Acute appendicitis–advances and controversies

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Abstract

Being one of the most common causes of the acute abdomen, acute appendicitis (AA) forms the bread and butter of any general surgeon's practice. With the recent advancements in AA's management, much controversy in diagnostic algorithms, possible differential diagnoses, and weighing the management options has been generated, with no absolute consensus in the literature. Since Alvarado described his eponymous clinical scoring system in 1986 to stratify AA risk, there has been a burgeoning of additional scores for guiding downstream management and mortality assessment. Furthermore, advancing literature on the role of antibiotics, variations in appendicectomy, and its adjuncts have expanded the surgeon's repertoire of management options. Owing to the varied presentation, diagnostic tools, and management of AA have also been proposed in special groups such as pregnant patients, the elderly, and the immunocompromised. This article seeks to raise the critical debates about what is currently known about the above aspects of AA and explore the latest controversies in the field. Considering the ever-evolving coronavirus disease 2019 situation worldwide, we also discuss the pandemic's repercussions on patients and how surgeons' practices have evolved in the context of AA.

Key Words: Appendicitis; Diagnosis; Management; COVID-19; Controversy; Advances

Core Tip: Many controversies exist for the management of acute appendicitis (AA). Imaging modalities complement the clinical examination in AA diagnosis. Various imaging features of different imaging modalities should be considered to reduce diagnostic inaccuracies. Various diagnostic scoring systems augment clinical

judgment, but uncertainty exists about the best score. Non-operative management of both uncomplicated and complicated AA is possible and reasonable, especially during the coronavirus disease 2019 pandemic. Intra-operative techniques of securing the base of the appendix stump *via* suture, clips, or stapling devices are all debated for superiority. Adjuncts and novel treatment ideas using endoscopic retrograde appendicitis therapy are emerging.

INTRODUCTION

Acute appendicitis (AA) is a commonly encountered surgical emergency at all levels of seniority and across different specialties. First described by Fitz[1] in 1886, it is characterized by inflammation of the vermiform appendix. Treves[2] is credited as the first to treat AA in 1902. AA occurs when there is obstruction of the appendiceal orifice (such as lymphoid hyperplasia or fecaliths), resulting in inflammation. This causes progressive distension of the appendix, eventually leading to vascular compromise, allowing the growth of pathogenic microorganisms[3]. Left untreated, this culminates in the perforation of the appendix with a localized abscess or generalized peritonitis.

The diagnosis and management of AA have not changed radically over the years despite advances in imaging and technology and an improved understanding of sepsis. To consolidate these advancements, we set out to review current literature to reassess relevant issues in the diagnosis and management of AA, including the impact of the coronavirus disease 2019 (COVID-19) pandemic on previously accepted protocols.

LITERATURE SEARCH

A search of relevant articles on PubMed, OVID/MEDLINE, and Web of Science was conducted on 6 May 2021 for literature published in English by Teng TZJ, Thong XR, and Lau KY. Disagreements were resolved by mutual discussions and consensus with senior authors Balasubramaniam S and Shelat VG. The following terms were used, and relevant articles were considered: ["appendicitis" (MeSH Terms)/etiology, surgery, therapy, "appendectomy" (MeSH Terms), "diagnosis" or "differential", "Guidelines"]. Results were screened by title, and relevant articles were obtained in full text for review. We present our findings as a narrative review covering current practices and advancements in appendicitis diagnosis, followed by management, differentials, histological variations, and finally, surgical variations in AA management

DIAGNOSIS AND CLASSIFICATION

The diagnosis of AA has historically been based on clinical judgment, though imaging is increasingly common where resources permit. The classic sequence of periumbilical pain radiating to the right iliac fossa (RIF), nausea or vomiting, and fever is Murphy's syndrome. Many clinical signs, such as Blumberg's sign (rebound tenderness), Rovsing's sign (RIF pain on left iliac fossa palpation), or the Psoas sign (pain upon right hip flexion suggesting retrocecal appendicitis) are described to augment diagnosis of AA. Clinical diagnosis is not absolute. Therefore, scoring systems combining clinical signs with serum markers of inflammation are widely advocated.

CLINICAL SCORING SYSTEMS

Scoring systems combine information from multiple sources to increase accuracy. Each score has its own merits and demerits discussed in Table 1[4-20]. The mere existence of so many systems endorses that none is perfect. The Alvarado score is widely cited and adopted in routine clinical care. However, the Alvarado score lacks specificity and is not widely validated in Asian populations. The Raja Isteri Pengiran Anak Saleha (RIPASA) scoring system was developed explicitly for the Asian population. Frountzas *et al*[17]'s meta-analysis comparing RIPASA and Alvarado reported higher accuracy for RIPASA score [area under the curve (AUC) 0.9431 *vs* 0.7944][17]. According to a retrospective study, including pregnant and non-pregnant female patients by Mantoglu *et al*[21], the RIPASA score was most helpful in pregnant patients (highest AUC at 0.806)[21]. In a trial involving 3878 patients, Andersson *et al* [5] noted the Appendicitis Inflammatory Response (AIR) score to have high sensitivity for complicated appendicitis[5]. As the AIR score more correctly identifies those with a high likelihood of appendicitis in whom supplemental imaging is unlikely to change management, AIR helps guide patient triaging for imaging. Sammalkorpi *et al*[6] compared the Adult Appendicitis Score (AAS) performance to the Alvarado and AIR scores in a prospective study of 829 patients. They reported that AAS had the highest AUC (0.882, 95%CI: 0.858-0.906)[6]. AAS is not widely validated. There are many other scoring systems, such as the Ohmann score, the Lintula score, the Tsanakis score, and the Fenyo-Lindburg score[22-27]. Validation studies for each scoring system are few. Ohmann's score differentiated innocent appendices from phlegmonous ones and phlegmonous from gangrenous appendices[22]. The Lintula score was developed for use in the pediatric population[28]. The Lintula score is advantageous in resource-limited settings, as no laboratory parameters are required. Tzanakis score includes the ultrasound scan (US), which can is validated in pregnant patients. Due to inter-observer variability for US scans, the scoring is not objective[29].

