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Journal of Visceral Surgery (2020) xxx, xxx-xxx



REVIEW

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# Adult appendicitis: Clinical practice guidelines from the French Society of Digestive Surgery and the Society of Abdominal and Digestive Imaging



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#### **KEYWORDS**

Acute appendicitis; Adult appendicitis; Guidelines; Société française de chirurgie digestive; Société d'imagerie abdominale et digestive.

#### Summary

*Introduction:* The French Society of Digestive Surgery (SFCD) and the Society of Abdominal and Digestive Imaging (SIAD) have collaborated to propose recommendations for clinical practice in the management of adult appendicitis.

*Methods:* An analysis of the literature was carried out according to the methodology of the French National Authority for Health (HAS). A selection was performed from collected references and then a manual review of the references listed in the selected articles was made in search of additional relevant articles. The research was limited to articles whose language of publication was English or French. Articles focusing on the pediatric population were excluded. Based on the literature review, the working group proposed recommendations whenever possible. These recommendations were reviewed and approved by a committee of experts.

https://doi.org/10.1016/j.jviscsurg.2020.11.013 1878-7886/© 2020 Published by Elsevier Masson SAS.

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*Results:* Recommendations about appendicitis in adult patients were proposed with regard to clinical, laboratory and radiological diagnostic modalities, treatment strategy for uncomplicated and complicated appendicitis, surgical technique, and specificities in the case of macroscopically healthy appendix, terminal ileitis and appendicitis in the elderly and in pregnant women.

*Conclusion:* These recommendations for clinical practice may be useful to the surgeon in optimizing the management of acute appendicitis in adults.

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# Methodology

A literature analysis was carried out according to the methodology of the French National Authority for Health (Haute Autorité de santé; HAS) by consulting the Cochrane and Medline databases for pertinent articles up to November 2019. A manual selection was made from the selected references as well. The articles selected were manually sorted as were the references listed in search of additional relevant articles. The search was limited to articles whose language of publication was English or French. Recommendations from major learned societies and the World Health Organization were also reviewed.

On the basis of the literature review, the working group proposed formal recommendations whenever possible. Depending on the level of evidence of the studies on which they were based, the recommendations were classified as grade A, B or C as follows:

- grade A: scientific evidence, established by studies with a high level of evidence (high-power randomized controlled trials, meta-analysis of randomized controlled trials, decision analysis based on well-conducted studies);
- grade B: scientific presumption, provided by studies of intermediate level of evidence (low-power randomized controlled trials, well-conducted non-randomized controlled studies, cohort studies);
- grade C: based on studies with a lower level of scientific evidence (case-control studies, comparative studies with substantial bias, retrospective studies, case series, descriptive epidemiological studies).
- expert agreement: in the absence of a satisfactory evidence-based study, the proposed recommendations were based on professional consensus within the working group and the reading group.

All of this work was submitted to an expert review committee for correction and validation of the recommendations, their justification and their grade.

# Diagnostic modalities of acute appendicitis

# Clinical and laboratory evidence

Diagnostic performance of individual clinical signs

Of the 1728 publications identified in Andersson's 2004 literature review [1], only 240 included data regarding modes of clinical diagnosis. The rate of confirmed acute appendicitis (AA) in the face of clinical suspicion ranged from 26.7% to 60.6% (median 41%). A total of 18 clinical items, grouped into five categories (gastro-intestinal dysfunction, pain, spontaneous signs of peritonism, tenderness, and peritonism at examination) were evaluated. The positive (PLR) and negative (NLR) likelihood ratios for these signs were low, thus not allowing clinical findings alone to be considered sufficient to make or exclude the diagnosis.

Clinical signs must be part of the diagnostic process but cannot by themselves allow a reliable diagnosis of AA (grade B).

# Laboratory markers of inflammation

Elevated white blood cell count (WBC) as a diagnostic feature of AA has been evaluated in numerous studies that were combined in a meta-analysis [1]. Regardless of the cut-off value chosen, the PLR and NLR were low, precluding the use of leukocytosis as the sole diagnostic feature. Likewise, the diagnostic performance of C-reactive protein (CRP) has been evaluated in several studies [1-3] (Table 1); the PLR and NLR are low, not allowing CRP to be used as the sole diagnostic element.

Laboratory markers of inflammation alone cannot be reliably used to diagnose AA (grade B).

# Combined analysis of clinical and laboratory data

Laméris et al. [3] tested 23 possible combinations of clinical and/or laboratory signs for the diagnosis of AA. While 89% of patients older than 50 years of age with abdominal pain that migrated to the right iliac fossa and with WBC > 10,000/mL and CRP > 12 mg/L proved to have AA, this rate was only 75% in patients younger than 30 years of age.

In order to optimize the diagnostic performance of clinical-laboratory associations, several authors have proposed the use of composite scores. The Alvarado score is the best known of these; its initial publication [4] reported a sensitivity of 81% and a specificity of 74%. In a meta-analysis that included 29 series, Ohle et al. [5] showed that a score  $\geq$  5 had a sensitivity of 99% but a specificity of 43% and a score  $\geq$  7 a sensitivity of 82% but a specificity of 81%. This indicated a good ability to exclude the diagnosis in patients

Table 1Diagnostic performance of CRP in the diagnosis of acute appendicitis.						
Author, year	Number of patients	CRP (mg/L)	Area under the ROC curve	Positive likelihood ratio (range)	Negative likelihood ratio (range)	
Andersson, 2004 [1]	3382	>10 >20	0.75 [0.66—0.85]	1.97 [1.58–2.45] 2 39 [1 67–3 41]	0.32 [0.20–0.51]	
Ortega-Deballon et al., 2008 [2] Laméris et al., 2009 [3]	134 942	67.7 >10	0.846 0.55 [0.49–0.60]	3.53 1.1	0.122 0.7	

with a score < 5, but, on the other hand, a score > 7 was not sufficiently reliable to retain a diagnosis. In 2008, Andersson et al. [6] proposed an optimized score, with improved performance (area under the ROC curve: 0.93 versus 0.88) but, despite this improvement, errors in classifying the patients were frequently observed (37%).

