Emergency surgery 1

Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management

Aneel Bhangu, Kjetil Søreide, Salomone Di Saverio, Jeanette Hansson Assarsson, Frederick Thurston Drake

Lancet 2015; 386: 1278–87

See **Editorial** page 1212

This is the first in a **Series** of three papers about emergency surgery

Academic Department of Surgery, Queen Elizabeth Hospital, Edgbaston, Birmingham UK (A Bhangu PhD); **College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK** (A Bhangu); **Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, Norway** (Prof K Søreide MD); **Department of Clinical Medicine, University of Bergen, Bergen, Norway** (Prof K Søreide); **Emergency and General Surgery Department, CA Pizzardi Maggiore Hospital, Bologna, Italy** (S Di Saverio MD); **Department of Surgery, Kalmar County Hospital, Kalmar, Sweden** (J H Assarsson MD); **and Department of Surgery, University of Washington, Seattle, WA, USA** (F T Drake MD)

Correspondence to: Prof Kjetil Søreide, Department of Gastrointestinal Surgery, Stavanger University Hospital, PO Box 8100, N-4068 Stavanger, Norway **ksoreide@mac.com**

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

Introduction

Acute appendicitis is one of the most common general surgical emergencies worldwide, with an estimated lifetime risk reported to be 7–8%.[1] Accordingly, appendectomy is one of the most frequently performed surgical procedures worldwide and represents an important burden on modern health systems. Despite being so common, a poor understanding of the causes of appendicitis and an absence of reliable discriminators for disease severity still persist. An insufficient amount of clinical research has led to uncertainty about best practice, with subsequent international variation in delivery and, as a possible consequence, variation in outcome. The aim of this review is to provide a state-of-the-art update about the existing controversies in pathogenesis, diagnosis, and clinical management of acute appendicitis.

Evolving understanding of acute appendicitis

Epidemiology

Acute appendicitis occurs at a rate of about 90–100 patients per 100 000 inhabitants per year in developed countries. The peak incidence usually occurs in the second or third decade of life, and the disease is less common at both extremes of age. Most studies show a slight male predominance. Geographical differences are reported, with lifetime risks for appendicitis of 16% in South Korea, 9·0% in the USA, and 1·8% in Africa.[2,3]

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and Embase, from Jan 1, 2000, to the final search date (Feb 1, 2015). We used the search terms "appendicitis" or "acute" in combination with the terms "diagnosis" or "treatment". We mostly selected publications from within the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged to be relevant. We also searched ClinicalTrials.gov (Jan 1, 2000–Feb 1, 2015) for ongoing trials in acute appendicitis.

Causes

Direct luminal obstruction can cause appendicitis (often by a faecolith, lymphoid hyperplasia, or impacted stool; rarely by an appendiceal or caecal tumour) but these tend to be exceptions rather than regular occurrences. Although several infectious agents are known to trigger or be associated with appendicitis,[4,5] the full range of specific causes remains unknown.[6] Recent theories focus on genetic factors, environmental influences, and infections.

Although no defined gene has been identified, the risk of appendicitis is roughly three-times higher in members of families with a positive history for appendicitis than in those with no family history,[7] and a study of twins suggests that genetic effects account for about 30% of the variation in risk for developing appendicitis.[8]

Environmental factors can play a part, since studies report a predominantly seasonal presentation during the summer, which has been statistically associated with a raised amount of ambient ground-level ozone, used as a marker of air pollution.[9] Time-space clusters of disease presentation might further indicate an infectious cause. Pregnant women seem to have a reduced risk for appendicitis, with the lowest risk in the third trimester, although appendicitis is a diagnostic challenge when it occurs in this subgroup.[10]

Population-level ethnicity data from the UK and USA show that appendicitis is less common in non-white groups than in white individuals, although we have little understanding of the reasons why.[11] Conversely, ethnic minority groups are at an increased risk of perforation when they have appendicitis, although this finding might be due to unequal access to care rather than predisposition; definitive evidence is scarce.[12]

Neurogenic appendicitis has also been suggested as a causative mechanism of pain. Characterised by excess proliferation of nerve fibres into the appendix with overactivation of neuropeptides, this poorly understood disorder might be quite common, especially in children. From a case series of 29 patients, neurogenicity was present in both inflamed and normal appendix specimens.[13] This finding could theoretically provide an explanation for improvement after normal appendectomy, although evidence for this and for its general importance is scarce.

The microbiome in appendicitis

The appendix might serve as a microbial reservoir for repopulation of the gastrointestinal tract in times of necessity, but relevant data are scarce. The bacterial growth in removed inflamed appendices consists of a mix of aerobic and anaerobic bacteria, most often dominated by *Escherichia coli* and *Bacteroides* spp. A small novel study that used next-generation sequencing recorded a larger number and greater variation of (up to 15) bacterial phylae than expected in patients with acute appendicitis.[14] Notably, the presence of *Fusobacterium* spp seemed to correspond to disease severity (including risk of perforation), corroborating findings from archival material in two other studies.[15]

Evidence for a role for immune balance comes from epidemiological studies showing a reduced risk of developing ulcerative colitis after appendectomy,[16] with a slightly increased risk of Crohn's disease.[17] Furthermore, appendectomy has been associated with increased risk of future severe *Clostridium difficile* colitis necessitating colectomy.[18] Whether or not these findings point to changes of the human gut microbiome or to the removal of a lymphoid organ with a role in human immune function is unknown at present.

Key messages

- An accurate preoperative diagnosis of acute appendicitis is challenging, since the diagnosis must be entertained in patients of all ages presenting with an acute abdomen.
- Worldwide variation in care is indicated by differences in use of computed tomography (CT), administration of antibiotics, and removal of a healthy (normal) appendix.
- A clinical classification system based on simple (non-perforated) and complex (gangrenous or perforated) inflammation allows a stratified approach to management. This stratification includes timing of surgery, trials of non-operative management, and use of postoperative antibiotics.
- Independent of diagnostic and management approach, the perforation rate has remained stable. The non-perforated appendicitis rate has changed, which suggests possible independent disease processes.
- Increased use of preoperative CT results in lower normal appendicectomy rates, at the cost of higher radiation exposure for patients.
- Some cases of simple appendicitis can be treated with antibiotics alone, although more accurate selection criteria to support this approach are needed. At present, patients should be counselled about a high rate of failure (25–30%) at 1 year.
- Appendicectomy is related to inflammatory bowel disease, suggesting immunological mechanisms and the potential role of the gut microbiome.
- Laparoscopy is the surgical approach of choice when local resources allow, with slightly improved short-term outcomes (including less postoperative pain and shorter length of hospital stay) but no difference in long-term outcomes compared with open surgery.