As most scoring systems are generated from retrospective data, a scoring system derived from prospective medical records may be more accurate, especially if it is derived from multiple hospitals. The World Society of Emergency Surgery (WSES) made such an attempt. Complicated intra-abdominal infections (cIAIs) are defined as abdominal infections that extend beyond organs, causing localized or diffused peritonitis. The WSES Sepsis Severity Score predicts mortality in patients with cIAIs, including AA. In a prospective multi-center validation study including 4533 patients from 132 hospitals, Sartelli *et al*[25] reported that the WSES sepsis severity score cut-off of 5.5 helps differentiate survivors from non-survivors (sensitivity 89.2%, specificity 83.5%)[25]. WSES sepsis severity score needs validation in AA patients. The systemic inflammatory response syndrome (SIRS) criteria are validated in the management of AA. In a single-center prospective study including 268 patients, Beltrán *et al*[26] reported that a longer interval between symptom onset and surgery was significantly correlated with a higher SIRS score and an increased rate of perforated appendicitis [26]. The perforation rate for patients rose from 7% for those operated on within 24 h to as high as 85% among those operated on after 73 h. This reinforces the fact that untreated AA worsens with time and supports the utility of SIRS in determining the urgency of surgical intervention. The SIRS score can be used as an adjunct in deciding between surgical and conservative antibiotic management. In a retrospective study including 125 patients, Nozoe *et al*[27] reported that the SIRS score was lower in patients who were recommended non-operative management (NOM)[27]. Similarly, diverticular disease of the appendix (DDA) is associated with a higher perforation rate, and Chia *et al*[30] have shown that a high SIRS score is useful in clinical decision making for surgery in DDA[30]. The total white blood cell count is a non-specific biochemical marker, and novel markers may improve the performance of scoring systems. The relationship between biochemical markers [C-reactive protein (CRP), leukocyte count, procalcitonin, bilirubin] and AA has been extensively studied, either as part of clinical scores mentioned above or as standalone diagnostic predictors. The appendistat™ scoring system uses biochemical parameters to differentiate uncomplicated from complicated AA. In a validation study, Birben *et al*[31] reported that CRP was adequate to differentiate uncomplicated from complicated AA[31]. In a prospective study involving 544 patients, Körner *et al*[32] noted that perforation was more likely when CRP concentration > 50 U/L (OR 4.6, 95%CI: 2.44-8.75)[32]. Birben *et al*[31] also reported that a high total bilirubin level at 0.75 mg/dL could diagnose AA even if leukocyte levels were normal[31]. In a meta-analysis of seven studies and 1011 patients by Yu *et al*[33], CRP had the best discriminative capability in diagnosing AA [33]. Although not helpful in diagnosing AA, procalcitonin has a high positive likelihood ratio in identifying complicated AA. Thus, different scoring systems serve

Table 1 Various scoring systems for acute appendicitis

Scoring system	Patient features	Clinical features	Laboratory/imaging features	Sensitivity	Specificity	Risk strata/recommended action
Alvarado	-	RIF tenderness (2); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (1); Anorexia (1); Nausea or vomiting (1)	Leucocytosis (2); Leukocyte left shift (1)	94.1%	90.4%	1-4: Discharge; 5-6: Admit and observe; 7-10: Surgery
AIR	-	Elevated temperature (1); Rebound tenderness: Light (1), medium (2), strong (3); RIF pain (1); Vomiting (1)	Leucocytosis, × 10^9/L: 10-14.9 (1); ≥ 15 (2); Polymorphonuclear leucocytosis, %: 70-84 (1); ≥ 85 (2); CRP level, mg/L: 10-49 (1); ≥ 50 (2)	97%		0-4: Outpatient follow-up; 5-8: Admit and observe; 9-12: Surgery
AAS	-	RIF tenderness: Women 16-49 yr (1); all other patients (3); Migration of pain (2); RIF pain (2); Guarding: Mild (2); moderate or severe (4)	Leucocytosis, × 10^9/L: ≥ 7.2 and < 10.9 (1); ≥ 10.9 and < 14.0 (2); ≥ 14.0 (3). Neutrophilia, %: ≥ 62 and < 75 (2); ≥ 75 and < 83 (3); ≥ 83 (4). CRP level, mg/L and symptoms < 24 h: ≥ 4 and < 11 (2); ≥ 11 and < 25 (3); ≥ 25 and < 83 (5); ≥ 83 (1). CRP level, mg/L and symptoms > 24 h: ≥ 12 and < 53 (2); ≥ 53 and < 152 (2); ≥ 152 (1)			1-10: Discharge without imaging; 11-15: Imaging; ≥ 16: Surgery
RIPASA	Age: < 40 (1); Age > 40 (0.5). Gender: Male (1); female (0.5). Foreign nationality registration identity card (1)	RIF tenderness (1); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (0.5); Anorexia (1); Nausea or vomiting (1); RIF pain (0.5); Duration of symptoms: < 48 h (1); > 48 h (0.5); Guarding (2); Rovsing sign (2)	Leucocytosis (1); Negative urine analysis (1)	91.67%	93.18%	-
Ohmann	Age < 50 (1.5)	RIF tenderness (4.5); Rebound tenderness (2.5); Migration of pain (1); No micturition difficulties (2.0); Steady pain (2); Rigidity (1)	Leucocytosis (1.5)	98.1% at cut-off score 9; 82.9% at cut-off score 13	94% at cut-off score 12	< 6: Low risk; 6-11.5: Monitoring; ≥ 12: Surgery
Lintula	Gender: Male (2); female (0)	Elevated temperature (3); Rebound tenderness (7); Migration of pain (4); Vomiting (2); RIF pain (4); Guarding (4); Pain intensity: severe (2); mild or moderate (0); Bowel sounds absent, tinkling or high-pitched (4)	-	79.0% at cut-off score 21	58.3% at cut-off score 21	≤ 15: Discharge; 16-20: Monitoring; ≥ 21: Surgery
Tzanakis	-	RIF tenderness (4); Rebound tenderness (3)	Leucocytosis (2); US imaging showing appendiceal inflammation (6)			0-4: Discharge; 5-7: Monitoring; 8-15: Surgery
Fenyo-Lindberg	Gender: Male (8); female (-8)	Rebound tenderness: Yes (5); no (-10); migration of pain to RIF: Yes (7); no (-9); Vomiting: Yes (7); no (-5); Duration of pain: < 24 h (3); > 48 h (-12); Progression of pain: Yes (3); no (-4); Aggravation with cough: Yes (4); no (-11); Rigidity: Yes (15); no (-4); Pain outside RIF: Yes (-6); no (4)	Leucocytosis, × 10^9/L: < 8.9 (-15); 9-13.9 (2); > 14 (10)	In a cross-sectional study including 100 patients with RIF pain, Sahu reported a sensitivity of 72% and specificity of 71%		≤ -17: Non-specific abdominal pain; ≥ -2: AA likely
Modified Alvarado Score	-	RIF tenderness (2); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (1); Anorexia (1); Nausea or vomiting (1)	Leucocytosis (2)			< 5: Surgery not required; 5-6: Monitor; 7-9: Surgery indicated
Christian	-	RIF tenderness (1); Elevated temperature (1); Vomiting (1); Abdominal pain (1)	Polymorphonuclear leucocytosis (1)			< 4: Monitoring; ≥ 4: Surgery

| van den Broek *et al*[14] | Gender: Male (2) | Elevated temperature (1); Rebound tenderness (2); Duration of symptoms ≤ 48 h (1) | Leucocytosis (3) | 0-3: Observe; 4-6: Diagnostic laparoscopy |
| Simplified Appendicitis Score | - | RIF tenderness (1); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (1) | Leucocytosis (1) | < 4: AA excluded with 90.1% sensitivity; ≥ 6: AA included with 91.7% specificity |

RIF: Right iliac fossa; CRP: C-reactive protein; US: Ultrasound; AIR: Appendicitis inflammatory response; RIPASA: Raja Isteri Pengiran Anak Saleha.

to aid diagnostic accuracy, triage for imaging, differentiate complicated from uncomplicated AA, determine the timing of surgical intervention, and predict morbidity outcomes. No one-size-fits-all, so prudence is required if a scoring system is used to guide bed-side decisions.