In the combined absence of clinical and laboratory signs (pain migrating to the right iliac fossa, elevated WBC, and elevated CRP), a diagnosis of AA is unlikely but cannot be completely ruled out (grade C).

In this situation, the physician can choose between systematic performance of an imaging study or ongoing monitoring appropriate to the context (expert opinion). The combination of clinical and laboratory criteria, even in the context of a score, is not sufficiently reliable to make the diagnosis of AA and an imaging test is therefore essential (grade B).

# Place of radiological imaging

Diagnostic performance of radiological imaging studies

The PLR of abdominal ultrasound (US) is high (values between 6 and 46), while the NLR is only moderate (0.08-0.30) [7]. However, the appendix is not consistently visualized, varying from 35% to 53% [8]. A positive US is therefore a reliable examination to confirm the presence of AA but not to exclude the diagnosis. Abdominal computed tomography (CT) has a 76–100% sensitivity and an 83–100% specificity for the diagnosis of AA [9,10]. Intravenous contrast injection (IV contrast) is recommended to optimize the diagnostic performance of CT [11]. As for MRI, a meta-analysis of 30 studies published between 1997 and 2015 that included 2665 children, adults and pregnant women reported a sensitivity and specificity for the diagnosis of AA of 96% and 96%, respectively [12].

A recent meta-analysis evaluating the diagnostic accuracy of CT, MRI and repeat US after a normal or inconclusive initial US, did not show a significant difference between the diagnostic performance of these three types of imaging as a second-line examination [13].

If AA is suspected, the first-line examination may be an abdominal US or a CT scan with IV contrast (grade B). If US is preferred, it should be performed by an experienced examiner (grade C). If US is normal or inconclusive, a CT scan with IV contrast, an MRI, or a repeat US performed a

few hours later can be performed as a second-line examination (grade B).

#### Imaging in the pregnant patient

Because of the risk of ionizing radiation to the fetus with CT, abdominal US is the first-line examination in pregnant women because it is widely available as an emergency study compared to MRI. Note that difficulty in visualizing the appendix due to the change in cecal position (often displaced upward by the gravid uterus) impairs its diagnostic performance. Thus, the appendix cannot be visualized by US in 34% of pregnant patients [14]. If the US is normal or inconclusive, CT scan or MRI (depending on the technical platform and availability) is the second-line imaging examination and should be performed rather than proceeding directly to exploratory laparoscopy due to the unfavorable cost-effectiveness balance and the risk associated with this surgical procedure [15].

If AA is suspected in a pregnant woman, US or MRI without IV contrast can be performed as a first-line examination (grade B). If US is normal or inconclusive in a pregnant woman with suspected AA, and if access to MRI is unavailable, CT scan with IV contrast may be performed as a second-line examination (grade C).

#### **Obese patient**

Obesity significantly impairs the performance of abdominal ultrasound in the diagnosis of AA [16]. Likewise, obesity limits the benefit of MRI for these patients, since its performance is reduced by overweight. Conversely, the diagnostic performance of CT is not affected by overweight [17], which makes it the test of choice.

> If AA is suspected in an obese patient, abdomino-pelvic CT scan with injection can be performed as a first-line imaging study (grade C).

## **Elderly patient**

The age at which a patient is considered ''elderly'' varies considerably in different studies. However, all studies seem to agree that the symptoms of acute appendicitis are less consistent, the rate of complications is higher, and the differential diagnosis more complex in patients older than 75 years of age, motivating the performance of a first-intention CT scan in these patients.

#### If AA is suspected in an ''elderly'' patient, abdominal-pelvic CT scan with or without IV contrast can be performed as a first-line diagnostic study (grade C).

Fig. 1 reports an algorithm synthesizing imaging recommendations as refined for specific clinical settings.

# Management strategy for uncomplicated acute appendicitis in the adult

# Place of non-surgical treatment with antibiotic therapy

#### Effectiveness of medical treatment

Among the six prospective randomized trials evaluating the efficacy of medical treatment alone, the methodology is very heterogeneous [18–23] (Table 2). Three of these six trials are of low quality (no initial size calculation and poorly defined primary endpoint) [18,20,23]. A fourth trial defined its size calculation based on both one-year efficacy and the overall complication rate without making it a true composite endpoint [19]. Thus, only two trials have a satisfactory methodology [21,22]. These two trials were



Figure 1. Algorithm synthesizing the choice of imaging studies for suspected appendicitis.

Table 2Principal outcome criteria of prospective randomized studies that compared non-surgical antibiotic treatmentalone versus appendectomy in the setting of non-complicated acute appendicitis.

Study	Principal outcome criteria (POC)ª	Results on the POC	Results of antibiotic treatment alone on the POC
Eriksson and Granström, 1995 [23]	Not defined	-	-
Styrud et al., 2006 [18]	Not defined	_	_
Hansson et al., 2009 [19]	Superiority of medical treatment alone on 1-year efficacy of treatment and on major complications	Effectiveness at one year: 78.2% for antibiotic therapy alone versus 89.2% for appendectomy P<0.050	Negative for 1-year effectiveness
		Major complications: 2.5% for antibiotic therapy alone versus 10.0% for appendectomy <i>P</i> < 0.050	Positive for major complications
Turhan et al., 2009 [20]	Not defined	_	_
Vons et al., 2011 [21]	Non-inferiority for the rate of peritonitis at 30 days	8% for antibiotic therapy alone versus 2% for appendectomy Difference 5.8 (95% CI: 0.3 to 12.1)	Negative: non-inferiority not demonstrated
Salminen et al., 2015 [22]	Non-inferiority (difference < 24%) on the rate of recurrent AA at 1 year	72.7% for antibiotic therapy alone versus 99.6% for appendectomy ( <i>P</i> = 0.89)	Negative: non-inferiority not demonstrated

<sup>a</sup> Criteria from which the calculation of sample numbers was made.

