Current approaches to diagnosing acute appendicitis: pitfalls and progress

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Purpose of review
Pediatric appendicitis remains a common diagnostic challenge faced in the emergency department. In this review, we provide an update on recent literature regarding the diagnosis of pediatric appendicitis via labs, imaging, and clinical prediction scores, and provide a summary of key pitfalls in diagnosing this condition.

Recent findings
Progress has been made in laboratory evaluation for the diagnosis of pediatric appendicitis with newer markers being under investigation, though standard markers such as white blood cell count and C-reactive protein remain prominent. From an imaging standpoint, there is emphasis on the use of ultrasound as the primary imaging modality, and creating new protocols for magnetic resonance imaging as a secondary imaging method if ultrasound is inconclusive. Clinical prediction scores continue to be a promising diagnostic tool with the literature indicating high specificity but rather low sensitivity. A wide array of diagnostic practices exist creating disparities in care, particularly with imaging.

Summary
Pediatric appendicitis is a challenging diagnosis with ongoing research efforts focused on novel laboratory markers that are more sensitive and specific, prioritizing the use of nonionizing radiation imaging modalities, and improving reliability of clinical prediction scoring tools. Reducing disparities in care surrounding pediatric appendicitis should be a focus for future research.

Keywords
adolescent, appendicitis, children, pediatric

INTRODUCTION

Acute appendicitis accounts for a large number of pediatric abdominal emergencies and hospitalizations. Conservative management, as seen in the adult literature, has not been established in pediatric patients. Delays in the diagnosis of pediatric appendicitis can lead to increased risk for perforation and complications. Conversely, performing abdominal surgery on a pediatric patient is risky, and therefore, accurate preoperative diagnosis of appendicitis in pediatric patients is critical. However, pediatric appendicitis has proven to be a challenging diagnosis as early symptoms are not specific. Our understanding of laboratory evaluation, imaging studies, and clinical prediction scores continues to evolve via ongoing research to allow for prompt and accurate diagnosis. In this paper, we review the latest literature on the current approaches to diagnosing appendicitis in the pediatric population.

LABORATORY EVALUATION

The diagnostic value of laboratory markers in pediatric appendicitis has long been studied. In addition to clinical history, physical exam, and imaging, laboratory evaluation could be of great diagnostic value if the most sensitive and specific markers are identified. Literature has consistently found that single laboratory values alone have low predictive values [1]. The recent literature has compared the standard laboratory markers such as white blood cell (WBC) count, C-reactive protein (CRP), mean platelet volume (MPV), and absolute neutrophil count

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KEY POINTS

- Laboratory evaluation for diagnosis of pediatric appendicitis such as white blood cell count and C-reactive protein have moderate sensitivity and specificity which increases when combined.
- Ultrasound remains the recommended first diagnostic imaging modality though is operator dependent with a wide range of sensitivity and specificity.
- Magnetic resonance imaging is increasingly utilized as a means of cross-sectional imaging to follow inconclusive ultrasound evaluations, replacing computed tomography as a safer alternative.
- There are several popular clinical prediction scores used to estimate risk of appendicitis, with the Appendicitis Inflammatory Response Score and the Pediatric Appendicitis Risk Calculator emerging as the most sensitive and specific.
- Challenges and disparities exist in diagnosing pediatric appendicitis, which results in missed diagnoses and patient morbidity.

(ANC) to specific biomarkers within the inflammatory cascade (e.g. interleukin-6, fibrinogen, and tumor necrosis factor-alpha). It is prudent to weigh the cost and availability of these markers with their clinical significance. This section focuses on the accuracy of laboratory markers and their utility in the diagnosis of pediatric appendicitis.

Despite recent literature focusing on less conventional laboratory markers to aid in the diagnosis of pediatric appendicitis, it remains important to continue to evaluate valuable laboratory markers that are readily available and affordable. A recent systematic review identified WBC count (≥10 cells/l) and ANC (≥7.5 cells/l) as the most sensitive laboratory marker in pediatric appendicitis with a sensitivity of nearly 85% and 90%, respectively [1]. The combination of WBC count and CRP (≥10 mg/l) increased sensitivity to 97% [1]. CRP alone (≥50 mg/l) was found to be the most specific singular marker at 87%, and combined with WBC count, the specificity rises to 93% [1].