INTERNATIONAL GUIDELINES

The European Association of Endoscopic Surgery (EAES) recommended a diagnostic algorithm in 2016. It risk stratifies patients into three main groups based on clinical scoring. Low-risk patients can be discharged following work-up for other possible causes. Moderate risk patients first undergo US, with computed tomography (CT) being recommended as a second-level diagnostic study only for those with inconclusive US results[34]. The EAES algorithm features only the Alvarado score as the initial risk stratification tool but differs from the original authors in that it follows Ebell and Shinholser[4]'s recommended cut-off of < 4 for differentiating low-risk AA.

In 2018, the American Academy of Family Physicians published their clinical recommendations on the efficient diagnosis and management of AA[35]. Some key recommendations for AA diagnosis include the use of Alvarado, Pediatric Appendicitis Score or AIR, and US as a front-line diagnostic sieve to reduce CT use. Unlike in EAES' guidelines, CT with IV or oral contrast or magnetic resonance imaging (MRI) is recommended for patients with negative (in addition to intermediate) US findings and high clinical suspicion to account for US' lower sensitivity.

The 2020 WSES algorithm recommends using either the Alvarado, AIR, or AAS systems to classify low, moderate, and high-risk AA patients. This algorithm differs from EAES by using the original < 5 cut-off for low-risk AA based on the Alvarado score. WSES applies a graded imaging strategy with US as the first-line imaging choice like the above two guidelines. Low-risk patients can be discharged as appropriate or worked up for other causes of abdominal pain[36]. Moderate-risk patients are recommended to undergo an US, proceeding to CT or MRI only if the US is equivocal or negative, but the patient fails to respond to treatment. Whether CT or US should be used as second-line imaging after the US for pediatric patients is mainly dependent on

local resources[36]. High-risk patients may proceed for surgery without further imaging.

IMAGING STUDIES

Imaging is widely accessible and has become integral to AA's management–as an adjunct to confirm the diagnosis, rule out differential diagnoses, or assist surgical planning. Free air under the diaphragm on erect chest radiograph is rare in patients with perforated AA[37]. The plain abdominal radiograph showing an appendicolith, right lower quadrant soft tissue mass or extraluminal air, and psoas margin concealment is of historical interest[38]. As such, radiographs have a minimal role in AA diagnosis. Figure 1 illustrates the key imaging features of the US scan, CT scan, and MRI scan[39-44].

US scan and CT scan

Although CT scans having higher sensitivity in diagnosis[45], WSES and EAES guidelines recommend the US scan as the first line and reserve CT scan in patients with inconclusive US findings. Such a strategy increases cost-effectiveness and reduces radiation exposure. CT scan may be a more appropriate first-line investigation in overweight or elderly patients. In a prospective cohort study of 106 patients with suspected AA, Keller *et al*[46] reported that the US scan was five times more likely to be non-diagnostic in overweight patients[46]. Similarly, Sauvain *et al*[39] reported that the US scan was seven times more likely to be inconclusive in patients with a body mass index (BMI) > 25 kg/m^2[39]. In a retrospective study including 105 patients, Pelin *et al*[40] reported that CT scan was more accurate in patients with high BMI [26.7 ± 4.3 (mean ± SD) kg/m^2] and increased age [31 ± 14 (mean ± SD) years], possibly because of higher rates of complicated appendicitis[40]. This is consistent with the American College of Radiology Appropriateness Criteria's call for a lower threshold for CT imaging in elderly patients with RIF pain[41].

Intravenous contrasted CT scan enhances appendiceal wall thickening and aids AA diagnosis[38]. Per-rectal contrast does not increase diagnostic accuracy and is unnecessary[42]. Recently, there has been interest in low-dose CT scans that reduce radiation exposure without compromising diagnostic accuracy or impact on normal appendectomy rates (NARs). Randomized controlled studies and meta-analyses have shown that the low-dose protocol's diagnostic accuracy was non–inferior[43].

The role of CT scans in the evaluation of the complications of AA is well established. In particular, CT accurately detects periappendiceal abscess, peritonitis, and gangrenous changes[44]. CT scan findings of appendix mass, asymmetric wall abnormality, and diameter > 15 mm can also accurately detect concomitant appendiceal neoplasm[47]. Appendiceal mucocele, defined as a dilated mucin-filled appendix, can also be diagnosed *via* CT scan, with a luminal diameter > 1.3 cm having 88.2% accuracy in diagnosing a mucocele[48]. CT scan also aids in diagnosing complications such as portal vein thrombosis[49], pyogenic liver abscesss[50], and pylephlebitis[51]. Hence, imaging modalities in AA are not restricted to purely diagnostic purposes but serve prognostic utility.

MRI scan

MRI is a reasonable alternative to CT in diagnosing AA and confers the advantage of avoiding ionizing radiation and intravenous contrast in the investigation of pregnant and pediatric patients. Unfortunately, the cost and logistics involved in MRI mean it is usually not used as a first-line modality except in children[52] and pregnant women [53]. A meta-analysis of 11 studies has reported that an MRI scan improves diagnostic accuracy, reduces time to appendectomy, NAR, and aids in alternative diagnosis. Other considerations for children include an incomplete MRI due to fear from claustrophobia, staying still, and noise emitted from MRI. These concerns can be addressed with child and parental counseling or sedation[54].

