre RCTIt excluded women as a condition for ethical approval. There was no explanation given for the choice of age range. However, they clearly detailed the method of random assignment, which appeared to be blinded. The primary outcome measures were not specifically reported but appeared to include complications, level of pain and number of sick days over the preceding 1 year of follow-up. All of the participants were accounted for at the conclusion of the study. The authors concluded that antibiotic treatment for acute appendicitis was sufficient in most patients; though there was some discrepancy between the numbers quoted in the discussion and those quoted in the re-

Table 2 - Characteristics of the RCTs analysed

Autor	Eriksson	Styrud	Hansson	Malik	Vons
Study design	Monocenter RCT in a single hospital in Sweden	Multicenter RCT in 6 hospitals in Sweden	Multicenter RCT in 2 hospitals in Sweden	Monocenter RCT in a single hospital in India	Multicenter RCT RCT in 6 hospitals in France
Participants	Patients aged 18-75 yrs with history and clinical signs of AA, positive findings at US, and raised levels of CRP or WBC	Men aged 18-50 yrs with clinically suspected non-perforated AA and CRP>10 mg/	Patients 18 yr of age or older with a diagnosis of AA based on disease history, clinical signs, laboratory tests and in some cases US, CT and gynecological exams	Men and women aged 17-64 yr with typical AA history and clinical signs (Alvarado's score), positive US findings and either increase WBC and CRP values or elevated WBC and CRP values measured in two separate occasions within a 4-hr interval	Patients aged 18-68 yrs with uncomplicated CT diagnosed AA
Randomization criteria	No blinding (Based on date of birth)	Blinding	No blinding	Ns (Systemic random sampling)	No Blinding
Antibiotic regime	Intravenous cefotaxime 2 g twice daily and tinidazole 800 mg once daily for 2 days, followed by oral ofloxacin 200 mg and tinidazole 500 mg twice daily for 8 days	Intravenous cefotaxime 2 g twice daily and tinidazole 800 mg once daily for 2 days, followed by oral ofloxacin 200 mg and tinidazole 500 mg twice daily for 10 days	Intravenous cefotaxime 1 g twice daily and Intravenous metronidazole 1.5 g daily (only in the absence of clinical improvement); then ciprofloxacin 500 mg twice daily per os and metronidazole 400 mg 3 times daily per os for 10 days following discharge.	Intravenous ciprofloxacin 500 mg twice daily and Intravenous metronidazole 500 mg 3 times daily for a period of 2 days; then ciprofloxacin 500 mg twice daily per os and tinidazole 600 mg 2 times daily per os for 7 days following discharge.	Amoxicillin plus clavulanic acid 3-4 g daily for 8-15 days, intravenously to those with nausea or vomiting, and orally to all others. Appendicectomy undertaken if: Symptoms and abdominal tenderness failed to resolve after 48 h. Persistence of pain or fever at 8 days prompted CT and possible appendicectomy or Sustained high WBC or high CRP concentration on day 15 prompted appendicectomy without additional CT
Appendectomy: Open or Laparoscopic	Open 100%	Open 94%, Laparoscopic (6%)	Ns	Ns	Open 34%, Laparoscopic 66% appendicectomy with
Follow-up	6, 10, 30 days	1wk, 6wks,1yr	1 month, 1 yr	7, 12, 30 days	8, 15, 30, 90, 180, 360 days

AA: acute appendicytis, Ns: Not stated, Wk: Week, Yr: Year

sults. The authors declared that they would present *p* values for any statistically significant results, but none were provided. The level of evidence provided was not sufficient to affect the management of acute appendicitis locally.

Primary outcome measures in the RCT of Hansson and colleagues were treatment efficacy and the occurrence of major complications. Efficacy with antibiotic treatment was defined as "definite improvement without the need for surgery within a median follow-up of 1 year," while surgical efficacy was defined as "confirmed appendicitis at operation or another appropriate surgical indication for operation." Patients were randomly assigned to a treatment group based on date of birth; 202 patients with an uneven birth date were assigned to antibiotic treatment and 167 patients with an even birth date were assigned to surgical treatment. There was no blinding, as the surgeon could change a patient's treatment option at any point. In fact 96 of 202 patients in the antibiotic group actually received surgery and 13 of 167 patients in the surgical group received antibiotic treatment only. Hence, in this study there was a clear bias toward surgical intervention, and the patients with more severe conditions potentially received surgery. This was highlighted by the fact that patients who underwent surgery had a higher white cell count, pyrexia and peritonism compared with patients who were treated with antibiotics. In this study 15 of the 106 patients initially treated with antibiotics returned for further treatment and 12 of them required surgery. Two of the patients who proceeded to surgery were found to have malignancies and underwent hemicolectomies. The authors determined a treatment efficacy of 90.8% for antibiotic therapy and 89.2% for surgical treatment. They also demonstrated that the overall incidence of major complications was 3 times higher in patients who underwent surgery compared with those treated with antibiotics ($p<0.05$). Even though this was an interesting initial study that explored the possible use of antibiotics in the treatment of appendicitis, the conclusion that antibiotics appeared to be a safe first-line therapy in the treatment of patients presenting with acute appendicitis was not justified. The authors demonstrated that patients presenting with symptoms and signs suggestive of appendicitis can be initially managed with antibiotics; however, once the diagnosis of appendicitis becomes clear, then the patient should undergo an appendectomy.