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unable to demonstrate the non-inferiority of non-surgical antibiotic treatment versus surgery on their main endpoint, respectively the rate of peritonitis at D30 [21] or the risk of recurrence at one year [22]. In one meta-analysis [24], despite the inclusion of postoperative morbidity, the success rate of management at one year without complications was significantly higher for the appendectomy group (89.8%) compared to the antibiotic therapy alone group (68.4%), (P < 0.001). Finally, in the long term, the cumulative rate of recurrent AA after medically treated appendicitis that required secondary appendectomy was 35.2% at three years and 39.1% at five years [25].

Antibiotic therapy alone is not recommended as first-line treatment in uncomplicated AA and surgical treatment remains the standard of care (grade A). It nevertheless constitutes an acceptable alternative to appendectomy in the event of a contraindication or the impossibility of surgery (grade A).

## Antibiotic therapy protocol and method of administration

In all of the randomized trials, medical treatment was initiated in hospital for a period of between one and three days [18–23]. With the exception of the study by Vons et al. [21], all the studies initially used intravenous treatment followed by oral treatment after hospital discharge. The Vons et al. study administered antibiotics via the oral route from the start and did not report lower efficacy than the other studies (Table 2), suggesting that oral antibiotic therapy from the outset is safe if this is not contra-indicated by patient nausea or vomiting.

With regard to the choice of antibiotics, each trial proposed an empirical protocol based on probabilistic antibiotic sensitivity; the superiority of one protocol over another has never been assessed. Among the different protocols, Salminen et al. [22] suggested initial treatment with ertapenem. This choice was based on the emergence of beta-lactamase producing enterobacteriaceae with broad-spectrum resistance to amoxicillin and 3rd-generation cephalosporins [26]. The reported efficacy of this antibiotic therapy is not superior to other antibiotic therapy protocols but increases the risk of selection of bacteria resistant to ertapenem [27].

If medical therapy is chosen for uncomplicated AA, antibiotic therapy should be started in a hospital setting in order to detect initial failure or a diagnostic error (grade A). The duration of hospitalization may be limited to 24 hours if the patient's clinical course is favorable (grade B). The oral route is recommended if the patient does not present with nausea or vomiting (grade B).

No formal recommendation can be made regarding the choice of the type of antibiotic therapy and its duration, but short-term antibiotic therapy (<8 days) with amoxicillin + clavulanic acid or a fluoroquinolone/imidazole combination is consistent with data from the literature (expert agreement).

# Place of surgical treatment

#### Indications

The risk of recurrence is the main limitation of medical treatment of AA, but appendectomy exposes the patient to the risk of postoperative complications, particularly the risk of surgical site infection (SSI), incisional hernia and peritoneal adhesions with bowel obstruction. The studies reviewed do not separate minor morbidity from major morbidity. It is regrettable that this data was not considered because major morbidity (Dindo-Clavien  $\geq$  3) is rare in this context [28]. Mortality after appendectomy for uncomplicated AA is extremely rare, estimated at 0.054% [29].

Surgery is the gold standard for uncomplicated AA (grade A).

# Appendectomy for uncomplicated appendicitis: how urgent is it?

A meta-analysis of 45 studies assessed the impact of the time delay between diagnosis of uncomplicated AA and surgery, particularly the risk of progression to secondary appendiceal perforation [30]. This study concluded that the risk of perforation was not increased if surgery was performed < 12 hours or between 12 to 24 hours after diagnosis.

Surgery can be postponed for up to 24 hours after the diagnosis of uncomplicated AA, without exposing the patient to an increased risk of a secondary complication (grade A).

# Therapeutic strategy for adult patients with complicated appendicitis

# Abscess/phlegmon/perforation/necrosis (gangrene)

# In urgent cases: conservative medical treatment versus surgical treatment

The 2019 retrospective American study by Nimmagadda et al. [31] compared the results of surgery versus those of medical treatment alone for the management of complicated AA (abscess, phlegmon, perforation or gangrene). Of 101 patients included, 36 patients received non-surgical treatment, with a success rate of 86%, but this included radio-guided percutaneous abscess drainage in 16% of cases. In contrast, among 65 patients operated on from the start, 10.8% required percutaneous abscess drainage postoperatively. This study suggested that surgery remained the gold standard, but that the associated intra-abdominal postoperative septic morbidity could justify the implementation of non-operative treatment.

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In the event of complicated AA with phlegmon or abscess, surgical treatment is the therapy of choice but first-line non-operative treatment can be discussed (grade C).

### For non-urgent cases who undergo conservative medical treatment: interval appendectomy versus surveillance

The 2016 meta-analysis by Darwazeh et al. using data from 26 studies, reported that the rate of recurrence after conservative treatment of complicated AA was high, reaching 12.4% [32]. In addition, a Finnish randomized trial [33] comparing interval surgery and simple MRI surveillance in patients who presented with AA complicated by abscess was stopped early in light of a 17% rate of appendicular neoplasia observed on surgical specimens of patients older than 40 years of age who were randomized to the ''surgery'' arm.

If non-operative management of complicated AA is undertaken, interval appendectomy should be systematically performed because of the risk of recurrent AA as well as the risk of appendicular neoplasia (grade A).

# Peritonitis

Peritonitis due to appendicular perforation, the final stage of complicated AA, corresponding to the spread of appendicular infection to the peritoneal cavity, thus causing peritonitis.

> Surgical treatment from the outset is recommended in cases of AA complicated by peritonitis (expert agreement).