Classification

Irrespective of the cause, clinical stratification of severity at presentation, which relies on preoperative assessment

	Macroscopic appearances	Microscopic appearances	Clinical relevance
Normal appendix (figure 1A)			
Normal underlying pathology	No visible changes	Absence of any abnormality	Consider other causes
Acute intraluminal inflammation	No visible changes	Luminal neutrophils only with no mucosal abnormality	Might be the cause of symptoms, but consider other causes
Acute mucosal/submucosal inflammation	No visible changes	Mucosal or submucosal neutrophils and/or ulceration	Might be the cause of symptoms, but consider other causes
Simple, non-perforated appendicitis (figure 1B)			
Suppurative/phlegmonous	Congestion, colour changes, increased diameter, exudate, pus	Transmural inflammation, ulceration, or thrombosis, with or without extramural pus	Likely cause of symptoms
Complex appendicitis (figure 1C)			
Gangrenous	Friable appendix with purple, green, or black colour changes	Transmural inflammation with necrosis	Impending perforation
Perforated	Visible perforation	Perforation; not always visible in microscope	Increased risk of postoperative complications
Abscess (pelvic/abdominal)	Mass found during examination or abscess seen on preoperative imaging; or abscess found at surgery	Transmural inflammation with pus with or without perforation	Increased risk of postoperative complications

Modified from the classification system by Carr.[6] Figure 1 provides photographic examples of macroscopic pathology.

Table 1: **Stratified disease approach to acute appendicitis**

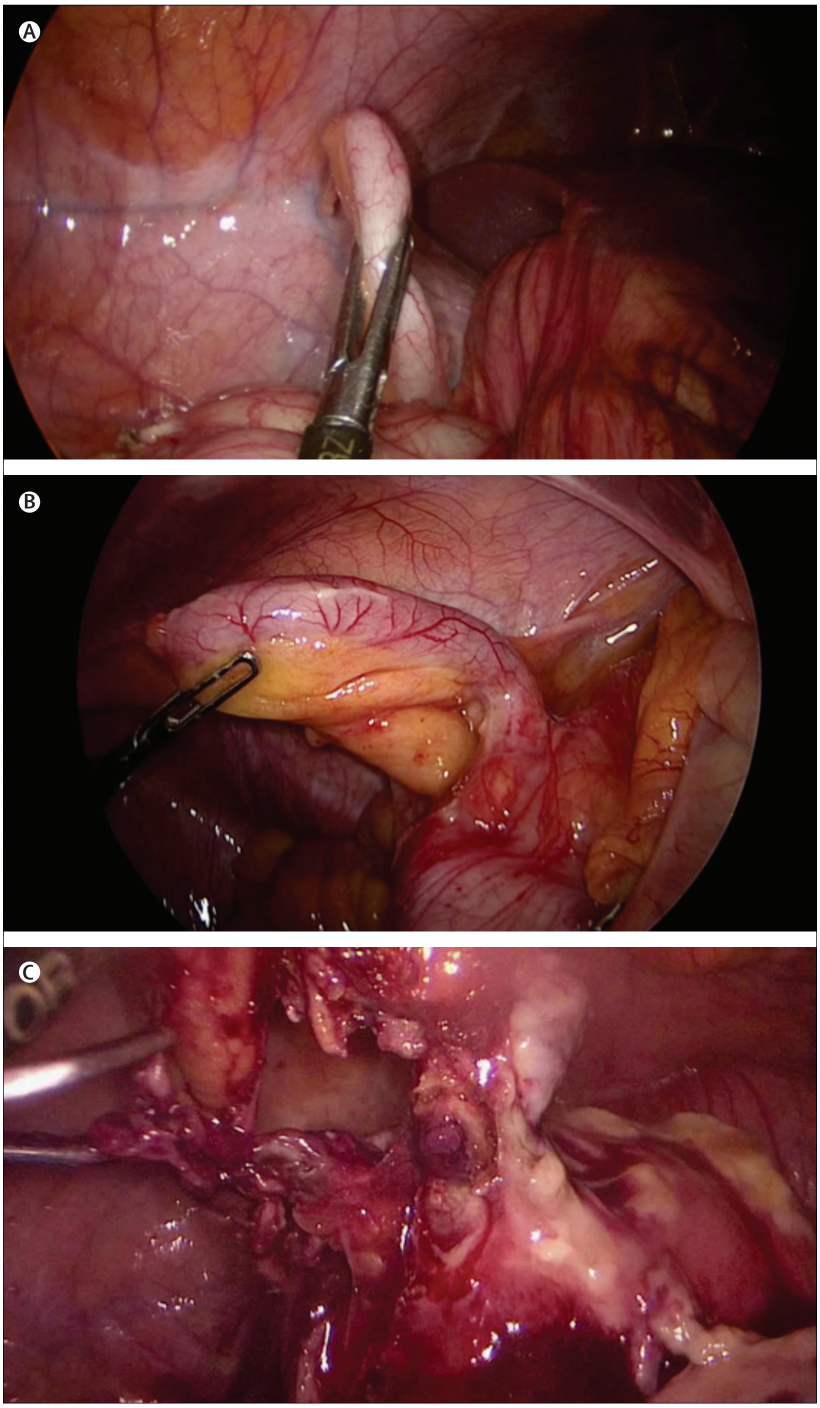

Figure 1: **Macroscopic pathological features of appendicitis**
(A) Macroscopically normal appendix. (B) Simple inflamed appendicitis. (C) Complex appendicitis showing perforation with pus formation.

rather than postoperative histopathology, is advantageous for surgeons and patients because it allows stratified perioperative planning. However, many patients can only be classified with an equivocal diagnosis, which remains one of the most challenging dilemmas in the management of acute abdominal pain. Table 1 and figure 1 show the pathological basis of each stratum of appendicitis.