In a retrospective review of 100 children who presented to the emergency department (ED) with concern for appendicitis, Dooki *et al.* found the sensitivity and specificity of CRP (>10 mg/dl) to be mid to high at 82% and 62%, respectively [2]. The sensitivity and specificity of WBC count (>12 cells/l), PMN (>73%), and ESR (>15 mm/h) was found to be relatively lower (WBC 78% and 66%, PMN 76% and 54%, and ESR 80% and 48%, respectively) [2]. Mean platelet volume (MPV < 8.1 fl) had low specificity of 8% and medium sensitivity of 70% [2]. Children with higher CRP levels were more likely to have appendicitis compared to children with lower levels [2]. CRP was found to be more sensitive than WBC count, which has been inconsistently noted in previous literature, but had lower specificity than reported in other studies [2]. They found a positive likelihood ratio (LR+) of nearly 21 in patients with CRP >10 mg/dl, suggesting an elevated CRP is more likely to correlate with pediatric appendicitis compared to WBC count (LR+ 2.3), PMN (LR+ 1.65), MPV (LR+ 3.75), and ESR (LR+ 1.54) [2]. Despite a lower mean level of MPV in children with appendicitis, they suggest that MPV is not effective in the diagnosis of pediatric appendicitis due to low sensitivity and specificity [2].

Recent studies have identified interleukin-6 (IL-6) as a potentially useful laboratory marker. A prospective observational study assessed whether IL-6 has enhanced sensitivity and specificity compared to the standard pediatric appendicitis laboratory markers, including WBC count, neutrophil count, fibrinogen, ferritin, activated partial thromboplastin time, international normalized ratio, and CRP [3]. The study concludes that there was a significant increase in IL-6 when comparing uncomplicated appendicitis and patients without appendicitis [3]. CRP was significantly increased when comparing severe appendicitis to patients without appendicitis, but there was no significant difference when comparing uncomplicated appendicitis to patients without appendicitis [3]. In distinguishing appendicitis from patients without appendicitis, they report the sensitivity and specificity of IL-6 as 82% and 54%, respectively, compared to sensitivity and specificity of CRP as 86% and 35%, respectively [3]. Each has relatively high sensitivity and low specificity, yet when used together, the sensitivity rises to 100% with a specificity of 40% [3]. The authors conclude that IL-6 may have an important role in the diagnosis of pediatric appendicitis, especially when coupled with CRP [3]. However, using IL-6 as a laboratory marker may not be generalizable as this may not be widely available nor timely at most hospitals.

A prospective observational study aiming to clarify the diagnostic accuracy of plasma fibrinogen concluded that it had the highest diagnostic accuracy when compared to total leukocyte count (TLC), ANC, neutrophil-lymphocyte ratio (NLR), and CRP [4]. Plasma fibrinogen (> 4.03 g/l) had the highest diagnostic accuracy rate of 82.5% followed by TLC (70.83%), ANC (70.8%), and CRP (70%) [4]. CRP was found to have the greatest sensitivity (89.9%) and TLC was found to have the greatest specificity (92.3%) [4].

Recent literature has recognized tumor necrosis factor-alpha (TNF-alpha) as a potentially valuable

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laboratory marker. Sahin *et al*. found that TNF-alpha was helpful in distinguishing patients with perforated appendicitis from uncomplicated appendicitis as well as distinguishing patients with perforated appendicitis from patients without appendicitis, but was not helpful in distinguishing uncomplicated appendicitis from patients without appendicitis [5]. Therefore, TNF-alpha appears to be helpful but only in very specific clinical scenarios.

Overall, recent literature continues to support the use of multiple laboratory markers to improve diagnostic accuracy and reinforces the utility of standard appendicitis markers including WBC count, CRP, and ANC, especially when used in combination. There remains a wide range of reported sensitivity and specificity of laboratory markers. There is promising evidence that IL-6 and plasma fibrinogen could add significant diagnostic value, although TNF-alpha was less helpful in diagnosing pediatric appendicitis. The benefit of these nonstandard laboratory evaluations must be balanced with their cost and availability at institutions.

IMAGING STUDIES

Use of imaging modalities that avoid ionizing radiation whenever possible remains a priority in the evaluation of pediatric patients. This also applies to acute appendicitis. While ultrasound and computed tomography (CT) remain the most widely available options, magnetic resonance imaging (MRI) protocols are becoming increasingly popular among pediatric centers as a radiation-free cross-sectional imaging modality for pediatric appendicitis.

Ultrasound

Ultrasound is frequently the first choice for both pediatric centers and community hospitals in assessing for pediatric appendicitis, despite this imaging modality being heavily operator dependent. Ultrasound use has increased dramatically over the last two decades. In an assessment of U.S. imaging practices, End *et al*. found that "ultrasound only" and "ultrasound first" approaches to diagnosing pediatric appendicitis have increased from 5.5% and 8.9% respectively in 2006 to 38.9% and 55.6% [6▪▪].