# Appendiceal mass

Appendiceal mass, a commonly used term, is in fact, poorly defined in the scientific literature. It classically corresponds to an inflammatory mass in the iliac fossa agglomerating small bowel loops and/or the colon, omentum or the tubo-ovarian adnexae around the appendicular inflammatory focus. The data available in the literature are relatively old and are often included in the data on appendicular abscesses. The recommendations on the management of abscessed forms therefore also apply to appendiceal mass and emergency non-operative treatment can be discussed.

# Appendicectomy for acute appendicitis in adults: surgical technique

# Surgical approach: laparoscopy versus laparotomy?

## **Uncomplicated appendicitis**

A meta-analysis of randomized trials found a benefit in favor of laparoscopy versus laparotomy in terms of postoperative pain, superficial SSI rate, duration of hospital stay and return to activities of daily living [34]. However, this meta-analysis suggested that laparoscopy was associated with a higher risk of deep SSI [34].

# **Complicated appendicitis**

Three randomized trials have compared the management of complicated AA by laparoscopy versus open surgery [35-37], and none have shown a significant difference in terms of morbidity or SSI, while the benefits of laparoscopy observed after uncomplicated AA were maintained.

## Single-trocar laparoscopy

A meta-analysis of randomized trials reported no clinical benefit of single-trocar laparoscopy [38].

Laparoscopy or laparotomy may be recommended for the management of uncomplicated AA (grade A). Laparoscopy should be preferred for the management of complicated AA.

# Choice of instruments

## **Dissecting instruments**

Two retrospective studies evaluated the choice of instruments for dissecting the mesoappendix and for hemostasis. In these two studies, the operative results using monopolar coagulation were similar to those using clips or mechanical stapling [39], or ultrasonic dissectors [40]. There was therefore a medico-economic benefit for monopolar coagulation.

#### Resection of the mesoappendix

No study has evaluated the benefit of systematic resection of the entire mesoappendix. However, a large French multicenter study noted that invasion of the mesoappendix was observed in 30% of patients with appendicular neuroendocrine tumor (NET) whose presentation mimicked AA [41]. Ligation of the mesoappendix at its base with en bloc resection could avoid classifying a small incidentallydiscovered NET as an incomplete, or R1 resection, leading to unnecessary and deleterious right hemi-colectomy in often young subjects [42].

## Control of the appendiceal stump

For uncomplicated AA, one of the most commonly used methods is endoloop ligation of the uninflamed or minimally inflamed appendiceal base using absorbable suture.

Closure of the appendiceal base by linear stapling is also possible with no impact on morbidity but with increased direct costs [43]. For complicated AA, a meta-analysis compared the use of a suture loop versus linear mechanical stapling; this found no decrease in the complication rate in the mechanical stapling group [44]. Finally, no benefit has been identified in favor of burying the appendiceal stump [45].

## Extraction of the appendix

In 2019, two contradictory studies were published in the journal Surgery on the benefit of extracting the appendix in a bag in order to avoid peritoneal contamination and thus

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reduce the risk of SSI [46,47]. A study based on retrospective data from the American registry concluded that use of the bag was beneficial with a reduction in the risk of intraabdominal abscess by 40% (odds ratio = 0.6 [0.42–0.95], P=0.03) while the other study concluded that there was no difference.

For appendectomy, the use of simple monopolar coagulation is recommended. (grade C). Complete excision of the mesoappendix is recommended when possible as long as it does not increase the surgical risk (expert agreement). Control of the appendiceal base by simple ligation is the preferred first-line treatment (grade A), but the use of a mechanical stapler or clip is feasible if simple ligature is not possible (grade B). The use of a single ligature is sufficient (grade B). The safety and low cost of the extraction bag argue in favor of its systematic use (grade B). Burying the appendiceal stump is not recommended (grade B).

#### Quality criteria for appendectomy

The development of AA in the appendicular stump is a rare complication (0.15%) and the persistence of a long residual appendiceal stump (>1 cm) is the only risk factor identified to date [48]. The purpose of electro-coagulating the mucous membrane of the appendiceal stump after appendectomy is to thermally destroy the bacteria present in the appendiceal lumen and thereby reduce the risk of contact-related abscess. However, there are no data in the literature to confirm its benefit.

The appendix should be ligated at its base and the length of the stump should not exceed one centimeter (grade C). No recommendation can be given regarding the benefit of electro-coagulation of the mucosa of the appendiceal stump (expert agreement).

#### Lavage and drainage

#### Uncomplicated appendicitis

A 1978 study found that for uncomplicated AA, there was no benefit for drainage [49], but no recent data have confirmed this result.

#### **Complicated appendicitis**

A meta-analysis of six randomized trials regarding open appendectomy for complicated AA found no benefit in favor of drainage and even showed a possible increase in the rate of complications and the duration of hospital stay in patients with a drain left in place [50]. In patients with peritonitis, peritoneal lavage + suction has not shown any benefit in reducing the risk of deep SSI compared to suction alone [51].

Drainage is not recommended after appendectomy for uncomplicated AA (grade B) or for complicated AA (grade A). Peritoneal lavage does not provide any benefit over suction alone and is therefore not recommended (grade A).

#### Pathology examination

A systematic review of the literature reported that systematic pathological analysis revealed incidental diagnosis of benign tumors in 0.5% and of malignant tumors in 0.2% of patients undergoing appendectomy for [52].

> In the absence of any evidence-based study, it is recommended that the resected appendix should be routinely sent for pathological examination (expert agreement).

#### Peri-operative management

#### Prophylactic antibiotic therapy

A Cochrane review confirmed the benefit of peri-operative antibiotic prophylaxis in reducing the SSI rate, regardless of the stage of AA [53].

#### Postoperative antibiotic therapy

A randomized study evaluated three modalities of antibiotic prophylaxis in uncomplicated AA: one group of patients received a single dose of antibiotics, another group received three doses, and a third group received antibiotic treatment for five postoperative days [54]. There was no statistically significant difference found between the three groups in terms of infectious complications. For complicated AA, only one retrospective study compared postoperative antibiotic therapy (combination of a 3rd-generation cephalosporin and an imidazole) for three days versus five days; this showed no benefit for prolonged antibiotic therapy [55].