A debated theory divides acute appendicitis into separate forms of acute inflammation processes with different fates. One is the simple inflamed appendicitis without gangrene or necrosis that does not proceed to perforation. This so-called reversible form can present as phlegmonous (pus-producing) or advanced inflammation (but without gangrene or perforation) that might need surgery, or alternatively as a mild inflammation that can settle, either spontaneously or with antibiotic therapy. By contrast, the more severe inflammatory type proceeds rapidly to gangrene, perforation, or both. Data to support separate types of inflammation arise from clinical registries[19] and laboratory studies.[20] In population-based studies, the rate of non-perforated appendicitis has overall decreased in male patients between 1970 and 2004, with even greater declines in female patients.[21] However, a similar decrease in rate of perforated appendicitis was not reported. Although this finding suggests that a disconnect exists between perforated and non-perforated disease, it might also be indicative of improved diagnosis with increased use of imaging during the period, reclassifying some previously labelled early appendicitis into other diagnoses.

Modern diagnostic strategies

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

Biomarkers

Biomarkers are used to supplement patient history and clinical examination, especially in children, women of fertile age, and elderly patients when diagnosis is difficult. No inflammatory marker alone, such as white blood cell count, C-reactive protein, or other novel tests, including procalcitonin, can identify appendicitis with high specificity and sensitivity.[22] However, white blood cell count is obtained in virtually all patients who are assessed for appendicitis, when available. A range of novel biomarkers has been suggested during the past decade, including bilirubin, but these do not have external validity and suffer repeatedly from low sensitivity, which means they are unlikely to come into clinical practice.[23]

Clinical decision rules or risk scores

Each and every clinical sign for appendicitis alone has a poor predictive value. However, in combination, their predictive ability is much stronger, although not perfectly accurate. Consequently, several clinical risk scores have been developed, the purpose of which is to identify low, intermediate, and high-risk patients for appendicitis (figure 2), allowing further investigations to be stratified according to risk (figure 3).[24]

The most widely used score so far is the Alvarado score. A systematic review and pooled diagnostic accuracy study showed that the score has good sensitivity (especially in men) but low specificity, limiting its clinical impact and meaning that few surgeons rely on it to guide management above and beyond their own clinical opinion. The predictive ability of each component of the recently derived modified Alvarado score in children is shown in appendix p 2.[25] Recently, the appendicitis inflammatory response score has been developed, and seems to outperform the Alvarado score in terms of accuracy.[26]

See Online for appendix

Transabdominal ultrasonography

Initial reliance on ultrasound has become more guarded recently because of moderate sensitivity (86%, 95% CI 83–88) and specificity (81%, 78–84) as shown through pooled diagnostic accuracy of 14 studies,[27] limiting its diagnostic ability. Owing to the need for a specialist operator, it is often unavailable out of hours and at weekends, further limiting its usefulness. Its first-line investigative role is greatest in children, who typically have thinner musculature, less abdominal fat, and a greater need for radiation avoidance than adult patients.

Computed tomography

In adolescent and adult patients, computed tomography (CT) has become the most widely accepted imaging strategy. In the USA, it is used in 86% of patients, with a sensitivity of 92·3%.[28] This approach has led to a normal appendectomy rate of 6%. Uptake outside North America is lower because of concerns about the risk of radiation exposure in children and young adults, variation in hospitals' remuneration systems, unavailability outside normal hours, and lack of scanners in low-resource hospitals.

In one randomised controlled trial comparing low-dose versus standard-dose CT in 891 patients, the normal appendectomy rate was 3·5% for low-dose CT versus 3·1% for standard-dose CT, although these advanced technology scanners are not in widespread use.[29] For older patients at increased risk of malignancy, preoperative CT is recommended to identify malignancy masquerading as (or causing) appendicitis. Selective CT based on clinical risk scores is likely to target its use and justify radiation exposure (figure 3).

MRI

MRI for patients with an acute abdomen might eliminate the risks associated with radiation use in young patients. However, little is known about the exact use and accuracy of MRI in the acute abdomen. First, few units worldwide are able to provide immediate-access MRI at present. Second, MRI has no better accuracy than ultrasound in discriminating perforated appendicitis.[30]

Clinical risk score

	Alvarado score	AIR score
Symptoms		
Nausea or vomiting	1	
Vomiting		1
Anorexia	1	
Migration of pain to the right lower quadrant	1	
Signs		
Pain in right lower quadrant	2	1
Rebound tenderness or muscular defence	1	
Light		1
Medium		2
Strong		3
Body temperature >37·5°C	1	
Body temperature >38·5°C		1
Laboratory tests		
Leucocytosis shift	1	
Polymorphonuclear leucocytes		
70–84%		1
≥85%		2
White blood cell count		
$>10·0\times10^9$/L	2	
$10·0–14·9\times10^9$/L		1
$\geq15·0\times10^9$/L		2
C-reactive protein concentration		
10–49 g/L		1
≥50 g/L		2
Total score	**10**	**12**

Risk of appendicitis

Alvarado score 1–4 AIR score 0–4 **Low risk**	Alvarado score 5–6 AIR score 5–8 **Intermediate risk**	Alvarado score 7–10 AIR score 9–10 **High risk**

Figure 2: **Clinical risk scoring for suspected acute appendicitis**
AIR=appendicitis inflammatory response.

Diagnostic strategies in young female patients

In female patients of reproductive age, the initial diagnostic approach includes urinary pregnancy test to identify possible ectopic pregnancy and transvaginal ultrasound to identify ovarian pathology. In equivocal cases, a thorough clinical assessment (including pelvic examination) by on-call gynaecologists can differentiate alternative pathology and direct further investigations. Early laparoscopy has been suggested as a method to improve diagnosis in female patients with an equivocal diagnosis, and has been assessed in single-centre randomised trials so far.[31] When compared with clinical observation and selective escalation, routine early laparoscopy increases the rate of diagnosis and could allow earlier discharge from hospital than observation alone.[32,33]

Differentiation of simple from complex disease

Neither CT nor emergency MRI are able to discriminate between non-perforated and perforated appendicitis,[30] which limits clinicians' ability to objectively stratify