Severity grading by imaging studies

In addition to diagnosis, imaging also assists in the severity grading of AA. With the increasing adoption of NOM of AA, it is essential to distinguish between complicated and uncomplicated AA. In a retrospective study of 223 patients, Rybkin and Thoeni [55] reported that retroperitoneal inflammatory changes predicted complicated AA (pars plana vitrectomy 0.64-0.92 for patients above 16-years)[55]. Imaging has also been shown to play a role in scoring systems, as previously mentioned, such as the
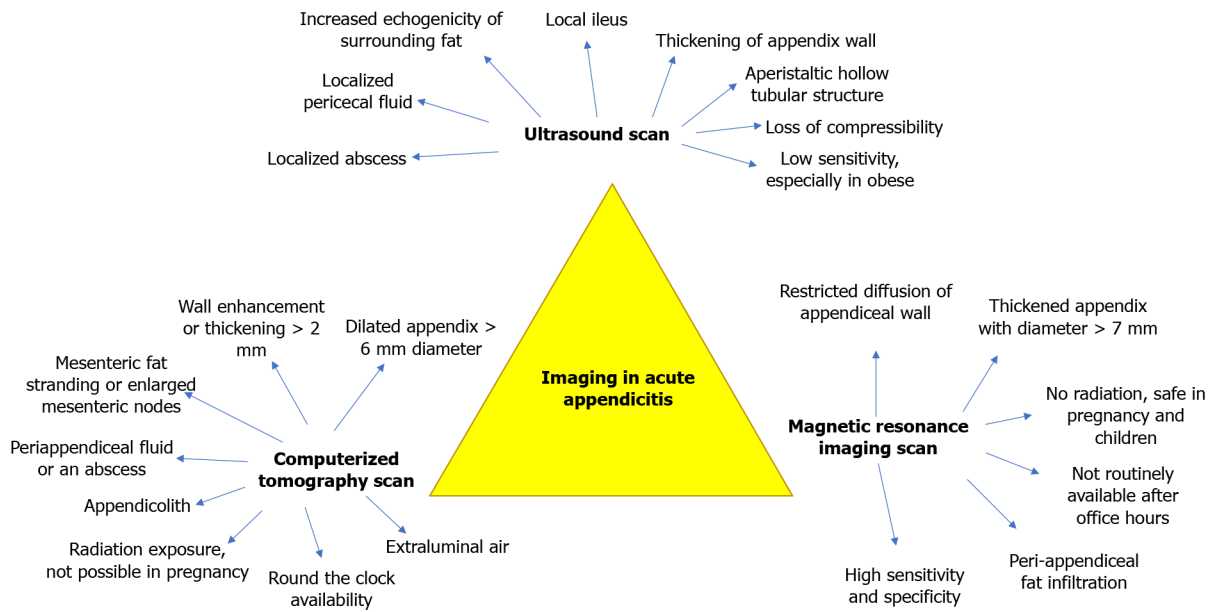
Figure 1 The key imaging features of the ultrasound scan, computed tomography scan, and magnetic resonance imaging scan.

Tzanakis scoring system[10]. A positive US finding of AA such as periappendiceal fluid, localized abscess, appendicolith, wall thickness, and other findings[56] yielded 6 out of the 15 points in the score, where a score of 8 and above is suggestive of AA.

Use of imaging across countries

Imaging improves diagnostic accuracy at a financial cost. Patients from lower-income countries may not have accessibility and affordability to CT scans and MRI scans. Management of AA in different countries revealed that CT scans were done more liberally in accordance with the countries' income level[36]. Within a country itself, there are discrepancies on which modality of imaging to consider first as well. This may be due to the proportion of special populations in the country (obese, children, pregnant women), the logistical constraints of the hospital (primary *vs* tertiary hospital) as well as the availability of radiologists' opinion (working hours, overnight shifts, public holidays)[57]. While prudence needs to be exercised to request imaging to aid AA diagnosis, a refusal or rejection of imaging request on the pretext of "appendicitis is a clinical diagnosis, and please do appendicectomy if clinically you feel so" or "do a serial examination and it will reveal itself over next few days" *etc.* from radiology colleagues is unacceptable. In our experience, liberal imaging policy is associated with low NAR. In a local audit of 2603 appendectomy patients, NAR was 3.34% ($n = 87$)[58]. The unmet need remains the lack of uniform standardized criteria that define imaging diagnosis of AA. In particular, the imaging features of the prominent or dilated appendix can be subjective and international collaboration is needed to define thresholds for AA imaging diagnosis.

DECISION TREE ANALYSIS

A decision tree (DT) analysis model is a tree-shaped graphical representation derived from empirical data to chart out a statistical probability outcome. In the setting of ambiguous CT scan findings, Kang *et al*[59] compared the diagnostic accuracy of various clinical scoring systems with DT analysis. DT analysis based on rebound tenderness severity, pain migration, urinalysis, symptom duration, leukocytosis, neutrophil levels, and CRP was more accurate (receiver operating characteristic and AUC 0.85) as compared to the Alvarado score (AUC 0.695), the Eskelinen score (AUC 0.715), and the AAS (AUC 0.749)[59]. In a study by Akmese *et al*[60] involving 595 clinical records, a boosted tree algorithm based on demographic data and serum biochemistry had predicted surgery necessity with 95.3% accuracy[60]. However, due to the retrospective nature, the subjective clinical judgment of the surgeon could influence the results. Evidence is emerging, and machine learning algorithms will have an increasing role in decision-making in AA management.

DIAGNOSTIC DILEMMA

No report on AA is complete without mentioning the common diagnostic pitfalls and possible differential diagnoses. Imaging is integral not only to establish a diagnosis but also to rule out another diagnosis. These include right colonic diverticulitis[30,61-63], *Yersinia* enterocolitis[64,65], right-sided renal disease[66], mesenteric lymphadenitis [67] and Meckel's Diverticulitis[68,69]. The meta-analysis investigating the role of MRI scan in pediatric AA reported that alternative diagnosis was present in about 20% of patients, most common being adnexal cyst and enteritis/colitis[61]. Various scoring systems, serum, and imaging biomarkers have improved diagnostic accuracy, and diagnostic dilemmas are uncommon. With the advent of minimal access surgery, the adage of "when in doubt, open and see" is replaced with "when in doubt, do a scan" or "when in doubt, look (diagnostic laparoscopy) and see."

MANAGEMENT OF APPENDICITIS

It is essential to distinguish between complicated and uncomplicated AA as it impacts management. Complicated AA typically includes perforation with peritonitis, phlegmon, or abscess formation, making up 2%-10% of all AA cases[70]. A phlegmon is described as an inflammatory mass including the inflamed adjacent viscera and greater omentum, while an abscess is described as a pus-containing appendiceal mass [71]. Appendicitis in the absence of these is defined as uncomplicated. Appendectomy (open or laparoscopic) is the standard of care for AA. However, recent evidence suggests that antibiotics alone may be adequate in selected patients–NOM. The classic description of NOM principles by Ochsner-Sherren relates to complicated AA-a patient with RIF mass. Currently, NOM is described both in uncomplicated and complicated AA[72].

