STATE OF THE ART

Pediatric appendicitis: pathophysiology and appropriate use of diagnostic imaging

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ABSTRACT
Evaluating children for appendicitis can be extremely difficult, and various strategies have been developed to improve the precision of preoperative diagnosis. Among these, ultrasound and computed tomography (CT) are now widely used but remain controversial. Although CT scanning is superior to ultrasound in terms of diagnostic accuracy for appendicitis, the large dose of ionizing radiation from CT and the risk of subsequent radiation-induced malignancy (RIM) are of particular concern in pediatric patients. This article reviews the literature on the pathophysiology, morbidity and mortality of appendicitis, summarizes the data regarding pediatric imaging in appendicitis, provides a practical approach to imaging for clinicians who evaluate pediatric patients, and makes recommendations for reducing the risk of RIM in pediatric patients.

Key words: appendicitis; infant; child; adolescent; ultrasonography; computed tomography; CT; radiation-induced malignancy

RÉSUMÉ
Il peut être extrêmement difficile d'évaluer les enfants pour diagnostiquer l'appendicite et diverses stratégies ont été mise au point pour améliorer la précision du diagnostic préopératoire. L'échographie et la tomodensitométrie (TDM), notamment, sont maintenant très répandues, mais elles demeurent controversées. Même si la TDM est supérieure à l'échographie pour ce qui est de l'exactitude du diagnostic d'appendicite, une dose importante de rayonnements ionisants provenant de l'appareil et le risque de tumeur maligne radio-induite (TMRI) subséquente préoccupe particulièrement chez les patients en pédiatrie. Dans cet article, les auteurs passent en revue les publications sur la pathophysiologie, la morbidité et la mortalité de l'appendicite, résument les données sur l'imagerie pédiatrique dans les cas d'appendicite, présentent une stratégie pratique d'imagerie pour les cliniciens qui évaluent des patients en pédiatrie et formulent des recommandations afin de réduire le risque de TMRI chez les patients en pédiatrie.

Historical perspective

The worldwide incidence of appendicitis is estimated to be 86 cases annually per 100 000 population,[1] with approximately 70 000 pediatric cases each year in the United States alone.[2] Appendicitis remains a diagnostic challenge for modern physicians. Infants and young children are among the most difficult group to diagnose because be-

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tween 33% and 50% will present atypically.[3,4] In light of this, various strategies have been developed and efforts have been made to improve diagnostic accuracy with the use of clinical scoring systems. Weyant and colleagues estimated that the diagnostic accuracy of an experienced physician is as high as 90%,[5] implying that less experienced physicians are less accurate.

In 1986, Alvarado reported the derivation of a clinical scoring tool for appendicitis called the MANTRELS criteria (Table 1), reported to result in a sensitivity of 89%, a specificity of 80% and an overall accuracy of 87% for patients with a score of ≥7.[3,6] Unfortunately, when Macklin and colleagues applied the MANTRELS criteria to children, the overall accuracy fell to <80%.[3,7] Other studies have found significant interphysician variability in the ability to clinically diagnose appendicitis using these criteria, with sensitivities and specificities ranging from 38%–97% and 85%–95%, respectively.[8–12]

Plain radiography, although relatively innocuous and inexpensive, is rarely beneficial in the diagnosis of appendicitis. Only half of patients with surgically proven disease have abnormal radiographic findings, most of which are non-specific. The appendicolith, a radio-opaque concretion located within the appendix, which is deemed to be the most specific finding of appendicitis on plain radiographs, is visualized in only 5%–15% of patients with appendicitis.[3,5]

In 1986, Puylaert described the technique of graded compression ultrasound to facilitate the diagnosis of appendicitis.[13] His initial study of 60 patients reported ultrasound had a sensitivity of 89%, a specificity of 100% and an overall accuracy of 95%. Later that year, Balthazar and colleagues[14] reported results from a series of 38 patients with proven appendicitis, 30 of whom were accurately diagnosed on CT, resulting in a sensitivity of 79%. Over the next 20 years, dozens of studies evaluated various aspects of each of these modalities and their perceived benefits and shortcomings, but only a few were specific to children. The remainder of this paper will focus on those pediatric studies.

Table 1. Alvarado Scoring System (MANTRELS criteria)[6] for appendicitis

Criteria	Score
Migration of pain	1
Anorexia	1
Nausea or vomiting	1
Tender right lower quadrant	2
Rebound tenderness	1
Elevated temperature	1
Leukocytosis	2
Shifted white blood cell count	1

Why the concern about the timely diagnosis of appendicitis?