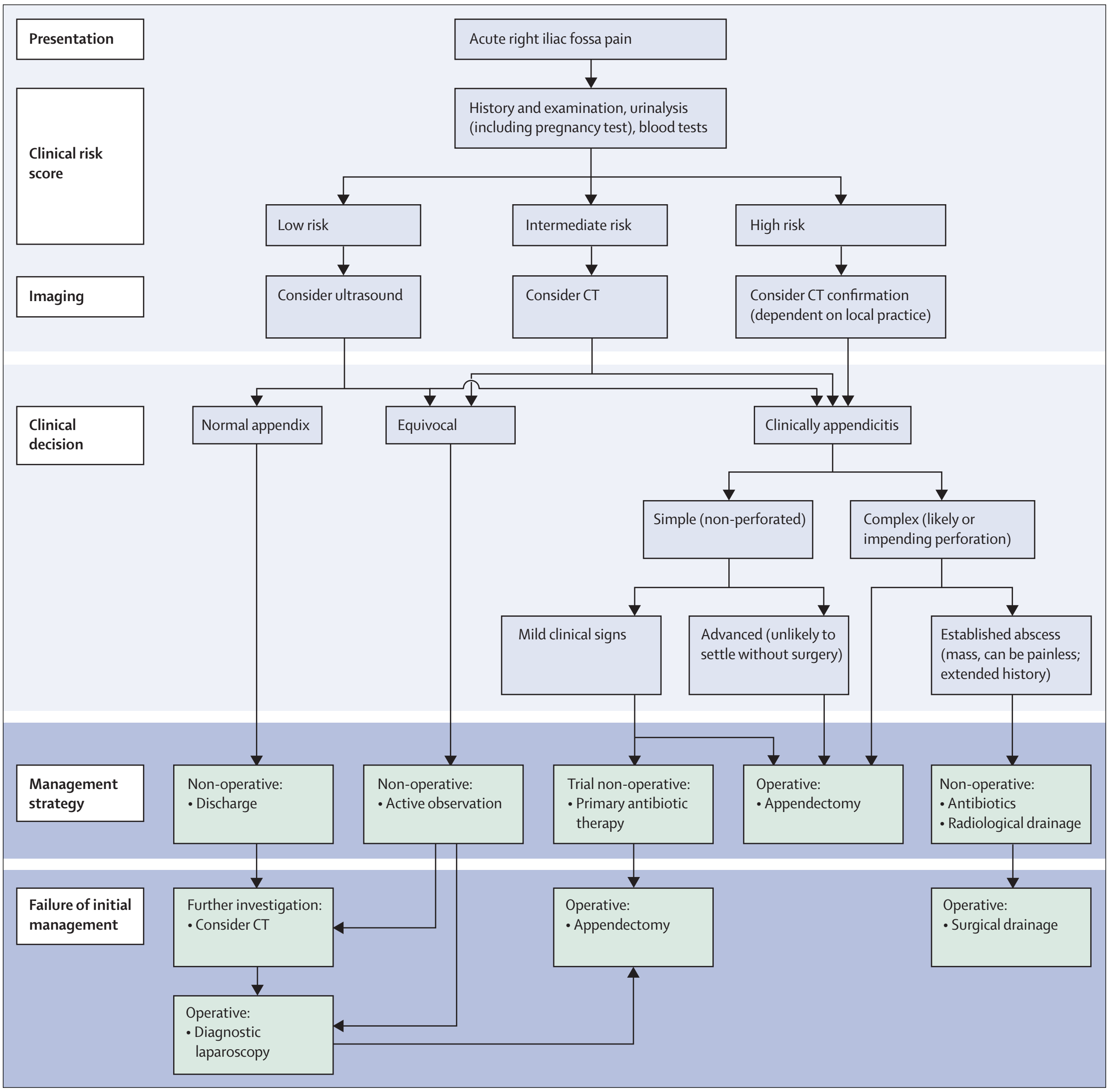

Figure 3: **Flowchart of guidance for a stratified approach to preoperative management of suspected appendicitis**

patients for short in-hospital delays before surgery or for selection to trials of nonoperative treatment with antibiotics. Presence of an appendicolith in radiological imaging is associated with both an increased risk of antibiotic failure and recurrence,[34] whereas the triad of C-reactive protein level below 60 g/L, white blood cell count lower than than 12×10^9, and age younger than 60 years has been reported to predict antibiotic success.[35]

Treatment strategies

Non-operative management

Primary antibiotic treatment of simple inflamed appendicitis

Recently, antibiotics have been proposed as a single treatment for uncomplicated appendicitis, but not without controversy. A meta-analysis[36] of randomised controlled trials comparing antibiotics with appendectomy has shown that although antibiotic treatment alone can be successful, patients should be made aware of a failure rate at 1 year of around 25–30% with need for readmission or surgery (table 2). A pilot randomised controlled trial suggests that this strategy might also be effective in children,[41] although similarly to adults, 38% need subsequent appendectomy during follow-up.

The randomised controlled trials done so far have methodological limitations, including different criteria for diagnosis, low inclusion rate of eligible patients, inadequate outcome measures, and different follow-up between groups.[37–40] Importantly, some studies did not

	Study design	Patients (n)	Antibiotic-treated patients (n)	Age (years)/sex	Diagnosis	Antibiotic administration route and duration (days)	Recovery rate* (%)	1-year failure rate† (%)	1-year efficacy rate‡(%)
Eriksson and Ganstrom (1995)[37]	RCT	40	0	≥18	Ultrasound	Intravenous 2 days, oral 8 days	95%	37%	60%
Styrud et al (2006)[38]	Multicentre RCT	252	128	18–50/male	Clinical	Intravenous 2 days, oral 10 days	88%	14%	76%
Hansson et al (2009)[39]	Multicentre RCT	369	119	≥18	Clinical (+ultrasound/CT)§	Intravenous 1 day, oral 9 days	91%	14%	78%
Vons et al (2011)[40]	Multicentre RCT	239	120	≥18	CT	Intravenous 2 days, oral 8 days	88%	25%	68%
Svensson et al (2015)[41]	RCT	50	24	5–15	Ultrasound (+CT)§	Intravenous 2 days, oral 8 days	92%	5%	62%
Turhan et al (2009)[42]	Prospective interventional	290	107	≥16	Ultrasound or CT	Intravenous 3 days, oral 7 days	82%	10%	74%
Hansson et al (2012)[43]	Prospective interventional	558	442	≥16	Clinical (+ultrasound/CT)§	Intravenous 1 day, oral 9 days	77%	11%	69%
Di Saverio et al (2014)[44]	Prospective interventional	159	159	≥14	Clinical (+ultrasound/CT)§	Total 5–7	88%	13%	77%
APPAC study (2015)[45]	Multicentre RCT (estimated completion in 2025)	530	257	18–60	Confirmed by CT	Intravenous 3 days, oral 7 days	94%	27%	73%

RCT=randomised controlled trial. CT=computed tomography. *Initially successful non-operative antibiotic treatment. †Need for surgery at 1 year after initially successful non-antibiotic treatment. ‡Overall efficacy at 1 year including recurrence. §If judged clinically necessary.