There is discourse, particularly among pediatric surgical groups, about the adequacy of ultrasound to detect findings of complicated appendicitis. A recent systematic review and meta-analysis that compared ultrasound to CT imaging found that ultrasound has a slightly lower sensitivity and a wider though overall favorable range of specificity (68.8–95%) in detecting signs of complicated appendicitis. Given this, it is still recommended as the first line imaging modality with cross sectional imaging to follow only if results are ambiguous or inconclusive [7].

Investigations have explored the role of secondary signs of appendicitis to diagnose or rule-out appendicitis. Secondary signs (or indirect signs) of appendicitis on ultrasound include findings such as periappendiceal fat inflammation, enlarged mesenteric lymph nodes, and free fluid. One study examining young children <5 years old with non-visualized appendix on ultrasound observed that the presence of secondary signs was predictive of complicated appendicitis [8]. Another study found that in children aged 3–13 years, the absence of secondary signs of appendicitis on ultrasound and a low pretest probability of appendicitis with low Alvarado score made the diagnosis of appendicitis unlikely [9▪]. Both of these studies evaluating secondary signs of appendicitis on ultrasound were retrospective observational studies; at this point, no prospective studies have been performed using secondary signs as a predictor for appendicitis.

Point-of-care ultrasound (POCUS) training is also increasingly common among pediatric emergency medicine programs. There has been recent discussion regarding the ability of emergency medicine physicians to diagnose appendicitis via POCUS rather than a radiology-based study. One recent study found that the accuracy of POCUS in identifying appendicitis was highest in the 5–10 years age range and there was a high overall rate of correctly identifying histopathology-confirmed appendicitis, but physicians had poor ability to rule out appendicitis in children who were ultimately confirmed to not have appendicitis [10]. Using POCUS to identify appendicitis was associated with a reduced length of stay [10]. Another single center study found POCUS to be highly sensitive (88%) and specific (90%) for diagnosis of pediatric appendicitis when compared to radiologist-based ultrasound [11]. Additional research is needed to understand the feasibility of POCUS for the diagnosis of appendicitis.

Computed tomography

CT is common for further evaluation, with goals of further reducing radiation dose, as evidenced by other imaging modalities emerging. Based on recent imaging trends over the last two decades to diagnose pediatric appendicitis, isolated CT use has declined from 91.1% to 44% between 2006 and 2020 [6▪▪].

Some centers have modified existing CT protocols to reduce the dose of radiation, such as one system where a height-based focused CT protocol was implemented and found to have similar diagnostic accuracy as a standard CT abdomen/pelvis

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[12]. Another study implemented a next day surgery clinic appointment as an option to follow up patients in the ED who had an inconclusive ultrasound which reduced CT use from 13.8% to 6% without changing ED return visits, ED length of stay, or hospital admission rates [13].

Reducing CT utilization for the diagnosis of pediatric appendicitis has barriers. One qualitative study delineated four categories of barriers to reducing CT use: consistent resource availability (e.g. ultrasound technicians, pediatric radiologists, magnetic resonance imaging), presence of and adherence to protocols, inter-departmental collaboration, and the presence of a "radiation reduction champion" [14].

Magnetic resonance imaging

More hospitals are introducing MRI-based protocols as an alternative to CT evaluation for pediatric appendicitis. Recently, the Society of Pediatric Radiology MRI and Emergency and Trauma Imaging Committees published a consensus statement on recommended rapid MRI protocols to diagnose pediatric appendicitis given the increasingly widespread availability of MRI as a resource for radiologists [15▪]. This option is appealing to avoid ionizing radiation in pediatric populations. Rapid MRI protocols have also been associated with reduced cost as well as reduced scan time for the patient, which is particularly important for pediatric populations [16]. One center successfully reduced CT use at their institution using a quality improvement initiative to promote the use of rapid sequence MRI protocols [17].

To examine accuracy, one center developed an ultrasound-rapid MRI pathway and found that in over 600 children evaluated for appendicitis, this imaging pathway demonstrated high clinical accuracy [18]. Studies of MRI use after an inconclusive ultrasound markedly reduced CT use without an increase in ED length of stay, time to antibiotics and surgery, or missed and negative appendectomies [19,20]. An overall increase in advanced imaging charges has been noted, along with greater than double time delays to preliminary imaging interpretation [20].

MRI is now being explored to help diagnose postappendectomy complications such as abscess. One center implemented an MRI protocol for postappendectomy abscess evaluation and found reduction in CT utilization without change in diagnostic and clinical outcomes; factors such as time to diagnosis, rates of missed abscess, readmission, and reoperation rates remained the same [21].