Intra-operative antibiotic prophylaxis is recommended regardless of the stage of appendicitis (grade B). The choice of treatment should be based on the local bacterial ecology (expert agreement). Postoperative antibiotic therapy is not recommended for uncomplicated AA (grade B). Postoperative antibiotic therapy using a combination of a 3rd-generation cephalosporin and an imidazole is recommended for complicated cases of AA but should not be routinely prolonged beyond three days (grade C).

# **Special cases**

# Normal appearing appendix at the time of appendectomy

Although the definitive diagnosis of AA can be difficult in early AA, it has long been recommended that appendectomy be carried out, even when the surgeon finds a normal appearing appendix. This recommendation was based on the fact that it is, at times, difficult to distinguish macroscopically at surgery between a normal appendix and one with histological findings of AA [56].

# Postoperative morbidity and mortality after removal of a normal appendix

Flum and Koepsell showed that performance of an appendectomy for a normal appendix was associated with an increased risk of infectious complications (2.5% versus 1.8%, P < 0.001), of mortality (1.5 versus 0.2%, P < 0.001), increased duration of stay (5.8 versus 3.6 days, P < 0.001), and increased total cost (\$18,825 versus \$10,535, P < 0.001). These differences were statistically significantly different from those in patients operated on for pathologically confirmed AA.

Removal of a normal appendix has finite risks but it is sometimes difficult for the surgeon to distinguish between AA and a healthy appendix during surgery. No recommendation can therefore be made as to whether appendectomy should be performed when a macroscopically normal appearing appendix is found (expert agreement).

## Intra-operative discovery of Crohn's ileitis

The 2019 European recommendations on Crohn's disease state that when terminal ileitis is incidentally detected during surgery for another indication, involved bowel should not be resected [57].

When Crohn's ileitis is discovered during surgery for AA, it is recommended not to perform intestinal resection (grade A).

## Appendicitis in pregnant women

The occurrence of AA during pregnancy remains a serious condition and a source of obstetrical complications. An Australian study of 1024 pregnant women who underwent appendectomy reported a significant increase in the risk of premature birth, and both maternal and neonatal morbidity [58]. Since the diagnosis of AA is often delayed in the context of pregnancy, the rate of complicated forms of AA and of peritonitis is higher than outside the setting of pregnancy [59].

#### Place of medical treatment

A 2014 American registry study showed that non-surgical treatment of AA in pregnant women was associated with

increased risk. When comparing the results of antibiotic treatment with those of surgical treatment, it appeared that medical treatment was associated with a significant increase in maternal morbidity in terms of severe sepsis, septic shock, peritonitis and thromboembolic episodes [60].

Surgical treatment is recommended for AA in pregnancy (grade C).

### Choice of surgical approach

Data are conflicting concerning the optimal surgical approach for AA in pregnant women. Although higher rates of fetal death after laparoscopic AA have been reported in some studies, this finding is widely debated [61-63] and has not been found for other conditions requiring surgery [64].

No recommendation can be made regarding the preferred surgical approach in pregnant patients. Laparoscopy is a safe option when it is not limited by the height of the uterine fundus (expert agreement).

#### Peri-operative care

#### Thromboembolic prophylaxis

Due to the increased risk of phlebothrombosis during pregnancy, thromboembolic prophylaxis should be initiated and include at least leg compression (with, if possible, intermittent pneumatic compression during surgery) and early mobilization [65]. However, there is no data in the literature regarding whether heparin thromboprophylaxis should be prescribed for pregnant patients after appendectomy.

#### Fetal monitoring

Fetal vitality should assess by ultrasound (before 25 weeks' gestation) or by monitoring of the fetal heart rate (after 25 weeks' gestation), which must be performed pre and postoperatively in order to assess fetal vitality as well as uterine activity [65].

#### Tocolytic treatment

A systematic review published in 2008 found no statistically significant difference in the rate of preterm delivery between the group with prophylactic tocolysis (0/15) and the group without tocolysis (3/79; P=0.59) [66].

After appendectomy for AA in pregnant women, leg compression and early mobilization are recommended (grade B). Heparin thromboprophylaxis should be discussed on a case-by-case basis (expert agreement). Monitoring of the fetal heart rate should be performed pre- and post-operatively in order to assess fetal vitality (expert agreement). Prophylactic tocolysis is not recommended for routine use (grade B).

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#### Appendicitis in the elderly

A recent meta-analysis [67] of 12 studies compared laparoscopy (126,237 patients) versus laparotomy (213,201 patients) in elderly patients (>65 years) who underwent surgery for AA and demonstrated that laparoscopic appendectomy was associated with a reduction in postoperative mortality, morbidity, and duration of hospital stay.

Laparoscopy is recommended in elderly patients undergoing appendectomy for AA (grade B).

# Funding

None.

#### Acknowledgements

The SFCD and the SIAD would like to thank the members of the working and review groups who participated in these recommendations: Catherine Arvieux (''service de chirurgie digestive, CHU de Grenoble-Alpes, Grenoble, France''), Laura Beyer-Berjot (''service de chirurgie viscérale et digestive, hôpital Nord, Marseille, France''), Quentin Denost (''service de chirurgie digestive, GH Sud Haut-Lévêque, Bordeaux, France''), Antoine Brouquet (''service de chirurgie digestive, hôpital Bicêtre, Kremlin-Bicêtre, France''), Muriel Mathonnet (''service de chirurgie digestive, générale et endocrinienne, CHU Dupuytren, Limoges, France''), Guillaume Meurette (''service de chirurgie cancérologique digestive et endocrinienne, CHU de Nantes, Nantes, France'').

## **Disclosure of interest**

The authors declare that they have no competing interest.