Table 2: **Clinical trials comparing primary antibiotic treatment versus surgery for acute appendicitis**

confirm diagnosis with imaging, which in combination with substantial crossover between study groups has led some surgeons to question the validity of the findings. Within the most recent meta-analysis, three studies originated from Sweden and one from France, meaning that these findings might not be automatically generalisable worldwide because of ethnicity and health-care access issues. The latest randomised trial, not included within this meta-analysis, was based on CT-confirmed diagnosis and adds more north European data (Finland); it showed a similar 1-year failure rate (27%) to previous studies.[45]

Until more accurate selection criteria emerge (based on combinations of clinical risk scores and imaging) for patients or subgroups who are likely to succeed in the long term from primary antibiotic treatment, suitable patients with mild symptoms (representing mild-to-moderate appendicitis) should ideally be entered into randomised clinical trials, or at least be advised about a 25–30% 1-year failure rate of antibiotic therapy alone.

Choice of antibiotic regimen

Antibiotics with aerobic and anaerobic coverage for ordinary bowel bacteria should be prescribed, taking into account local resistance patterns and the potential for heterogeneous causes. Antibiotics have been given intravenously for 1–3 days in all the referred trials; total oral therapy has not been tested. Therefore, a reasonable recommendation is at least 1 day of intravenous treatment and also hospital surveillance, in view of the fact that rescue appendectomy has been judged necessary for 5–23% of patients (table 2). Oral antibiotics have subsequently been given for 7–10 days as part of this regimen, showing the potential for slower recovery in some patients, albeit while avoiding early surgery. The length and nature of treatment should be investigated in future research.

Spontaneous resolution

Periods of active observation resulting in resolution suggest that spontaneous resolution of simple appendicitis is possible. Randomised controlled trials comparing active observation with antibiotic treatment have not been done and therefore we cannot know whether the reported recovery rates (77–95%; table 2) after primary antibiotics represent a true treatment effect or merely the natural course of uncomplicated, acute appendicitis. Safe selection criteria for active observation alone to treat confirmed appendicitis do not exist and therefore this is not recommended as a current treatment strategy outside trials.

Appendiceal abscess

Preoperative intra-abdominal or pelvic abscess occurs in 3·8% (95% CI 2·6–4·9) of patients presenting with appendicitis[46] and should be suspected in those presenting with a palpable mass. Although pre-hospital delay has traditionally been viewed as a risk factor for perforation and abscess formation, evidence of disconnect between the strata of disease severity means that some patients might be at risk of abscess formation despite prompt treatment.[21] Meta-analyses of mainly retrospective studies recommend conservative treatment consisting of antibiotics with percutaneous drainage of abscess if needed.[46] Immediate surgery is associated with increased morbidity (pooled odds ratio 3·3, 95% CI 1·9–5·6) and risk of unnecessary ileocaecal resection; the recurrence rate is 7·4% (95% CI 3·7–11·1).[46]

Follow-up after non-operative management

Following conservatively treated abscess, 1·2% of patients will subsequently be found to have malignancy.[46] Follow-up with colonoscopy, CT, or both after conservatively treated appendiceal abscess is recommended in patients aged 40 years or older, or those with symptoms or laboratory or radiological signs indicating suspected colonic malignancy.

The rate of occult appendiceal malignancy after initial successful antibiotic treatment for simple (non-perforated) appendicitis is unknown. Long-term (beyond 1 year) evidence of outcome and optimum follow-up of is scarce; only one study reports a recurrence rate of 14% after 2 years.[44] Extrapolating from abscess, patients aged 40 years and older or those with other suspicious symptoms should be considered for further investigation to identify malignancy, which might include interval appendectomy in selected cases based on age, ongoing symptoms, radiological findings, or a combination of these factors.

Operative treatment

See Online for videos

Timing of surgery

Outcomes in relation to timing of surgery have been controversial, especially since disease presentation can vary with time of day. A meta-analysis of 11 non-randomised studies (including a total of 8858 patients) showed that short in-hospital delays of 12–24 h in selected, stable patients were not associated with increased risk of perforation (odds ratio 0·97, 95% CI 0·78–1·19, p=0·750).[47] Notably, allowing a delay or, rather, a longer observation time in patients with equivocal signs, with renewed interval clinical assessment, increases diagnostic accuracy without raised risk of perforation in acute appendicitis. Delays can help service provision, through avoidance of night-time operations and increased access to daytime technological resources when available.[48]

Emergency surgery models can structurally separate elective from emergency care, reduce night-time surgery, and improve the efficiency of the emergency operating theatre.[49] Planned early laparoscopy in patients with an equivocal diagnosis can improve the diagnostic rate and enable early discharge from hospital (without increasing the risk of complications).[32,33] Ambulatory appendectomy, leading to day of surgery discharge, has been reported from single centres and is potentially attractive to improve patient satisfaction and reduce costs in patients with uncomplicated inflammation.[50]

Surgical approach

Use of laparoscopic appendectomy depends on availability and expertise, with equivalent results achievable from urban centres in India and Africa and hospitals in the UK and USA.[51] The concept of low-cost laparoscopy, with the use of straightforward, inexpensive, reusable devices can lead to equivalent costs and outcomes, even in complex appendicitis.[52]

Role of laparoscopic appendectomy in specific populations

Laparoscopy can be done safely in children and obese individuals with favourable outcomes and a low risk profile.[53,54] Its availability and use depends on expertise and access to specialist equipment and therefore does not need to be mandated. Appendicitis in pregnancy remains challenging because of displacement of the caecum by the growing uterus. Meta-analysis of low-grade observational evidence suggests that laparoscopic appendectomy in this group is associated with a higher rate of fetal loss than is an open approach (3415 women, 127 events; relative risk 1·91 [95% CI 1·31–2·77]).[55] However, selection bias and confounders might have affected these observational results; open appendectomy remains the standard approach. Appendix p 3 shows a selection of best available evidence for surgeons guiding intraoperative decision making.