NOM

In a meta-analysis including five studies and 1116 patients, Sallinen *et al*[73] reported lower rates of complications with NOM. However, the authors reported an increased incidence of recurrence of AA at one year and longer hospital stay[73]. Surgical intervention has higher treatment efficacy and a shorter length of stay than antibiotic treatment[74]. However, heterogeneity in antibiotic choice, dose and duration, inclusion and exclusion criteria, and other confounding variables could impact the results. In a retrospective cohort study of 81 uncomplicated AA patients, Loftus *et al* [75] reported NOM was more successful if patients had a longer duration of symptoms before admission, a lower temperature within 6 h of admission, lower modified Alvarado score, and a smaller appendiceal diameter[75]. Studies with long-term follow-up data are reported. In a 7-year prospective observational study involving 423 patients, Sippola *et al*[76] reported a 39.3% recurrence rate when uncomplicated AA patients were managed by NOM[76]. Patient satisfaction between the appendectomy and NOM group was similar (95%CI: 0.86-1.0; *P* = 0.96). Podda *et al*[77] reported that patients managed by NOM had a higher visual analog scale at 30-d follow-up (0.3 ± 0.6 *vs* 2.1 ± 1.7)[77]. O'Leary *et al*[78] reported that patients managed by surgery had a better quality of life (94.3 *vs* 91.0, *P* < 0.001)[78]. Thus, the decision for NOM *vs* surgery has multiple domains to consider, and each patient should be assessed and counseled on his own merits. Ideally, a patient-centric healthcare decision ought to be made, but a survey by Reinisch *et al*[79] involving 1300 surgeons revealed that decisions are made by surgeon preferences. Authors reported that only 14% of surgeons treat uncomplicated AA by NOM, 38.1% in selected cases, and 48.8% rejected NOM[79]. Thus, the inherent bias of the surgical community against NOM should be considered while critically appraising the evidence. More prospective multi-center collaborative studies, with long-term follow-up comparing NOM with appendectomy, including total cost of care, quality of life domains as outcome measures, are necessary before meaningful conclusions and valid recommendations can be made. In our opinion, NOM imposes a long-term recurrence risk and adds the burden of missing incidental tumours. In a systematic review of 455 patients, Peltrini *et al*[80] reported a 11% incidence of appendiceal neoplasms after interval appendectomies for complicated appendicitis[80]. It is possible that with such information, young patients may not participate in a randomized study due to fear of being allocated to the NOM group. Lastly, many authors have reported using carbapenems for NOM, which could contribute to antimicrobial resistance. Percutaneous drainage is integral to the NOM concept. Percutaneous drainage in perforated AA lowers the risk of hemorrhage,

fistula formation, wound infection, prolonged ileus, and adhesions compared to immediate appendectomy[81].

Prophylactic antibiotics peri-operatively

Antibiotics are the bare minimum in AA management, regardless of NOM or appendectomy. A 2005 Cochrane review included 45 studies with 9576 patients and reported that antibiotics were superior to placebo in preventing wound infection and intra-abdominal abscess[72]. Beyond 24-h postoperative antibiotics are generally prescribed in patients with complicated AA[82]. Three days of antibiotics are as effective as a five-day course in reducing infectious complications[83,84]. The commonly affirmed practice is to stop postoperative antibiotics within 24 h in patients with uncomplicated AA[85,86], which is widely considered acceptable since source control is achieved. Abounozha *et al*[87] reported that postoperative antibiotics in patients with uncomplicated AA do not decrease surgical site infections but increase the length of stay and costs[87].

Choice and selection of antibiotics are equally crucial as duration. Local antibiotic stewardship initiatives and individual surgeons must ensure that antibiotics are rationally used to reduce the emergence of multi-drug resistance organisms. Our unit uses amoxicillin-clavulanate with a stat dose of gentamicin or ceftriaxone and metronidazole in AA patients. Studies reporting NOM tend to use more broad-spectrum antibiotics to increase treatment success. A meta-analysis by Wang *et al*[88] involving nine randomized controlled trials with 4551 patients reported that carbapenems were associated with fewer treatment-related complications than an appendectomy in uncomplicated AA[88]. Additionally, carbapenems were noted to be the only antibiotic with one-year treatment success rates greater than appendectomy. However, we caution to generalize these results, as each institution should remain guided to select antibiotics based on local antibiogram.

Timing of antibiotic administration is essential in managing patients with sepsis, as delay can increase mortality. An early administration of antibiotics is recommended [74]. In a systemic review involving 34 studies and 2944 uncomplicated AA patients, Talan *et al*[86] reported that most patients showed treatment response within 1-2 d [86]. On the other hand, complicated AA patients had a mean response time of approximately three days. This suggests that prolonged course antibiotics may be necessary for complicated AA patients[12]. An electronic clinical decision support tool allows for the rational use of antibiotics[89].

Surgical intervention

Appendectomy or NOM both remain valid options in selected patients with both uncomplicated and complicated AA. There is enough data that NOM is safe, feasible, cost-effective, and restores quality of life. In a retrospective study including 231,678 patients, McCutcheon *et al*[90] reported no differences in mortality and cost between appendectomy and NOM[90]. We remain cautious about recurrent AA risk, missing tumors, and antimicrobial resistance. In patients selected for appendectomy, timing (interval *vs* index appendectomy) and approach (laparoscopic *vs* open appendectomy) need discussion. In addition, with the laparoscopic approach, single incision *vs* conventional three-port incision and stump closure methods need discussion.

Index vs interval appendectomy

The timing of an appendectomy depends on the patient's clinical stability, available resources, and patient preference. Emergency appendectomy is warranted in patients who manifest signs of sepsis with hemodynamic instability[91]. If the patient is deemed to have high risk due to medical co-morbidity or organ failure, then percutaneous drainage of an abscess may be considered. If the patient with perforated AA is clinically stable, an appendectomy can be performed at the next available opportunity. Various studies have demonstrated both superior and inferior outcomes with early appendectomy when compared to NOM. Young *et al*[92] reported that early appendectomy resulted in reduced bowel resection incidence[92]. Others have reported higher morbidity, including the need for hemicolectomy in patients with complicated AA[93]. This is consistent with Gavriilidis *et al*[83]'s recent meta-analysis, where the overall complications, abdominal/pelvic abscess, wound infections and unplanned procedure performance were significantly lower in conservative treatment cohorts[83]. In our experience, surgeon experience and skill are essential to avoid a limited right hemicolectomy. In patients treated conservatively, Snyder *et al*[35] reported a 12% risk of recurrence[35]. Thus, a patient must be counseled adequately for possible increased morbidity from imminent surgery or interval appendectomy

after a trial of conservative management.

Interval appendectomy can be done routinely following conservative management or selectively in patients with recurrent AA after NOM. We distinguish NOM from conservative management with relation to intent. NOM intends to avoid surgery, while conservative management intends to delay surgery later, accounting for safety. NOM can be repeated in patients with recurrent AA. In a systematic review by Darwazeh *et al*[84] involving 1943 patients and 21 studies, there was no morbidity difference between patients managed *via* interval appendectomy or repeat NOM (10.4% *vs* 13.3%)[84]. The study by Hall *et al*[94] involving 106 children who had a recurrence of AA recommended a conservative "wait-and-see" approach over interval appendectomy given the low incidence of complications[94]. A routine interval appendectomy may be beneficial in patients of advanced age to check for a possible malignancy. However, this could be circumvented by offering follow-up imaging and colonoscopy[95]. Due to the short follow-up duration of studies that recommend NOM, the authors practice recommending a routine interval appendectomy to all patients, especially in the presence of a fecolith at the appendix base.