### References

- Andersson REB. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. Br J Surg 2004;91:28–37, http://dx.doi.org/10.1002/bjs.4464.
- [2] Ortega-Deballon P, Ruiz de Adana-Belbel JC, Hernández-Matías A, García-Septiem J, Moreno-Azcoita M. Usefulness of laboratory data in the management of right iliac fossa pain in adults. Dis Colon Rectum 2008;51:1093–9, http://dx.doi.org/10.1007/s10350-008-9265-9.
- [3] Laméris W, van Randen A, Go PMNYH, et al. Single and combined diagnostic value of clinical features and laboratory tests in acute appendicitis. Acad Emerg Med 2009;16:835–42, http://dx.doi.org/10.1111/j.1553-2712.2009.00486.x.
- [4] Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med 1986;15:557-64, http://dx.doi.org/10.1016/s0196-0644(86)80993-3.
- [5] Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Med 2011;9:139, http://dx.doi.org/10.1186/1741-7015-9-139.
- [6] Andersson M, Andersson RE. The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the

Alvarado score. World J Surg 2008;32:1843-9, http://dx.doi.org/10.1007/s00268-008-9649-y.

- [7] Carroll PJ, Gibson D, El-Faedy O, et al. Surgeonperformed ultrasound at the bedside for the detection of appendicitis and gallstones: systematic review and meta-analysis. Am J Surg 2013;205:102–8, http://dx.doi.org/10.1016/j.amjsurg.2012.02.017.
- [8] Stewart JK, Olcott EW, Jeffrey RB. Sonography for appendicitis: nonvisualization of the appendix is an indication for active clinical observation rather than direct referral for computed tomography. J Clin Ultrasound 2012;40:455–61, http://dx.doi.org/10.1002/jcu.21928.
- [9] Xiong B, Zhong B, Li Z, et al. Diagnostic accuracy of noncontrast CT in detecting acute appendicitis: a meta-analysis of prospective studies. Am Surg 2015;81:626–9.
- [10] Hlibczuk V, Dattaro JA, Jin Z, Falzon L, Brown MD. Diagnostic accuracy of noncontrast computed tomography for appendicitis in adults: a systematic review. Ann Emerg Med 2010;55, http://dx.doi.org/10.1016/j.annemergmed.2009.06.509 [51-59.e.1].
- [11] Drake FT, Alfonso R, Bhargava P, et al. Enteral contrast in the computed tomography diagnosis of appendicitis: comparative effectiveness in a prospective surgical cohort. Ann Surg 2014;260:311-6, http://dx.doi.org/10.1097/SLA.0000000000272.
- [12] Duke E, Kalb B, Arif-Tiwari H, et al. A systematic review and meta-analysis of diagnostic performance of MRI for evaluation of acute appendicitis. AJR Am J Roentgenol 2016;206:508-17, http://dx.doi.org/10.2214/AJR.15.14544.
- [13] Eng KA, Abadeh A, Ligocki C, et al. Acute appendicitis: a meta-analysis of the diagnostic accuracy of US, CT, and MRI as second-line imaging tests after an initial US. Radiology 2018;288:717–27, http://dx.doi.org/10.1148/radiol.2018180318.
- [14] Hiersch L, Yogev Y, Ashwal E, From A, Ben-Haroush A, Peled Y. The impact of pregnancy on the accuracy and delay in diagnosis of acute appendicitis. J Matern Fetal Neonatal Med 2014;27:1357–60, http://dx.doi.org/10.3109/14767058.2013.858321.
- [15] Kastenberg ZJ, Hurley MP, Luan A, et al. Cost-effectiveness of preoperative imaging for appendicitis after indeterminate ultrasonography in the second or third trimester of pregnancy. Obstet Gynecol 2013;122:821–9, http://dx.doi.org/10.1097/AOG.0b013e3182a4a085.
- [16] Lourenco P, Brown J, Leipsic J, Hague C. The current utility of ultrasound in the diagnosis of acute appendicitis. Clin Imaging 2016;40:944–8, http://dx.doi.org/10.1016/j.clinimag.2016.03.012.
- [17] Anderson SW, Rhea JT, Milch HN, Ozonoff A, Lucey BC, Soto JA. Influence of body habitus and use of oral contrast on reader confidence in patients with suspected acute appendicitis using 64 MDCT. Emerg Radiol 2010;17:445–53, http://dx.doi.org/10.1007/s10140-010-0875-x.
- [18] Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. prospective multicenter Α randomized controlled trial. World J Surg 2006;30:1033-7, http://dx.doi.org/10.1007/s00268-005-0304-6.
- [19] Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg 2009;96:473–81, http://dx.doi.org/10.1002/bjs.6482.
- [20] Turhan AN, Kapan S, Kütükçü E, Yiğitbaş H, Hatipoğlu S, Aygün E. Comparison of operative and non operative management of acute appendicitis. Ulus Travma Acil Cerrahi Derg 2009;15:459–62.
- [21] Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet 2011;377:1573-9, http://dx.doi.org/10.1016/S0140-6736(11)60410-8.