New surgical technologies

Single-incision laparoscopic surgery and low-cost single-incision techniques (eg, “surgical glove port, appendix videos 1 and 2) have been described recently and can be done with inexpensive equipment and routine devices, leading to satisfactory functional and cosmetic results.[56] A meta-analysis of seven randomised controlled trials comparing single-incision laparoscopic surgery and conventional laparoscopy showed no real differences for single-incision laparoscopic surgery and that substantial heterogeneity exists between studies.[57]

Natural orifice transluminal endoscopic surgery (NOTES) is a technological adaptation of laparoscopy that is available in well-funded centres. Its role and application (transvaginal approach in women; trans-gastric approach in both sexes) is controversial and debated, due to scarce data about improvement in clinical outcome but at greater costs.[58]

Since the role of these technologies seems to be to provide marginal gains in selected patients (which might only be a neutral or, at best, improved cosmetic outcome at the cost of longer operative times and worse postoperative pain[57,59]), widespread adoption seems to be unlikely in light of the higher cost and increased procedural complexity.

Administration of preoperative and duration of postoperative antibiotics

Preoperative prophylactic antibiotics should be started well before skin incision commences (>60 min) and can be initiated as soon as the patient is scheduled for surgery. Broad coverage of Gram-negative bacteria is warranted based on studies on microbiology cultures. Metronidazole given intravenously is usually well tolerated, and is given alone or in combination in most studies.[60] Piperacillin or tazobactam is also adequate, especially if perforation or complex disease is suspected on preoperative diagnosis. A meta-analysis of randomised trials comparing prophylactic preoperative antibiotics to placebo showed a significant reduction of wound infection with either a single agent (11 studies, 2191 patients, odds ratio 0·34 [95% CI 0·25–0·45]) or several agents (two studies, 215 patients, odds ratio 0·14 [95% CI 0·05–0·39]).[61]

Administration of postoperative antibiotics is stratified by disease severity. Routine postoperative antibiotics after surgery for simple inflamed appendicitis are not recommended.[62] At present, 3–5 days of postoperative intravenous antibiotics are recommended for complex, perforated appendicitis. Adjusted observational data suggest that 3 days' postoperative antibiotic duration is as effective as 5 days.[63] A shorter duration of antibiotic treatment based on cessation following resolution of bedside clinical parameters (core temperature <38°C for 24 h, toleration of two consecutive meals, mobilising independently, and requiring only oral analgesia) might be equally as efficacious, as proven in paediatric populations.[64] Patients should be informed about a continued risk of postoperative abscess formation in perforated appendicitis.

Outcomes

Histopathological assessment and risk of neoplasm

Whether or not to do histopathological assessment of all appendectomy specimens has been debated (since to not do so could be a way of reducing costs), but nonetheless remains a best-practice recommendation, mainly because it offers the ability to identify malignancy in 1% of patients, most often in the form of a neuroendocrine tumour of the appendix (so-called carcinoid), an adenocarcinoma, or mucinous cystadenoma.[65] Specific definitions of appendiceal inflammation lack consensus agreement. This means that some patients with a histopathologically normal appendix might subsequently be subject to further investigation to find a source of pain, while they actually had subtle inflammation that was not diagnosed by the pathologist.[66]

Mortality

Although the most severe of all adverse events, mortality in developed health systems is low (between 0·09%[67] and 0·24%[68]) and does not have sensitivity to detect differences in care processes that lead to variation in other outcomes. In low-income and middle-income countries, mortality is reported as 1–4%, and therefore it might represent a useful marker for worldwide care.[69,70]

Perforation rate

Low perforation rates were previously used as an indicator of better performing units with more prompt access to surgical intervention. However, compared with patients from urban areas, patients presenting from rural locations in both developed and developing countries have longer duration of symptoms with higher rates of perforation, although this finding could also be the result of ethnic predisposition to perforation.[71] Additionally, since perforation might result from a separate clinical process than the one at work in non-perforated disease,[21] it is increasingly recognised that, as a marker of hospital quality, it is a poor measure.

Normal appendectomy rate

In countries with rapid access to CT and diagnostic laparoscopy, the normal appendectomy rate has fallen during the past decade. Rates vary from 6% in the USA (high use of preoperative CT)[28] and 6·1% in Switzerland (routine use of laparoscopy)[72] to 20·6% in the UK (selective use of CT and laparoscopy),[73] with variable rates from 9% to 27·3% across India, China, sub-Saharan Africa, north Africa, and the Middle East.[65,69] This rate also depends on interobserver variability of histopathological examination and definitions used.[66] Although the normal appendectomy rate can act as a marker of individual hospital pathways, it is one-dimensional in approach, since it does not take into account patients treated nonoperatively and is therefore quite a poor universal marker of quality.

Short-term morbidity

Postoperative adverse event profiles vary depending on disease severity, the specific complication, method of detection, and geographical location. Overall complication rates of 8·2–31·4%, wound infection rates of 3·3–10·3%, and pelvic abscess rates of up to 9·4% have been reported.[73,74]

Long-term morbidity

Population-level data comparing laparoscopic and open surgery show small long-term outcome differences of little clinical relevance.[75] These data also showed that negative appendectomy was associated with increased mortality at 30 days and at 5 years compared with perforated appendicitis.[76] Although this difference could be attributable to an association with underlying undetected morbidity, it could also represent morbidity associated with surgical exploration, potentially justifying increased use of preoperative cross-sectional imaging. Trials with outcome measures related to medium-term and long-term patient-reported satisfaction are very scarce.

Future research directions

A variety of research projects for every step of the patient pathway is needed to modernise and standardise the treatment of acute appendicitis worldwide; ongoing research is shown in appendix p 4. Research relevant to both low-income and middle-income countries and high-income countries should be promoted. Both randomised and non-randomised research can promote equality of access to care and reduce variation in outcome. Correct application of technology, for both diagnosis and treatment, needs to be rationalised, justified, and optimised through formal research programmes. Population-level data that are being gathered now should be used to better define variation, plan relevant research questions, and develop networks for delivery of trials.

Contributors

AB and KS planned the review. Each co-author drafted a topic section outline. AB collated the sections and drafted the first version. AB, KS, SDS, JHA, and FTD did rounds of revisions, edited the draft, and approved the final version of the report.

Declaration of interests

We declare no competing interests.

Acknowledgments
SDS provided the images and videos from his surgical procedures, for which patient consent is held.

References

1 Stewart B, Khanduri P, McCord C, et al. Global disease burden of conditions requiring emergency surgery. *Br J Surg* 2014; **101:** e9–22.

2 Lee JH, Park YS, Choi JS. The epidemiology of appendicitis and appendectomy in South Korea: national registry data. *J Epidemiol* 2010; **20:** 97–105.