Laparoscopic vs open appendectomy

Laparoscopic appendectomy is as safe as open appendectomy. Smaller wounds translate to less pain, a faster return to normal activities, and a shorter length of stay [23,96,97]. A surgical scar is a determinant of adhesive small bowel obstruction[98]. It is debatable if minimal access approach results in lower rates of postoperative adhesions and small bowel obstruction in patients with AA. In a retrospective analysis of 619 children managed with appendectomy, Håkanson *et al*[99] concluded that the risk for small bowel obstruction after appendectomy was significantly related to perforation or postoperative intra-abdominal abscess and not to the surgical approach [99]. Buia *et al*[96] revealed in a systematic review of 185 articles that laparoscopic appendectomy provides lower short-term bowel obstruction rates in pediatric and perforated AA populations while having lower long-term bowel obstruction rates in all patients[96]. There is a paucity of data regarding postoperative incisional hernia incidence. In a systematic review of 37 studies on appendectomy with sample size > 500 patients each and follow-up > 30 d, Rasmussen *et al*[100] reported a pooled estimate of 0.7% for incisional hernia at follow-up of 6.5 (range 1.9-10) years[100]. In our opinion, minimal access surgery probably reduces the rates of postoperative adhesions and incisional hernia.

Surgical site infection and intra-abdominal infection are crucial key performance indicators of appendectomy. Surgical site infection results in prolonged hospital stay, extended recovery time, increased total cost of care, and drain on healthcare resources [101]. In an umbrella review including ten meta-analyses, Poprom *et al*[102] concluded that surgical site infection rate was 48% to 70% lower in laparoscopic appendectomy than an open appendectomy, and intra-abdominal abscess rate was 1.34 to 2.20 higher in laparoscopic appendectomy than open appendectomy[102]. A higher rate of intra-abdominal abscess could be mitigated by judicious peritoneal lavage and a standard policy to aspirate peritoneal cavity dry before closure.

Laparoscopic appendectomy is associated with reduced 30-d readmission. In a meta-analysis including 45 studies and 836921 appendectomies, Bailey *et al*[103] has reported a 4.3% (range 0.0-14.4%) 30-d readmission rate. Diabetes mellitus, complicated appendicitis, and open appendectomy predicted 30-d readmission[103], and thus laparoscopic appendectomy may be superior if available and accessible. Laparoscopic appendectomy is also notably more cost-effective compared to not only open surgery but NOM as well. In an umbrella study by Sugiura *et al*[104], it is noted that three meta-analyses revealed NOM costs $235 more than operative management, making it less cost-effective than laparoscopic management[104].

Laparoscopic appendectomy can be performed by a single port or conventional three-port technique. A study involving 101 patients by Kim *et al*[105] reported that Single-incision laparoscopic appendectomy (SILA) reduced the length of hospitalization (1.2 ± 0.8 d *vs* 1.6 ± 0.8 d, *P* = 0.037) *vs* three-port appendectomy[105]. Systematic reviews and meta-analyses report that SILA is associated with a shorter length of hospital stay but longer operation duration and increased risk of open conversion[106,107]. SILA requires special training and may be associated with an increased risk of incisional hernia.

Laparoscopic appendectomy is safe and reduces postoperative morbidity in patients with morbid obesity[96]. In a systematic review and meta-analysis including 12 studies with 126237 elderly patients in the laparoscopy group and 213201 elderly patients in the open group, Wang *et al*[108] reported that laparoscopic appendectomy was associated with lower postoperative mortality, wound infection, and shorter length of

hospital stay[108]. Thus, laparoscopic appendectomy is safe in obese and elderly patients. While there is the benefit of percutaneous drainage to manage a postoperative intra-abdominal abscess > 4 cm in size[109,110], routine abdominal drainage following an appendectomy for complicated appendicitis has no clinical benefit[111].

Stump closure

Appendiceal stump closure techniques, *e.g.*, surgical stapler or conventional sutures such as Endoloop, are debated. In a study of 333 patients, Rakić *et al*[112] reported that Endoloop was preferred over the stapler given the cost benefits and lack of difference in perioperative morbidity[112]. In a retrospective study of 708 patients, Escolino *et al* [113] reported that the use of Endoloop was associated with a higher incidence of an intra-abdominal abscess, postoperative ileus, and re-operations/readmissions compared to the use of a stapler[113]. Sohn *et al*[114] made a simplified recommendation for using Endoloops in low-grade AA and staplers in high-grade AA [114]. Other options for stump closure include intra-corporeal knotting and clips. In a prospective study of 61 patients by Ates *et al*[115], the use of titanium endoclips was associated with a shorter operation time than intracorporeal knot tying (41.27 ± 12.2 min *vs* 62.81 ± 15.4 min, P = 0.001)[115]. A similar comparison of Hem-o-lok and Endoloop was made in a study by Wilson *et al*[116]. Wilson *et al*[116] noted significantly reduced operative time when using polymer clips like Hem-o-lok compared to Endoloop (59 min *vs* 68 min, P = 0.008)[116]. We perform laparoscopic appendectomy using one 10 mm camera port and two 5 mm working ports. A surgeon requires two 10 mm ports for stapling devices, thus theoretically predisposing the patient to a higher risk of incisional port site hernia. Further, a stapler pin is associated with an increased risk of postoperative adhesions[117]. In our opinion, routine use of stapling devices for stump closure is not justified.

Incidental findings

Two categories of incidental findings need discussion. Firstly, situations where intra-operative AA is established, but a separate incidental pathology is detected[118]. In such instances, it is our opinion that a surgeon should proceed with an appendectomy and document the operative findings. The incidental pathology can be investigated and managed later. Secondly, situations where the appendix appears normal to visualization. Laparoscopy has an advantage in such situations; a surgeon can thoroughly explore the peritoneal cavity. If a definitive pathology is detected and the patient appropriately consented, the surgeon can proceed accordingly. It is debatable and controversial if a normal appendix must be removed, especially if another pathology is established. Our practice is to remove a "normal-appearing" appendix in the absence of other established diagnoses[119]. We do this for two reasons. Firstly, a "normal-appearing" appendix may be an early AA. Secondly, removal of the appendix eliminates future diagnostic dilemmas for RIF symptoms.

Endoscopic appendectomy

Other techniques such as endoscopic retrograde appendicitis therapy have also been proposed to treat uncomplicated AA[120]. In another retrospective study by Ding *et al* [121] involving 210 patients, there was a 100% success rate with a recurrence rate of 2.86% during the first 6 mo of postoperative follow-up[121]. Given the relatively low-powered studies currently, more evidence is necessary.