The RCT performed by Malik and Bari included 80 patients, which was a small number for even 1 centre over such a long period. The randomization criteria was not clearly explained. There was also no clear indication of whether there was blinding. Further, whereas the inclusion criteria were clearly stated, there was no mention of the exclusion criteria, which must have had an impact owing to the low participant numbers over such a long study period. No specific criteria for assessing a primary outcome were described. They confirmed a significantly lower analgesic consumption and less pain at 12 hours in the antibiotic group ($p<0.001$). Four patients (10%) who were treated initially with antibiotics had recurrent appendicitis and proceeded to surgery. Even though they concluded that within their locality antibiotic treatment appeared to be a viable alternative to surgery, they accepted the limitations of this study.

In the trial of Vons et al, 30-day post-intervention peritonitis was significantly more frequent in the antibiotic group than in the surgery one. The treatment difference was 5.8% (95% CI: 0.3-12.1%) showing that antibiotics were not non-inferior to urgent appendectomy for the treatment of acute appendicitis. No significant difference was identified between the two groups for secondary endpoints (duration of severe pain, duration of hospital stay and absence from work). In the surgical group, 21 (18%) of 119 patients had a complicated appendicitis with peritonitis identified at surgery despite CT-scan findings. The logistic regression model revealed that the presence of stercolith on a preoperative CT scan was the only factor associated with an increased risk of complicated appendicitis in this group of patients ($p<0.0001$). In the antibiotic group, 14 (12%) of 120 patients had no improvement with treatment and underwent appendectomy within the first month. Nine of them were identified to have a complicated appendicitis at surgery. In this gruop, the presence of a stercolith on CT scan was the only factor associated with failure of antibiotic treatment for appendicitis on a logistic regression analyses ($p=0.0072$). The systematic performance of urgent CT scan to confirm the diagnosis of acute appendicitis in this trial is not a common procedure. Consequently, inclusion

criteria of the present study may have selected a population that does not reflect the spectrum of individuals presenting for suspected acute appendicitis in most emergency departments.

Discusion

Study design

Limitations of this review were mainly those of the primary trials.

The diagnosis of appendicitis was made without CT in three of the 5 RCTs (38% of the patients), and in the studies that used CT, the rate of intra-operative diagnoses of perforated appendix was high (about 18% in the appendicectomy group in the French study (9). This could be due to inaccuracy of the CT scans or progression of initially non-perforated appendicitis.

Risk of bias was a problem in all studies, with major limitations reported in four of the five studies for blinding and in many with respect to loss to follow-up.

There were also reported problems that required some interferences in data abstraction. For example only one of the five studies classified complications according to their severity, in major or minor.

All RCTs reported in-hospital intravenous pACT for 2-3 days, wheras it might be possible to reduce length of stay by using a different antibiotic regimen.

Controversies can also exist regarding the fact that these RCTs had follow-up up to 1 year only, hence little is known about recurrence rates with longer follow-up. It is unknown how much this rate might rise with longer follow-up.

Furthermore, doubts could arise on whether patients recruited in these trials represent a real sample of the worlds' polulation as selection criteria differed in all RCTs as corncerns the age, sex and country of origine of the patients.

Unfortunately, the quality of complication reporting was so poor as to permit only few conclusions. First, no RCT used any of the validated complication classification systems. Second, none of the RCTs reported antibiotic-related complications such as diarrhea or Clostridium difficile infection (10).