3 Ohene-Yeboah M, Abantanga FA. Incidence of acute appendicitis in Kumasi, Ghana. *West Afr J Med* 2009; **28:** 122–25.

4 Lamps LW. Infectious causes of appendicitis. *Infect Dis Clin North Am* 2010; **24:** 995–1018.

5 Dzabic M, Bostrom L, Rahbar A. High prevalence of an active cytomegalovirus infection in the appendix of immunocompetent patients with acute appendicitis. *Inflamm Bowel Dis* 2008; **14:** 236–41.

6 Carr NJ. The pathology of acute appendicitis. *Ann Diagn Pathol* 2000; **4:** 46–58.

7 Ergul E. Heredity and familial tendency of acute appendicitis. *Scand J Surg* 2007; **96:** 290–92.

8 Sadr Azodi O, Andren-Sandberg A, Larsson H. Genetic and environmental influences on the risk of acute appendicitis in twins. *Br J Surg* 2009; **96:** 1336–40.

9 Wei PL, Chen CS, Keller JJ, Lin HC. Monthly variation in acute appendicitis incidence: a 10-year nationwide population-based study. *J Surg Res* 2012; **178:** 670–76.

10 Zingone F, Sultan AA, Humes DJ, West J. Risk of acute appendicitis in and around pregnancy: a population-based cohort study from England. *Ann Surg* 2015; **261:** 332–37.

11 Anderson JE, Bickler SW, Chang DC, Talamini MA. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995–2009. *World J Surg* 2012; **36:** 2787–94.

12 Lee SL, Shekherdimian S, Chiu VY. Effect of race and socioeconomic status in the treatment of appendicitis in patients with equal health care access. *Arch Surg* 2011; **146:** 156–61.

13 Sesia SB, Mayr J, Bruder E, Haecker FM. Neurogenic appendicopathy: clinical, macroscopic, and histopathological presentation in pediatric patients. *Eur J Pediatr Surg* 2013; **23:** 238–42.

14 Guinane CM, Tadrous A, Fouhy F, et al. Microbial composition of human appendices from patients following appendectomy. *mBio* 2013; **4:** e00366-12.

15 Swidsinski A, Dorffel Y, Loening-Baucke V, et al. Acute appendicitis is characterised by local invasion with *Fusobacterium nucleatum/necrophorum. Gut* 2011; **60:** 34–40.

16 Frisch M, Pedersen BV, Andersson RE. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. *BMJ* 2009; **338:** b716.

17 Kaplan GG, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. *Gut* 2007; **56:** 1387–92.

18 Clanton J, Subichin M, Drolshagen K, Daley T, Firstenberg MS. Fulminant *Clostridium difficile* infection: an association with prior appendectomy? *World J Gastrointest Surg* 2013; **5:** 233–38.

19 Andersson RE. The natural history and traditional management of appendicitis revisited: spontaneous resolution and predominance of prehospital perforations imply that a correct diagnosis is more important than an early diagnosis. *World J Surg* 2007; **31:** 86–92.

20 Ruber M, Andersson M, Petersson BF, Olaison G, Andersson RE, Ekerfelt C. Systemic Th17-like cytokine pattern in gangrenous appendicitis but not in phlegmonous appendicitis. *Surgery* 2010; **147:** 366–72.

21 Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. *Ann Surg* 2007; **245:** 886–92.

22 Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. *Br J Surg* 2013; **100:** 322–29.

23 Andersson M, Ruber M, Ekerfelt C, Hallgren HB, Olaison G, Andersson RE. Can new inflammatory markers improve the diagnosis of acute appendicitis? *World J Surg* 2014; **38:** 2777–83.

24 Leeuwenburgh MM, Stockmann HB, Bouma WH, et al. A simple clinical decision rule to rule out appendicitis in patients with nondiagnostic ultrasound results. *Acad Emerg Med* 2014; **21:** 488–96.

25 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.

26 Kollar D, McCartan DP, Bourke M, Cross KS, Dowdall J. Predicting acute appendicitis? A comparison of the Alvarado score, the appendicitis inflammatory response score and clinical assessment. *World J Surg* 2015; **39:** 104–09.

27 Terasawa T, Blackmore CC, Bent S, Kohlwes RJ. Systematic review: computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents. *Ann Intern Med* 2004; **141:** 537–46.

28 Cuschieri J, Florence M, Flum DR, et al. Negative appendectomy and imaging accuracy in the Washington State Surgical Care and Outcomes Assessment Program. *Ann Surg* 2008; **248:** 557–63.

29 Kim K, Kim YH, Kim SY, et al. Low-dose abdominal CT for evaluating suspected appendicitis. *N Engl J Med* 2012; **366:** 1596–605.

30 Leeuwenburgh MM, Wiezer MJ, Wiarda BM, et al. Accuracy of MRI compared with ultrasound imaging and selective use of CT to discriminate simple from perforated appendicitis. *Br J Surg* 2014; **101:** e147–55.

31 Maggio AQ, Reece-Smith AM, Tang TY, Sadat U, Walsh SR. Early laparoscopy versus active observation in acute abdominal pain: systematic review and meta-analysis. *Int J Surg* 2008; **6:** 400–03.

32 Decadt B, Sussman L, Lewis MP, et al. Randomized clinical trial of early laparoscopy in the management of acute non-specific abdominal pain. *Br J Surg* 1999; **86:** 1383–86.

33 Morino M, Pellegrino L, Castagna E, Farinella E, Mao P. Acute nonspecific abdominal pain: a randomized, controlled trial comparing early laparoscopy versus clinical observation. *Ann Surg* 2006; **244:** 881–86.

34 Shindoh J, Niwa H, Kawai K, et al. Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. *J Gastrointest Surg* 2010; **14:** 309–14.

35 Hansson J, Khorram-Manesh A, Alwindawe A, Lundholm K. A model to select patients who may benefit from antibiotic therapy as the first line treatment of acute appendicitis at high probability. *J Gastrointest Surg* 2014; **18:** 961–67.

36 Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ* 2012; **344:** e2156.

37 Eriksson S, Granstrom L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995; **82:** 166–69.

38 Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 2006; **30:** 1033–37.

39 Hansson J, Korner 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.

40 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:** 1573–79.

41 Svensson JF, Patkova B, Almstrom M, et al. Nonoperative treatment with antibiotics versus surgery for acute nonperforated appendicitis in children: a pilot randomized controlled trial. *Ann Surg* 2015; **261:** 67–71.

42 Turhan AN, Kapan S, Kutukcu E, Yigitbas H, Hatipoglu S, Aygun E. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2009; **15:** 459–62.