AA AND THE COVID-19 PANDEMIC

There are reports of AA associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Many authors have also made suggestions for NOM and avoid surgery in selected AA patients. In patients managed by surgery, the use of personal protective equipment, strategies to reduce surgical aerosols, and the role of peritoneal fluid in viral isolation is proposed.

Associations of COVID-19 infection with AA

In a case series by Prichard *et al*[122], including 6047 patients, it was noted that AA was more likely in patients with COVID-19 positive results compared to those without (10.8% *vs* 1.3%, P < 0.001)[122]. Meyer *et al*[123] reported a higher prevalence of SARS-CoV-2 infection in children. Ahmad *et al*[124] reported a case where SARS-CoV-2 isolates were found in tissue samples of mesenteric lymph nodes despite having a

SARS-CoV-2 negative swab[124]. The converse was also reported, where a patient reported by Ngaserin *et al*[125] was COVID-19 positive but did not detect SARS-CoV-2 in the peritoneal fluid[125]. However, a small sample size limits the generalizability of such observations. We have not observed a similar trend in Singapore (unpublished data). More evidence is required, including histology analysis, before any meaningful conclusions can be drawn.

Management of AA during a pandemic

To reduce risk exposure to healthcare personnel and intra-operative airborne or droplet transmission of the virus, various societies have made recommendations including but not limited to: (1) Strict donning of personal protective equipment; (2) Goggles; (3) N-95 mask; (4) Gradual decompression of pneumoperitoneum; and (5) Reducing the operating personnel to bare necessary, *etc.* and so on. One of the primary considerations is the possibility of avoiding surgery to reduce COVID-19 risk, *i.e.*, NOM[126]. This is supported by the high risk of perioperative COVID-19-associated mortality[127]. In a large, randomized trial comparing outcomes of drugs and appendectomy involving 1552 patients, 29% of patients in the NOM group required surgical intervention[128]. Mai *et al*[127] did not detect perioperative COVID-19 infections and advocate that surgical treatment should be first-line unless COVID-19 infections have been proven or suspected[127]. However, the management should not only be dictated by the COVID-19 pandemic. Collard *et al*[126] propose using the Saint-Antoine scale, including BMI < 28 kg/m^2, leucocyte count < 15000/uL, CRP < 3 mg/dL, and no radiological signs of perforation and diameter of appendix ≤ 10 mm each for 1 point. A score of ≥ 4 is more likely to respond to antibiotic treatment only [126]. More evidence is required if such criteria could guide NOM during a pandemic.

Complications of appendicitis from COVID-19

The effect of COVID-19 on the severity of AA has to be considered in two ways–the fear of the virus delaying COVID-19 negative patients from seeking treatment and the effect of the virus itself in worsening AA.

The combination of government restrictions to leaving the house and fear of exposure in high-risk environments such as hospitals may cause a delay in seeking treatment. In a prospective study by Mowbray *et al*[129], only 64 patients presented with AA in April 2019 (before lockdown) compared to those previously (190 patients in April 2020 during lockdown)[129]. Patients were also noted to have increased their threshold for seeking treatment, presenting to the hospital one day later (2 d *vs* 3 d, *P* = 0.03). Consequently, some authors noted that the delay in seeking AA treatment might have resulted in more complex AA presentations. Mowbray *et al*[129] noted a higher American Society of Anesthesiology (ASA) score (*P* = 0.049)[129]. Finkelstein *et al*[130]'s retrospective analysis of 107 patients revealed a similar increase in AA perforations (33% *vs* 17% *P* = 0.04) than pre-COVID-19[130]. Interestingly, Finkelstein *et al*[130] did not notice a delay in presentation to the hospital (2 ± 3 d in both 2019 and 2020, *P* = 0.50) but noted that complicated AA seemed to present with a longer duration of symptoms (2 d *vs* 1 d, *P* = 0.03). The idea that more complicated AA presented in the COVID-19 era is also supported by Yang *et al*[131] in a study of 235 patients, where there was a significantly longer interval from onset of symptoms to seeking treatment (37.92 h *vs* 24.57 h comparing registration time of onset of symptoms to registration, *P* = 0.028) and higher incidence of complex AA (35.8% *vs* 19.4%, *P* = 0.005)[131]. However, the converse has also been reported where no differences in complications or severity in AA presentation were seen in other regions. In a retrospective study by Griffith *et al*[132] comparing 2020 and 2019 AA admissions, there was an increased admission rate (40.8% *vs* 34.1%, *P* = 0.036)[132]. Kohler *et al*[133] revealed in a population-based study in Germany that there was no difference in the number of perforated AA diagnosed during the pandemic or pre-pandemic[133]. Additionally, Bajomo *et al*[134] noted, in a study involving 78 patients, higher inflammatory markers (CRP 103 mg/L *vs* 53 mg/L, *P* = 0.03) and more severe disease on the histological examination pre-pandemic[134].

Adopting new practices post-COVID-19

Liberal use of imaging may improve diagnostic accuracy and reduce NAR. In a study by Somers *et al*[135] comparing AA management in 2020 and 2019, there was increased use of imaging (89.3% *vs* 69.3%, *P* = 0.007) and an accompanying decrease in NAR (0% *vs* 24.6%)[135]. Other additional measures enforced for surgeons' safety during the pandemic can also be considered in future circumstances where aerosol-driven pathogens are suspected. Examples include the presence of a negative-pressure

operating room, enhanced personal protective equipment, and avoiding the use of electrocautery and other aerosol-generating instruments[136].

SPECIAL CONSIDERATIONS

Children, pregnant women, the elderly, and immunocompromised status pose unique diagnostic and management challenges for AA. We briefly discuss pertinent issues in Figure 2. The US scan is simple, cheap, readily available, and an accurate diagnostic modality. It also avoids radiation exposure. Mittal *et al*[137] conducted a 10-center prospective observational study on 2625 pediatric patients with suspected AA and reported that the US scan had an overall sensitivity of 72% and specificity of 97% in diagnosing AA[137]. The US is operator-dependent, and US sensitivity is higher at sites using it more frequently. US scan is also recommended in pregnant patients as it eliminates fetus radiation exposure[56]. However, Wi *et al*[138] reported very low appendix visualization rates and proposed using MRI scan as first-line imaging in pregnant patients with abdominal pain suspicious for AA[138]. We suggest that hospitals conduct regular audits and implement quality improvement practices to track US performance. Prompt management can reduce spontaneous abortion. In a study by Nakashima *et al*[139] involving 169 pregnant women, the incidence of fetal loss was low in NOM compared to appendectomy (4% *vs* 5%)[139]. Surgeons must be aware that gestational age leads to a significant change in the location of the appendiceal base relative to McBurney's point[140]. We routinely offer laparoscopic appendectomy in pregnant patients. Low-pressure pneumoperitoneum, left lateral tilt to reduce uterine compression of vena cava, and an anesthetic team with obstetric training are essential to good outcomes. In a systematic review and meta-analysis of 22 comparative cohort studies, including 4694 pregnant women (905 Laparoscopic appendectomies and 3789 open appendectomies), Lee *et al*[141] reported that fetal loss was significantly higher for laparoscopic appendectomy patients (pooled OR was 1.72, 95%CI: 1.22-2.42). However, the results were skewed due to one study. On excluding the outlying study, there was no significant difference between laparoscopic and open appendectomy concerning the risk of fetal loss (OR 1.163, 95%CI: 0.68-1.99; *P* = 0.581) [141]. As such, while caution should be taken, patients should not be unduly refused appendicectomy while pregnant. We recommend that appendectomy be done in a facility with resources available to deal with obstetric urgencies.