Treatment options

The antibiotic therapy has been suboptimal in many previous randomized studies, as for example in the study by Vons et al. amoxicillin-clavulanic acid was used even though this combination has been associated with considerable *Escherichia coli* non-susceptibility. Hence, the use of this combination may play a role in both the initial antibiotic treatment failures and the recurrence of AA considering that this antibiotic treatment is not recommended to be used in the non-operative treatment of AA. The most common microorganism in AA is *Escherichia coli*, and the next most common is *Enterococcus* and other *Streptococcus* species. *Pseudomonas*, *Klebsiella*, and *Bacteroides* species are less commonly isolated. Hence the selection of antibiotics should cover both aerobic and anaerobic bacteria (13-15).

In spite the trend toward a lower complication rate with antibiotic therapy compared to appendicectomy, amongst the RCTs that reported the type of surgery, open or laparoscopic, only 43% of the procedures in the appendicectomy group were performed laparoscopically. Systematic reviews of RCTs comparing open with laparoscopic appendicectomy have shown that the laparoscopic approach is associated with reduced wound infections, as well as a lower rate of bowel obstruction. As the majority of minor complications were wound infections and incisional discomfort, it is likely that a laparoscopic approach will reduce the rate of minor complications. Furthermore, more frequent use of a laparoscopic approach should shorten hospital stay and sick leave (16, 17).

Diagnoses of uncomplicated appendicitis

In case of suspected acute appendicitis (paucisymptomatic clinical objectivity in lower right quadrant, Alvarado score ≤2, Alvarado modified score ≤3, borderline US findings), the current tendency in the scientific literature aims at reaching imaging techniques with high diagnostic accuracy when ultrasonography findings orientated for suspected appendicitis (doubtful ultrasonography tenderness, non compressible appendices, borderline size (6-8 mm) external appendix diameter) through eco-color doppler,

MRI, low dose TAC, and standard dose TAC. Ionizing radiation and low cost render ultrasound (US), when available, the first-line imaging technique for the diagnosis of suspected acute appendicitis. US examination is considered to be operator dependent and is technically challenging in obese patients or women in late pregnancy. However, US is less sensitive and specific than computed tomography (CT) or magnetic resonance imaging (MRI) scans, which are often performed after non diagnostic US.

In relation to the predictors of ultrasound visualization of the appendix in patients with suspected acute appendicitis, Kaewlai R et al in their retrospective cohort of 238 consecutive patients found that the chances of visualizing the appendix in patients with body mass indexes ≤ 22, pain scores ≥6, and Alvarado scores ≥6 were 2.3, 2.9, and 3.8 times higher than those of their counterparts, respectively. Therefore, in patients with these factors, the use of ultrasound may be beneficial in the diagnosis of acute appendicitis (18).

Computed tomography (CT) remains the predominant test for diagnosing acute appendicitis in adults and high BMI patients with US suspected acute appendicitis. The routine use of CT in patients suspected of having appendicitis has also been reported to be cost-effective, since it prevents delayed or inaccurate diagnoses (19). However this technique in consideration of its high cost and the exposure to high doses of radiation doesn't meet the criteria of routine implementation.

In a retrospective review of Konrad J et al enrolling 140 pregnant women to evaluate the sensitivity, specificity, and accuracy of ultrasound (US) as compared to magnetic resonance imaging (MRI) in pregnant patients with suspected appendicitis, the appendix was visualized in 7% (8/117) of US exams and in 80% (91/114) of MRI exams, whilst the sensitivity and specificity of MRI for acute appendicitis were both 100% and 98%, respectively, as compared to 18% and 99%, respectively, with US. Alternate etiologies of pathology were determined in 3% (3/117) of US exams and in 12% (14/114) of MRI exams GA did not affect MRI or ultrasound visualization rates of the appendix. They therefore concluded, given the low likelihood of visualization of the appendix at US, the excellent accuracy of MRI and the ability of MRI to identify alternate diagnoses, suggesting that at certain institutions MRI may be considered a first-line imaging modality for pregnant patients of any GA with suspected appendicitis (20). Duke E at al. in a meta-analysis of 30 studies that comprised 2665 patients performed to determine the accuracy of MRI in the diagnosis of acute appendicitis in the general population and in subsets of pregnant patients and children, the sensitivity and specificity of MRI were 94% (95% CI, 87-98%) and 97% (95% CI, 96-98%), respectively for the pregnant patients. They also concluded proposing MRI, in relation to the high accuracy for the diagnoses of acute appendicitis, as a first-line diagnostic test for a wide range of patients (21).