43 Hansson J, Korner U, Ludwigs K, Johnsson E, Jonsson C, Lundholm K. Antibiotics as first-line therapy for acute appendicitis: evidence for a change in clinical practice. *World J Surg* 2012; **36:** 2028–36.

44 Di Saverio S, Sibilio A, Giorgini E, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. *Ann Surg* 2014; **260:** 109–17.

45 Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA* 2015; **313:** 2340–48.

46 Andersson RE, Petzold MG. Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. *Ann Surg* 2007; **246:** 741–48.

47 Bhangu A. Safety of short, in-hospital delays before surgery for acute appendicitis: multicentre cohort study, systematic review, and meta-analysis. *Ann Surg* 2014; **259:** 894–903.

48 Drake FT, Mottey NE, Farrokhi ET, et al. Time to appendectomy and risk of perforation in acute appendicitis. *JAMA Surg* 2014; **149:** 837–44.

49 Leppaniemi A, Jousela I. A traffic-light coding system to organize emergency surgery across surgical disciplines. *Br J Surg* 2014; **101:** e134–40.

50 Lefrancois M, Lefevre JH, Chafai N, et al. Management of acute appendicitis in ambulatory surgery: is it possible? How to select patients? *Ann Surg* 2015; **261:** 1167–72.

51 Adisa AO, Alatise OI, Arowolo OA, Lawal OO. Laparoscopic appendectomy in a Nigerian teaching hospital. *JSLS* 2012; **16:** 576–80.

52 Di Saverio S, Mandrioli M, Sibilio A, et al. A cost-effective technique for laparoscopic appendectomy: outcomes and costs of a case-control prospective single-operator study of 112 unselected consecutive cases of complicated acute appendicitis. *J Am Coll Surg* 2014; **218:** e51–65.

53 Ciarrocchi A, Amicucci G. Laparoscopic versus open appendectomy in obese patients: a meta-analysis of prospective and retrospective studies. *J Minim Access Surg* 2014; **10:** 4–9.

54 Cheong LH, Emil S. Pediatric laparoscopic appendectomy: a population-based study of trends, associations, and outcomes. *J Pediatr Surg* 2014; **49:** 1714–18.

55 Wilasrusmee C, Sukrat B, McEvoy M, Attia J, Thakkinstian A. Systematic review and meta-analysis of safety of laparoscopic versus open appendicectomy for suspected appendicitis in pregnancy. *Br J Surg* 2012; **99:** 1470–78.

56 Di Saverio S. Emergency laparoscopy: a new emerging discipline for treating abdominal emergencies attempting to minimize costs and invasiveness and maximize outcomes and patients' comfort. *J Trauma Acute Care Surg* 2014; **77:** 338–50.

57 Chen JM, Geng W, Xie SX, et al. Single-incision versus conventional three-port laparoscopic appendectomy: a meta-analysis of randomized controlled trials. *Minim Invasive Ther Allied Technol* 2015; published online Jan 20. DOI:10.3109/13645706.2014.995675.

58 Bingener J, Ibrahim-zada I. Natural orifice transluminal endoscopic surgery for intra-abdominal emergency conditions. *Br J Surg* 2014; **101:** e80–89.

59 Carter JT, Kaplan JA, Nguyen JN, Lin MY, Rogers SJ, Harris HW. A prospective, randomized controlled trial of single-incision laparoscopic vs conventional 3-port laparoscopic appendectomy for treatment of acute appendicitis. *J Am Coll Surg* 2014; **218:** 950–59.

60 Daskalakis K, Juhlin C, Pahlman L. The use of pre- or postoperative antibiotics in surgery for appendicitis: a systematic review. *Scand J Surg* 2014; **103:** 14–20.

61 Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. *Cochrane Database Syst Rev* 2005; **3:** CD001439.

62 Daskalakis K, Juhlin C, Pahlman L. The use of pre- or postoperative antibiotics in surgery for appendicitis: a systematic review. *Scand J Surg* 2014; **103:** 14–20.

63 van Rossem CC, Schreinemacher MH, Treskes K, van Hogezand RM, van Geloven AA. Duration of antibiotic treatment after appendicectomy for acute complicated appendicitis. *Br J Surg* 2014; **101:** 715–19.

64 Yu TC, Hamill JK, Evans SM, et al. Duration of postoperative intravenous antibiotics in childhood complicated appendicitis: a propensity score-matched comparison study. *Eur J Pediatr Surg* 2014; **24:** 341–49.

65 Charfi S, Sellami A, Affes A, Yaich K, Mzali R, Boudawara TS. Histopathological findings in appendectomy specimens: a study of 24,697 cases. *Int J Colorectal Dis* 2014; **29:** 1009–12.

66 Riber C, Tonnesen H, Aru A, Bjerregaard B. Observer variation in the assessment of the histopathologic diagnosis of acute appendicitis. *Scand J Gastroenterol* 1999; **34:** 46–49.

67 Bliss LA, Yang CJ, Kent TS, Ng SC, Critchlow JF, Tseng JF. Appendicitis in the modern era: universal problem and variable treatment. *Surg Endosc* 2014; **146:** 1057.

68 Faiz O, Clark J, Brown T, et al. Traditional and laparoscopic appendectomy in adults: outcomes in English NHS hospitals between 1996 and 2006. *Ann Surg* 2008; **248:** 800–06.

69 Ali N, Aliyu S. Appendicitis and its surgical management experience at the University of Maiduguri Teaching Hospital Nigeria. *Niger J Med* 2012; **21:** 223–26.

70 Ohene-Yeboah M, Togbe B. An audit of appendicitis and appendicectomy in Kumasi, Ghana. *West Afr J Med* 2006; **25:** 138–43.

71 Kong VY, Van der Linde S, Aldous C, Handley JJ, Clarke DL. Quantifying the disparity in outcome between urban and rural patients with acute appendicitis in South Africa. *S Afr Med J* 2013; **103:** 742–45.

72 Guller U, Rosella L, McCall J, Brugger LE, Candinas D. Negative appendicectomy and perforation rates in patients undergoing laparoscopic surgery for suspected appendicitis. *Br J Surg* 2011; **98:** 589–95.

73 Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy. *Br J Surg* 2013; **100:** 1240–52.

74 Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2010; **10:** CD001546.

75 Andersson RE. Short-term complications and long-term morbidity of laparoscopic and open appendicectomy in a national cohort. *Br J Surg* 2014; **101:** 1135–42.

76 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.