Classically, appendicitis is described as a dynamic disease process that comprises 5 stages occurring over a 24- to 36-hour period. The inciting event is the obstruction of the appendiceal lumen, which is unable to drain and, as a result, distends.[1] The etiology is multifactorial, but fecaliths, lymphoid hyperplasia, foreign bodies, malignancy and parasites have all been described.[1] The appendix ranges in length from <5 cm to >25 cm, and the obstruction can occur at any point from the tip to the appendico-cecal junction.[15] During the second stage, stimulation of the 8th–10th visceral afferent thoracic nerves causes a mild to moderate peri-umbilical pain that typically lasts from 4–6 hours.[1]

As intraluminal pressure increases, appendiceal wall perfusion decreases due to arterial insufficiency.[1] This third stage results in tissue ischemia and mucosal compromise.[1] Bacteria are then able to invade the luminal wall, leading to transmural inflammation — the fourth stage.[1] As transmural inflammation extends beyond the appendix, the parietal peritoneum and adjacent structures also become inflamed.[1] This final stage causes a shift in pain perception from the peri-umbilical region to the right lower quadrant of the abdomen.[1] At this stage the pain is typically more severe, continuous, and often associated with constitutional symptoms, such as anorexia, fever, nausea and vomiting.[1]

Appendectomy is the standard of care for acute appendicitis. If untreated, appendicitis rarely resolves spontaneously, and usually progresses to perforation. Studies have suggested that a delay of >48 hours in the diagnosis or in the treatment of appendicitis results in perforation and complication rates greater than 80% and 60%, respectively.[4,16] Reported rates of perforation at the time of appendectomy in pediatric cases range from 23% to 88%.[4,16,17] Bacterial peritonitis can subsequently arise, which may result in overwhelming sepsis and death. In fact, before the universal acceptance of appendectomy, the mortality for this disease was more than 50%.[5] Today the overall mortality rate in North America has decreased to 1.7%.[1]

A rate of negative appendectomy (i.e., appendectomy performed after a false-positive diagnosis of acute appendicitis) as high as 25% in children has traditionally been considered an acceptable means of preventing high perforation rates.[3,16] This approach is based on the inherent trade-off between sensitivity and specificity, and is supported by studies demonstrating a direct relationship between diagnostic accuracy and perforation rates.[18,19] However, negative laparotomies and unnecessary appendectomies are not without risk and complications. In North America, the risk of mortality from a negative appendectomy is 1 in 714 (0.14%), and the risk of a significant complication is 4.6%.[16] The spectrum of morbidity ranges from early complications, such as abscess formation and wound infection, to late complications such as infertility, adhesions and bowel obstruction.[16] An appendectomy is clearly not a completely innocuous procedure, thus any imaging modality that could expedite the accurate evaluation of suspected appendicitis and reduce the negative appendectomy rate would be beneficial.

Ultrasound

Graded compression ultrasound is an operator dependant technique in which manual pressure is applied using a linear array ultrasound transducer to compress or displace loops of bowel in order to visualize the appendix.[4,13] Adequate pressure is achieved if the iliac vessels and psoas muscle are visualized, because the appendix is located anterior to these structures in more than 99% of patients.[4,13,20] In acute appendicitis, the appendix can be seen as a fluid filled, non-compressible tubular structure with a diameter of more than 6 mm.[4,13] Other signs consistent with appendicitis include the presence of an appendicolith, peri-cecal or peri-appendiceal fluid, and increased peri-appendiceal echogenicity secondary to inflammation.[4] If colour Doppler imaging is added, the appendiceal wall may appear hyperemic due to increased local blood flow from inflammation; however, this does not occur in gangrenous or distal tip appendicitis.[4]

Ultrasound has been found to be most useful in patients without excessive abdominal fat, and thus is typically better in children and females. In addition to diagnosing appendicitis, ultrasound has been found by several series to be a useful tool for establishing alternative diagnoses.[4,5,21,22] Weaknesses of ultrasound include its operator-dependant nature, the inability of ultrasound to visualize the appendix in obese individuals, and its insensitivity in cases where the appendix is perforated or only the distal tip is involved.[5,21,22] Table 2 presents a list of causes of false-positive and false-negative results associated with the use of ultrasound.[4,5]

Sensitivity, specificity and diagnostic accuracy have been reported over a very wide range.[8,9,11–13,21,23–44] The reported sensitivity of ultrasound in the diagnosis of appendicitis varies from 34% to 99%, but pediatric studies suggest a narrower window of 78%–94%. The specificity of ultrasound ranges from 33%–100%, with pediatric studies

Table 2. Causes of false-positive and false-negative results associated with ultrasound for the diagnosis of appendicitis

False positives	False negatives
Resolving appendicitis	Retrocecal appendix
Peri-appendicitis	Perforated appendix
Inspissated stool	Gangrenous appendix
Psoas muscle fibers mistaken for appendix	Involvement of only the distal tip of the appendix
Normal appendix of larger diameter	Inability to visualize the appendix*
	Gas-filled appendix

*Studies suggest that only 10%–50% of normal appendices can be visualized in children.[4,5]

Table 3. Diagnostic accuracy of ultrasound in pediatric patients with suspected appendicitis