Xu Y et al in a recent (2016) retrospective blind observational study of 94 consecutive patients who underwent sonography for suspected appendicitis concluded that in non compressible appendices of diagnostically US borderline size (6-8 mm), continuous intramural linear or curvilinear signal measuring at least 3 mm on color Doppler imaging is a highly specific (94.9%), although relatively insensitive (57.1%), sign of acute appendicitis (22). This diagnostic option could be reserved for young and pregnant adults in emergency settings were MRI is not available or feasible.

Kim K et al in their single-institution single blind trial of 891 patients that evaluated the rate of negative (unnecessary) appendectomy after low-dose versus standard-dose abdominal CT in young adults with suspected appendicitis, concluded that Low-dose CT (116 mGy cm) was non inferior to standard-dose CT (521 mGy cm) with respect to negative appendectomy rates in young adults with suspected appendicitis (23). Lee YJ et al. in another retrospective study 149 patients further propose the multiplanar sliding-slab averaging technique review of thin sections (2-mm-thick respect to the standard of 5-mm-thick) when the diagnosis of appendicitis is difficult at low dose (2-mSv) CT in adolescents and young adults (24).

Diagnostic laparoscopy remains the last resort in case of persistent RLQ pain and failure of the above imaging and clinical features to meet a definite diagnoses. However the choice of an ideal diagnostic tool should be well measured to suite the clinical setting and favour the use of low cost radiation free diagnostic tools that can be routinely implemented.

High operetive risk adult patients

There is a universal consensus in the scientific literature regarding the indication for the use of minimally invasive therapeutic procedures for high risk patients. Boyd O et al in the work concerning goal-directed therapy, showed that both mortality and morbidity are reduced when risk is assessed based on very simple preoperative scores, and when treatment is targeted to various goals of cardiorespiratory function (25). High risk surgical patients are considered those undergoing non-cardiac surgery who are at such high risk of post operative morbidity and mortality that they might benefit from high-dependency unit or intensive care unit (ICU) care perioperatively or might benefit from haemodynamic manipulation to improve their outcomes. Risk is assessed to allow suitable targeting of therapeutic options and decision-making with regard to treatment choices so that a suitable balance of risks, often between the possible side effects and dangers of surgery and the potential success of treatment, can be made. A doctor may assess the individual patient's risk in order to better inform the patient and to allow consensual decisions for procedures to be undertaken.

'High risk' is used to donate the global risk of mortality or morbidity, particularly with regard to organ failure, compared with other groups at lower risk , and entails a general perioperative risk stratification that comprises the risks associated to the patients comorbidity, the risks related to the surgical procedure and whether that procedure is undertaken in an elective fashion or as an emergency (A number of databases have demonstrated the higher risk associated with emergency procedures) and the risk related to the type of anesthesia. Boyd O et al also suggested that a far more understandable description of high risk would be if the individual's risk of mortality is either >5% or twice the risk of the population undergoing that procedure a or procedure with mortality greater than 5%. Furthermore, they suggested that surgical patients for whom the probable mortality is greater than 20% should be considered 'extremely high-risk' patients (26).

Pre-operative risk stratification

The simplest and most widely used method for assessing the comorbidity is the American Society of Anesthesiologists (ASA) grading on a scale of I to IV; this combined with the type of urgency of surgery has been shown to be related to postoperative mortality (27) (Table 3). More recently an additional suffix 'E' for emergency operation has been added. A high ASA score is predictive of both increased postoperative complications and mortality after non-cardiac surgery. It may be surprising that it is predictive, as ASA scoring does not take into account age, weight or the nature of the intended operation.

Post-operative risk stratification

The scoring system that has been specifically designed for surgical patients is the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) score (28). This is generally accepted to be a good scoring system for routine use (29), and is better than the APACHE system for a general surgical group of patients (30). The POSSUM score describes 18 factors in two component parts; 12 physiological factors (PS) and 6 operative factors (OS). Each factor is scored exponentially increasing from 1 to 8 (1, 2, 4, 8) dependent upon grading. From these values predicted mortality in per-

Table 3. American Society of Anesthesiologists' status classification: modified from Wolters and colleagues

Class	Description	Mortality (%)
I	Healthy	0.1
II	Mild systemic disease – no functional limitation	0.7
III	Severe systemic disease – definite functional limitation	3.5
IV	Severe systemic disease – constant threat to life	18.3
V	Moribund patient unlikely to survive 24 hours with or without operation	93.3

centage can be calculated using a particular formula. The POSSUM score can be used as a tool to aid in the prediction of the mortality risk for surgery patients.