#### 10

- [22] Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs. appendectomy for treatment of uncomplicated acute appendicitis: the APPAC ran-2015;313:2340-8, domized clinical trial. JAMA http://dx.doi.org/10.1001/jama.2015.6154.
- [23] Eriksson S, Granström L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. Br J Surg 1995;82:166–9.
- [24] Harnoss JC, Zelienka I, Probst P, et al. Antibiotics versus surgical therapy for uncomplicated appendicitis: systematic review and meta-analysis of controlled trials (PROS-PERO 2015: CRD42015016882). Ann Surg 2017;265:889–900, http://dx.doi.org/10.1097/SLA.00000000002039.
- [25] Salminen P, Tuominen R, Paajanen H, et al. Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC Randomized Clinical Trial. JAMA 2018;320:1259-65, http://dx.doi.org/10.1001/jama.2018.13201.
- [26] Pitout JDD, Laupland KB. Extended-spectrum betalactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008;8:159–66, http://dx.doi.org/10.1016/S1473-3099(08)70041-0.
- [27] Maldonado N, Castro B, Berrio I, Manjarrés M, Robledo C, Robledo J. Ertapenem resistance in 2 tertiarycare hospitals: Microbiology, epidemiology, and risk factors. Enferm Infecc Microbiol Clin 2017;35:511–5, http://dx.doi.org/10.1016/j.eimc.2015.11.009.
- [28] Lasek A, Pędziwiatr M, Kenig J, et al. The significant impact of age on the clinical outcomes of laparoscopic appendectomy: results from the Polish Laparoscopic Appendectomy multicenter large cohort study. Medicine (Baltimore) 2018;97:e13621, http://dx.doi.org/10.1097/MD.00000000013621.
- [29] Andersson RE. Short and long-term mortality after appendectomy in Sweden 1987 to 2006. Influence of appendectomy diagnosis, sex, age, co-morbidity, surgical method, hospital volume, and time period. A national population-based cohort study. World J Surg 2013;37:974–81, http://dx.doi.org/10.1007/s00268-012-1856-x.
- [30] van Dijk ST, van Dijk AH, Dijkgraaf MG, Boermeester MA. Metaanalysis of in-hospital delay before surgery as a risk factor for complications in patients with acute appendicitis. Br J Surg 2018;105:933-45, http://dx.doi.org/10.1002/bjs.10873.
- [31] Nimmagadda N, Matsushima K, Piccinini A, et al. Complicated appendicitis: immediate operation or trial of nonoperative management? Am J Surg 2019;217:713-7, http://dx.doi.org/10.1016/j.amjsurg.2018.12.061.
- [32] Darwazeh G, Cunningham SC, Kowdley GC. A systematic review of perforated appendicitis and phlegmon: interval appendectomy or wait-and-see? Am Surg 2016;82:11–5.
- [33] Mällinen J, Rautio T, Grönroos J, et al. Risk of appendiceal neoplasm in periappendicular abscess in patients treated with interval appendectomy vs. follow-up with magnetic resonance imaging: 1-year outcomes of the peri-appendicitis acuta randomized clinical trial. JAMA Surg 2019;154:200–7, http://dx.doi.org/10.1001/jamasurg.2018.4373.
- [34] Jaschinski T, Mosch CG, Eikermann M, Neugebauer EA, Sauerland S. Laparoscopic versus open surgery for suspected appendicitis. Cochrane Database Syst Rev 2018;11, http://dx.doi.org/10.1002/14651858.CD001546.pub4 [CD001546].
- [35] Thomson J-E, Kruger D, Jann-Kruger C, et al. Laparoscopic versus open surgery for complicated appendicitis: a randomized controlled trial to prove safety. Surg Endosc 2015;29:2027–32, http://dx.doi.org/10.1007/s00464-014-3906-y.
- [36] Taguchi Y, Komatsu S, Sakamoto E, Norimizu S, Shingu Y, Hasegawa H. Laparoscopic versus open surgery for complicated appendicitis in adults: a randomized controlled trial. Surg Endosc 2016;30:1705–12, http://dx.doi.org/10.1007/s00464-015-4453-x.
- [37] Talha A, El-Haddad H, Ghazal A-E, Shehata G. Laparoscopic versus open appendectomy for perforated appendicitis in adults: randomized clinical trial. Surg Endosc 2019, http://dx.doi.org/10.1007/s00464-019-06847-2.

- [38] Vettoretto N, Cirocchi R, Randolph J, Morino M. Acute appendicitis can be treated with single-incision laparoscopy: a systematic review of randomized controlled trials. Colorectal Dis 2015;17:281-9, http://dx.doi.org/10.1111/codi.12839.
- [39] Davila D, Russek K, Franklin ME. Laparoscopic appendectomy: vascular control of the appendicular artery using monopolar cauterization versus clips. J Laparoendosc Adv Surg Tech A 2012;22:165–7, http://dx.doi.org/10.1089/lap.2010.0312.
- [40] Lee JS, Hong TH. Comparison of various methods of mesoappendix dissection in laparoscopic appendectomy. J Laparoendosc Adv Surg Tech A 2014;24:28–31, http://dx.doi.org/10.1089/lap.2013.0374.
- [41] Rault-Petit B, Do Cao C, Guyétant S, et al. Current management and predictive factors of lymph node metastasis of appendix neuroendocrine tumors: a national study from the French Group of Endocrine Tumors (GTE). Ann Surg 2019;270:165-71, http://dx.doi.org/10.1097/SLA.00000000002736.
- [42] Pape U-F, Niederle B, Costa F, et al. ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). Neuroendocrinology 2016;103:144–52, http://dx.doi.org/10.1159/000443165.
- [43] van Rossem CC, van Geloven AAW, Schreinemacher MHF, Bemelman WA, Snapshot appendicitis collaborative study group. Endoloops or endostapler use in laparoscopic appendectomy for acute uncomplicated and complicated appendicitis: no difference in infectious complications. Surg Endosc 2017;31:178–84, http://dx.doi.org/10.1007/s00464-016-4951-5.
- [44] Ceresoli M, Tamini N, Gianotti L, Braga M, Nespoli L. Are endoscopic loop ties safe even in complicated acute appendicitis? A systematic review and meta-analysis. Int J Surg 2019;68:40–7, http://dx.doi.org/10.1016/j.ijsu.2019.06.011.
- [45] Street D, Bodai BI, Owens LJ, Moore DB, Walton CB, Holcroft JW. Simple ligation vs. stump inversion in appendectomy. Arch Surg 1988;123:689–90, http://dx.doi.org/10.1001/archsurg.1988.01400300031003.
- [46] Fields AC, Lu P, Palenzuela DL, et al. Does retrieval bag use during laparoscopic appendectomy reduce postoperative infection? Surgery 2019;165:953-7, http://dx.doi.org/10.1016/j.surg.2018.11.012.
- [47] Turner SA, Jung HS, Scarborough JE. Utilization of a specimen retrieval bag during laparoscopic appendectomy for both uncomplicated and complicated appendicitis is not associated with a decrease in postoperative surgical site infection rates. Surgery 2019;165:1199–202, http://dx.doi.org/10.1016/j.surg.2019.02.010.
- [48] Dikicier E, Altintoprak F, Ozdemir K, et al. Stump appendicitis: a retrospective review of 3130 consecutive appendectomy cases. World J Emerg Surg 2018;13:22, http://dx.doi.org/10.1186/s13017-018-0182-5.
- [49] Stone HH, CA, Millikan WJ. Abdom-Hooper inal drainage following appendectomy and Surg cholecystectomy. 1978:187:606-12. Ann http://dx.doi.org/10.1097/00000658-197806000-00004.
- [50] Li Z, Zhao L, Cheng Y, Cheng N, Deng Y. Abdominal drainage to prevent intra-peritoneal abscess after open appendectomy for complicated appendicitis. Cochrane Database Syst Rev 2018;5, http://dx.doi.org/10.1002/14651858.CD010168.pub3 [CD010168].
- [51] Siotos C, Stergios K, Prasath V, et al. Irrigation versus suction in laparoscopic appendectomy for complicated appendicitis: a meta-analysis. J Surg Res 2019;235:237–43, http://dx.doi.org/10.1016/j.jss.2018.10.005.
- [52] Swank HA, Eshuis EJ, Ubbink DT, Bemelman WA. Is routine histopathological examination of appendectomy specimens useful? A systematic review of the literature. Colorectal Dis 2011;13:1214–21, http://dx.doi.org/10.1111/j.1463-1318.2010.02457.x.
- [53] Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. Cochrane Database Syst Rev 2005, http://dx. doi.org/10.1002/14651858.CD001439.pub2 [CD001439].