No age is immune to AA. AA in the elderly is uncommon and atypical. Late presentation, association with malignancy, association with DDA, and complicated AA are common. In a meta-analysis involving 12 studies and 126,237 patients, Wang *et al*[108] report that postoperative mortality was lower in elderly patients treated with laparoscopy *vs* open appendectomy (OR, 0.33; 95%CI: 0.28-0.39)[108]. Elderly and immunocompromised patients have limited inflammatory responses. In such patients, clinical scoring systems have a lesser role in diagnosis. Anshul *et al*[142] reported a patient with a silent abdomen but AA diagnosed on CT scan[142]. Perioperative care must be customized with a low threshold to suspect complications.

HISTOLOGY EVALUATION

Routine histopathological examination after appendectomy is the prevalent standard practice globally. In a meta-analysis of twenty-five studies and 57357 patients, Bastiaenen *et al*[143] reported 2.5% unexpected findings. They also observed that surgeons could rarely (3%) detect unexpected findings during surgery. Though granulomatous diseases such as Crohn's could be macroscopically detected almost half of the time (47.1%), endometriosis and parasitic infections could only be diagnosed following histopathology.

Neoplasms account for 1% of appendectomy histology specimens[144]. Patients above 50 years of age, with family history of colon cancer or inflammatory bowel disease, or with unexplained anemia are at risk of appendiceal neoplasm[47]. The most common appendiceal neoplasm is neuroendocrine tumours[145]. Appendiceal carcinoid tumors are seen in 1% of appendectomy specimens and same managed with the same caution as adenocarcinomas[139,140,146]. The presence of adenocarcinoma in the appendectomy specimen requires a right hemicolectomy. In a meta-analysis of six studies including 261 patients who had an appendiceal carcinoid tumor, Ricci *et al*[147] found a significant recurrence rate in tumors larger than 2 cm in size compared to those smaller than 2 cm, with a higher risk of lymph node metastases in the former
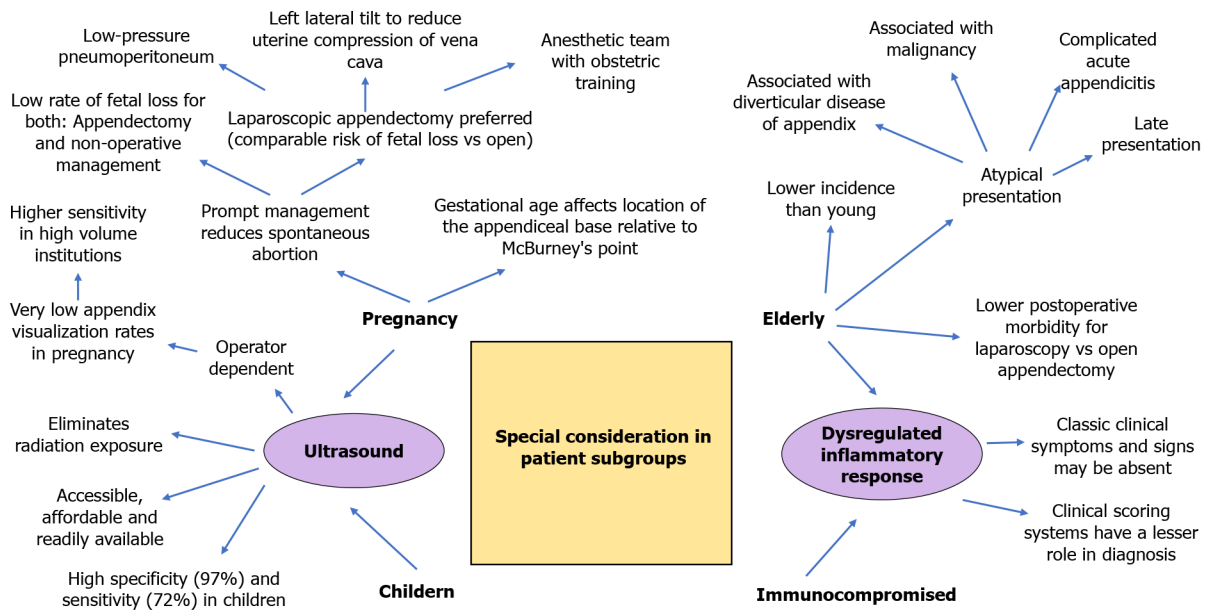
Figure 2 Special considerations in children, pregnancy, elderly and immunocompromised.

group[147]. A right hemicolectomy is warranted for carcinoid tumors > 2 cm size, located at the base of the appendix, or involved lymph nodes. Locally, the multidisciplinary oncology board makes management recommendations in such instances. In perforated AA, the goblet cell subtype of appendiceal carcinoid is associated with a greater risk of peritoneal metastasis than the classical subtype. In a systematic review involving 121 cases of appendiceal carcinoid tumors with perforation, Madani *et al* [148] noted that perforation accelerates the metastatic process[148]. A surgeon should avoid a spill of luminal contents. Metastasis to the appendix is a rare occurrence. The gastrointestinal tract is the most likely site of breast tumor metastases. Ng *et al*[149] reported 15 patients with breast cancer and appendix metastasis[149]. Each patient's treatment should be determined by multidisciplinary oncology teams considering disease stage, the extent of metastases, patient performance status, physician expertise, and patient choices. Appendiceal endometriosis (AE) may be associated with low-grade appendiceal mucinous neoplasms and small bowel obstruction secondary to an endometrial ileal stricture[150]. Prophylactic appendectomy in patients with AE may reduce intestinal obstruction risk, and further data is needed.

CONCLUSION

Multiple aspects of approach to management of AA remain well debated in the literature. The role of clinical scoring systems and imaging in the early and accurate diagnosis of AA can reduce NARs. NOM and appendectomy both remain valid options with their own merits and demerits. Laparoscopic appendectomy is widely accepted as safe with the benefits of early recovery and reduced wound infection compared to open appendectomy. Fear-related behavior is proven during the COVID-19 pandemic, as evidenced by a delay in presentation. Histologic evaluation of appendix specimens has value in detecting incidental malignancies. As the management of AA evolves with technological strides and a more refined understanding of the pathology, we foresee more flavorful discussions on such a staple condition.

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