In cases of uC-AA in HORAP like the advance aged patient, obese patient, immunodeficient patient (HIV, Transplant), patient with severe cardiovascular illness, severe respiratory pathology or other sever chronic systemic ilnesses/failures, a routine evaluation of the pre and post-operative risk stratification using the ASA and POSSUM scoring systems, could represent a valuable element to identify patients who could benefit more from the pACT.

Appropriate antimicrobiale regimen for intra abdominal infections

Intra-abdominal infections (IAI) such as uC-AA are an important cause of morbidity and are frequently associated with poor prognosis, particularly in high-risk patients. Antimicrobial therapy in patients with IAIs is typically empirical in nature because they need immediate treatment (especially in critically-ill patients), and because microbiological data (culture and susceptibility results) usually requires ≥24 h for the identification of pathogens and antibiotic susceptibility patterns (31). In these patients, empiric antimicrobial therapy must be broad enough to cover all likely organisms because inappropriate initial antimicrobial therapy is associated with poor patient outcomes and the development of bacterial resistance.

Sartelli et al. in their position paper, involving an international task force of the world's leading experts from 79 different countries, reviewed the rational use of antimicrobials for patients with IAIs and outlined a series of evidence based recommendations in the 2016 world society of emergency surgery (WSES) guidelines for optimizing the use of antimicrobial therapy in IAIs. They recommended that the choice of an appropriate empiric antibiotics in patients with IAI should be based on the severity of the infection, the individual risk for infection by resistant pathogens, and the local resistance epidemiology. They also recommended Amoxicillin/clavulanate or cephalosporins in combination with metronidazole, as good options for the treatment of non-severe IAIs, while piperacillin/tazobactam were considered a better choice if P. aeruginosa coverage is needed. Other recommendation was made for the use of carbapenems be limited so as to preserve activity of this class of antibiotics because of the concern of emerging carbapenem-resistance. Ciprofloxacin and levofloxacin were no longer considered appropriate first-line choices for empiric treatment in many regions because of the prevalence of fluoroquinolone resistance. Other options in thier review include aminoglycosides, particularly for suspected infections by Gram negative bacteria, and tigecycline especially when multi-drug resistant organisms (MDROs) are suspected, though they adviced caution for the latter, in the situation of a bacteremia. They approveded Ceftolozone/tazobactam and ceftazidime/avibactam as new antibiotics for treatment of IAI infections (in combination with metronidazole) including infection by ESBLs and P. aeruginosa, though their role for the empirical therapy remains to be defined. Further recommendations were made to perform and report antimicrobial susceptibility testing (AST) in patients with healthcare-associated infections or with community-acquired infections at risk for resistant pathogens, when a microorganism is identified in clinical cultures from blood or fluid/tissue, in order to guide antibiotic therapy, as microbiological cultures would allow to expand antimicrobial regimen if the initial choice is too narrow or to perform a de-escalation if the empirical regimen is too broad (32). They also recommended that empiric antifungal therapy should be considered in patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis such as recent abdominal surgery, anastomotic leaks, necrotizing pancreatitis and failure of treatment for bacterial infections, even though clinical evidence supporting the use of antifungal therapy for patients with suspected intra-abdominal invasive candidiasis is limited and the epidemiological role of Candida spp. in IAI has not yet been conclusively defined (33).

It could therefore be rational to suggest that in HORAPs were the risk of antibiotic failure could result in a more unfavourable outcome than a low risk procedure as appendectomy, a routine use of local antibiogram data, acquisition of knowledge of local rates of resistance, performance of clinical cultures from blood or fluid/tissue consultation of current recommendations preferably with the consultation of an

infectivologist, should be implemented to guide the choice of an appropriate initial antimicrobial regimen , that should comprise empirical large spectrum antibiotic therapy with or without antifungal therapy were indicated, while awaiting the results of blood specimens for a target therapy.

Conclusion

Based on the current body of evidence, pACT could be as efficient as surgery in the treatment of AA. However, with respect to pSOLA, pACT is characterised by a lower rate of post-therapeutic complications, a higher in hospital LOS and a higher rate of recurrence. Hence an appropriate empiric pACT could be a rational tailored primary treatment option for CT proven uC-AA in HORAP as well as a rational primary treatment option upon decision sharing in low risk patients, with the intent, in the later group, of either a definite treatment or as bridge to appendectomy. Accurate diagnoses of uC-AA and surgical risk stratification in patients with uC-AA could aid tailor decision making for target therapy. Results of large sample prospective multicenter RCTs are required to routinely recommend the use of pACT for uC-AA in the clinical practice for AA.

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