- [54] Mui LM, Ng CSH, Wong SKH, et al. Optimum duration of prophylactic antibiotics in acute nonperforated appendicitis. ANZ J Surg 2005;75:425–8, http://dx.doi.org/10.1111/j.1445-2197.2005.03397.x.
- [55] van Rossem CC, Schreinemacher MHF, van Geloven AAW, Bemelman WA, Snapshot Appendicitis Collaborative Study Group. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. JAMA Surg 2016;151:323–9, http://dx.doi.org/10.1001/jamasurg.2015.4236.
- [56] Strong S, Blencowe N, Bhangu A. How good are surgeons at identifying appendicitis? Results from a multi-centre cohort study. Int J Surg 2015;15:107–12, http://dx.doi.org/10.1016/j.ijsu.2015.01.032.
- [57] Bemelman WA, Warusavitarne J, Sampietro GM, et al. ECCO-ESCP consensus on surgery for Crohn's disease. J Crohn Colitis 2017;12:1–16, http://dx.doi.org/10.1093/ecco-jcc/jjx061.
- [58] Ibiebele I, Schnitzler M, Nippita T, Ford JB. Appendicectomy during pregnancy and the risk of preterm birth: a population data linkage study. Aust N Z J Obstet Gynaecol 2019;59:45–53, http://dx.doi.org/10.1111/ajo.12807.
- [59] Cappell MS, Friedel D. Abdominal pain during pregnancy. Gastroenterol Clin North Am 2003;32:1–58, http://dx.doi.org/10.1016/s0889-8553(02)00064-x.
- [60] Abbasi N, Patenaude V, Abenhaim HA. Management and outcomes of acute appendicitis in pregnancy-populationbased study of over 7000 cases. BJOG 2014;121:1509–14, http://dx.doi.org/10.1111/1471-0528.12736.
- [61] Chakraborty J, Kong JC, Su WK, et al. Safety of laparoscopic appendicectomy during pregnancy: a systematic

review and meta-analysis. ANZ J Surg 2019;89:1373-8, http://dx.doi.org/10.1111/ans.14963.

- [62] Frountzas M, Nikolaou C, Stergios K, Kontzoglou K, Toutouzas K, Pergialiotis V. Is the laparoscopic approach a safe choice for the management of acute appendicitis in pregnant women? A meta-analysis of observational studies. Ann R Coll Surg Engl 2019;101:235–48, http://dx.doi.org/10.1308/rcsann.2019.0011.
- [63] Lee SH, Lee JY, Choi YY, Lee JG. Laparoscopic appendectomy versus open appendectomy for suspected appendicitis during pregnancy: a systematic review and updated meta-analysis. BMC Surg 2019;19:41, http://dx.doi.org/10.1186/s12893-019-0505-9.
- [64] Shigemi D, Aso S, Matsui H, Fushimi K, Yasunaga H. Safety of laparoscopic surgery for benign diseases during pregnancy: a nationwide retrospective cohort study. J Minim Invasive Gynecol 2019;26:501-6, http://dx.doi.org/10.1016/j.jmig.2018.06.008.
- [65] Pearl JP, Price RR, Tonkin AE, Richardson WS, Stefanidis D. SAGES guidelines for the use of laparoscopy during pregnancy. Surg Endosc 2017;31:3767–82, http://dx.doi.org/10.1007/s00464-017-5637-3.
- [66] Walsh CA, Tang T, Walsh SR. Laparoscopic versus open appendicectomy in pregnancy: a systematic review. Int J Surg 2008; 6:339–44, http://dx.doi.org/10.1016/j.ijsu.2008.01.006.
- [67] Wang D, Dong T, Shao Y, Gu T, Xu Y, Jiang Y. Laparoscopy versus open appendectomy for elderly patients, a metaanalysis and systematic review. BMC Surg 2019;19:54, http://dx.doi.org/10.1186/s12893-019-0515-7.