CLINICAL PREDICTION SCORES

Clinical prediction tools have been introduced over decades with varying degrees of success and implementation into emergency department workflow. Assessment of the validity and feasibility of these tools has been ongoing, with four scores emerging on top. Components of each score discussed below are described in Fig. 1.

Alvarado score

The Alvarado Score, developed in the 1980s, continues to be studied in pediatric ED settings. Studies have paired the Alvarado score with imaging findings to risk stratify patients who are being evaluated for acute appendicitis. A retrospective observational study from a single center in Spain found that patients with low Alvarado score (<7) combined with absence of secondary signs of appendicitis, such as periappendiceal fat inflammation or free fluid, had low risk of having appendicitis when the appendix was not visualized on ultrasound [9▪]. However, a recent systematic review and meta-analysis of 26 studies found the Alvarado score performed with only moderate accuracy, concluding that it should not be relied upon solely as a tool for appendicitis diagnosis [22].

Pediatric appendicitis score

Developed in 2002, varying cut-off scores for the PAS continue to be explored. In general, patients at high risk of appendicitis tend to have scores of 7 and above. In a cross sectional study evaluating 391 patients presenting for appendicitis, one center found that a PAS score $\geq$7.5 combined with a CRP $\geq$25.5 mg/l had high sensitivity and specificity (95.8% and 94% respectively) for acute appendicitis [23]. In a retrospective review, Nemeh *et al.* established PAS score cut-offs that may help reduce CT utilization; they found that scores of $\geq$7 have a sensitivity and specificity of 90.2% and 90% for pediatric appendicitis, concluding that these high risk patients may not need CT for diagnosis [24]. Conversely, another pediatric tertiary care center examined the impact of implementing a modified PAS score into their emergency department workflow and found that this ultimately did not reduce the number of CT scans performed nor length of stay [25].

Appendicitis inflammatory response score

The appendicitis inflammatory response (AIR) score, published in 2008, relies upon subjective exam findings (such as pain) and laboratory data. In a meta-analysis that reviewed 26 reports published between

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Alvarado Score	Pediatric Appendicitis Score (PAS)	Appendicitis Inflammatory Response (AIR) Score	Pediatric Appendicitis Risk Calculator (pARC)
RLQ tenderness (2)	RLQ tenderness to palpation (2)	Right iliac fossa tenderness (1)	Maximal tenderness in RLQ
Migration of pain to RLQ (1)	Migration of pain to RLQ (1)	Degree of presence of rebound tenderness (1-3)	Migration of pain to right RLQ
Temperature ≥ 37.3˚C (1)	Fever ≥ 38˚C (1)	Fever ≥ 38.5˚C (1)	Abdominal guarding
Nausea/vomiting (1)	Nausea/vomiting (1)	Vomiting (1)	Presence of pain with walking
Leukocytosis (2)	Leukocytosis (1)	Elevated white blood cell count (1-2)	White blood cell count
Left shift (1)	Left shift (1)	Left shift (1-2)	Percent neutrophil count
Anorexia (1)	Anorexia (1)	Elevated C-reactive protein (1-2)	Duration of pain in hours
Rebound tenderness (1)	RLQ pain with cough, percussion, or hopping (2)		Sex
			Age in years
			Setting – Community versus pediatric emergency department

FIGURE 1. Common clinical prediction scores for pediatric appendicitis. Listed in this table are the four common clinical prediction scores for pediatric appendicitis, as discussed in this review. Listed below each clinical prediction score are the scores' components with the point value assigned to each component in parentheses ( ), if applicable. RLQ, right lower quadrant.

2008 and 2024 on the diagnostic accuracy of this score, Anderrson and Stark concluded that the AIR score has a better diagnostic capacity compared to the Alvarado score [26]. A score of > 8 points resulted in a specificity of 98% [26]. Another multicenter prospective study comparing sensitivity and specificity of the AIR score and Alvarado score concluded that the AIR score had both improved sensitivity and specificity, but only in low risk patients defined as an AIR score of 0–4 or Alvarado score of 1–4 [27]. In high risk patients, defined as an AIR score of 9–12 or Alvarado score of 7–10, neither score produced an acceptable sensitivity or specificity [27]. Conversely, Safaee *et al.* found the sensitivity and specificity of an AIR score >8 to be 32% and 100%, respectively, compared to a sensitivity and specificity of an Alvarado score of >8 to be 42% and 88%, respectively. They concluded that although both were reliable means to diagnose acute appendicitis, the AIR score may be favorable given its superior sensitivity and specificity [28].

Pediatric appendicitis risk calculator

The pediatric appendicitis risk calculator (pARC) score is a tool developed in 2018 that has been validated across multiple studies for children ages 5 years and older, outperforming the PAS in these studies [29,30]. One recent prospective observational study at a pediatric ED in Australia applied 30 different clinical prediction scores to over 480 patients being evaluated for appendicitis, and found that the pARC score performed the best with the lowest negative likelihood ratio of 0.08, sensitivity of 94.8%, and specificity of 63.2% [31]. Another recent study found that in children with nonvisualized appendix, low risk ultrasound findings combined with low pARC score suggested low risk for appendicitis, concluding that these children may be safely discharged home [32].

PITFALLS

Missed appendicitis represents a significant challenge in pediatric emergency medicine. The condition can result in considerable morbidity including complications such as perforation, abscess, and emergent surgical intervention. Diagnosing appendicitis in children is inherently difficult due to several factors, including:

(1) Challenges in obtaining an accurate medical history and conducting a thorough physical examination with pediatric patients.

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(2) The sensitivity and specificity of ultrasound imaging, particularly in cases of perforated appendicitis, are not 100%.
(3) The presence of concurrent diagnoses and conditions that mimic appendicitis.

Children may underreport their symptoms due to a fear of painful medical procedures, and some may not effectively communicate or localize their pain. Additionally, atypical findings during physical examinations further complicate the diagnostic process. A study indicated that 36% of patients who were imaged had a retrocecal appendix, which can obscure diagnosis [33].

Ultrasound is typically the preferred initial imaging modality for suspected appendicitis in children because it is safe, noninvasive, and does not involve radiation. However, its sensitivity is influenced by factors such as the quality of the equipment, the operator's expertise, and the presence of atypical features of appendicitis. In appendicitis-related litigation, approximately 75% of cases involve claims of delayed or missed diagnosis [34]. When an ultrasound fails to visualize the appendix, the negative predictive value is only 86% [35].

Complicating the diagnosis further, concurrent illnesses that cause fever and abdominal pain are common in children who are often exposed to contagious conditions in school and daycare settings. Conditions such as urinary tract infections, streptococcal pharyngitis, and lower lobe pneumonia can mimic appendicitis, adding to the complexity of the diagnostic process.

Disparities also exist in the diagnosis of pediatric appendicitis. Despite ultrasound being the recommended initial imaging modality for evaluating pediatric appendicitis, both hospital and patient characteristics can lead to overimaging of patients. A recent study looking at nearly 24,000 patients at 485 community-based hospitals found that centers with higher ultrasound utilization tended to have lower concurrent CT imaging [36]. Conversely, high volume hospitals tended to have higher concurrent CT utilization, and patient characteristics were also associated with higher concurrent CT utilization such as white race, public insurance, and lower socioeconomic status [36]. Another national assessment of ultrasound use for the diagnosis of pediatric appendicitis in over 49,000 children found that older children (aged 11–17 years) and children who were poorer or lived in rural areas were both less likely to visit hospitals that utilize ultrasound for diagnosis as well as receive ultrasounds even at ultrasound-capable hospitals [37▪▪].

From an equity standpoint, a large observational study including over 50,000 patients found that minority children were more likely to have missed diagnoses of appendicitis with a statistically significant difference between race/ethnicity and rates of imaging [38]. Similarly, another study using the National Hospital Ambulatory Medical Care Survey looked at over 1 million children diagnosed with appendicitis between 2010 and 2019 and found disparities in which imaging modalities were used to diagnose appendicitis based on both race and insurance status [39]. Some authors suggested that future efforts aiming to standardize the workup of appendicitis may result in reduced implicit bias [38]. Obesity also plays a role in imaging and diagnosis of pediatric appendicitis. One study found that children with an elevated body mass index greater than or equal to the 95th percentile had decreased diagnostic accuracy when using ultrasound to evaluate for appendicitis [40].

Overall, multiple challenges exist in diagnosing pediatric appendicitis, leading to potential missed diagnoses and patient morbidity. Further work is needed to help improve clinicians' diagnostic accuracy and reduce disparities.

CONCLUSION

Pediatric appendicitis remains a diagnostic challenge, though advances in laboratory evaluation, imaging, and clinical prediction scores have occurred in recent years. Disparities in diagnosis of pediatric appendicitis are also noted, with race and socioeconomic status possibly impacting the choice of imaging modality and an overall increased risk of missed diagnosis in minority groups. With multifaceted options to diagnose pediatric appendicitis, we hope that future research can further improve diagnostic accuracy and reduce disparities in practice.

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Conflicts of interest

There are no conflicts of interest.

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▪ of special interest
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