Study, primary author, year	No. of patients	Negative appendectomy rate,* %	Perforation rate, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Rubin,[9] 1990	134	0.7	–	89	94	89	94
Vignault,[23] 1990	70	11	33	94	89	89	94
Hayden,[24] 1992	133	7	43	–	–	–	–
Sivit,[25] 1992	180	11.5	40	88	96	90	95
Hahn,[26] 1998	3859	–	–	90	97	82	98
Schulte,[27] 1998	1285	–	–	92	98	90	98
Sivit,[28] 2000	315	–	–	78	93	79	92

PPV = positive predictive value; NPV = negative predictive value
Note: All studies cited above were prospective evaluations.
*Rate of appendectomy performed following a false–positive diagnosis of acute appendicitis.

suggesting a smaller range of 89%–98%. Likewise, the range of overall accuracy has been reported to be 59%–98%, but narrows to 89%–98% when only pediatric studies are examined (Table 3).[9,23–28] A 2004 study reported a sensitivity of 100%, a specificity of 93% and an overall accuracy of 98% using contrast-enhanced Doppler ultrasound.[45] Another study evaluated operator-dependant techniques in 877 patients (age range 2–85 yr) with abdominal ultrasound to which they applied 4 additional manoeuvres to the standard examination. These included the use of upward graded compression, posterior manual compression, use of the left oblique lateral decubitus position, and the use of a low frequency convex transducer. This study reported above average sensitivity, specificity and accuracy rates of 99%, and the ability to visualize the appendix in 99% of cases.[46]

Table 4. Computed tomography findings in acute appendicitis

- Appendiceal diameter >6 mm
- Appendiceal wall thickening (target sign)
- Appendicolith
- Circumferential or focal apical cecal thickening
- Pericecal fat stranding
- Adjacent bowel wall thickening
- Appendiceal wall enhancement
- Free peritoneal fluid
- Lymphadenopathy
- Extramural air
- Intramural air
- Phlegmon

Table 5. Causes of false-positive and false-negative results associated with computed tomography for the diagnosis of appendicitis

False positives	False negatives
Normal appendix of larger caliber	Inflamed appendix mistaken for unopacified bowel loop
Lymphoid hyperplasia	Appendix not visualized

Computed tomography

When appendicitis is present, many changes can be visualized with CT (Table 4). The changes most useful in assisting in the diagnosis of appendicitis are an appendiceal diameter >6 mm, thickening or enhancement of the appendix, and peri-appendiceal fat stranding.[47] The strengths of CT include the facts that there is no operator dependence and the resulting greater reproducibility of the exam. CT is also very useful for evaluating the complications of appendicitis and identifying alternative diagnoses, and is reported to be able to identify a normal appendix in 67%–100% of patients evaluated.[4] The weaknesses of CT include an overlapping range of normal and abnormal appendiceal wall diameters, and the fact that the compressibility of the appendix cannot be measured.[4,5] The accuracy of CT may be further diminished if scans are interpreted by non-radiologists or radiology residents.[5] Finally, the large dose of ionizing radiation from CT and the risk of subsequent malignancy are of particular concern in pediatric patients. Table 5 lists false-positive and false-negative errors associated with CT.

The most impressive aspect of CT in suspected appendicitis is its high degree of accuracy. Reported sensitivity with CT ranges from 66% to 100%, with the majority of studies reporting 95%–99%.[17,28,37,39,40,42,43,48–57] The specificity ranges from 83% to 100%, and most studies suggest a sensitivity of >95%. The few solely pediatric studies report sensitivities from 88% to 97% and specificity ranges from 94% to 97%. Overall accuracy ranges from 79% to 99% in mixed population studies.[17,37,48] Table 6 outlines the results of pediatric studies evaluating CT. CT is a better imaging modality because of its superior diagnostic accuracy. Unfortunately, the use of CT confers a significant dose of ionizing radiation.

Table 6. Diagnostic accuracy of computed tomography in pediatric patients with suspected appendicitis

Study, primary author, year	Type of study	No. of patients	Negative appendectomy rate,* %	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy rate, %
Pena,[10] 1999	Retrospective	75	–	97	97	–	–	97
Pena,[17] 2000	Prospective	108	10	97	94	85	99	93
Hoecker,[48] 2005	Retrospective	112	–	88	94	91	91	91

PPV = positive predictive value; NPV = negative predictive value
*Rate of appendectomy performed following a false-positive diagnosis of acute appendicitis.

Ionizing radiation and associated risk of malignancy

Humans are constantly exposed to low doses of ionizing natural background radiation. Levels of background radiation vary depending on the geographic location of the exposure; the average person in North America is exposed to roughly 4 millisieverts (mSv) per year (1 mSv is equal to 1×10^{-6} Joules per gram of exposed tissue) (Department of Radiology, Children's Hospital of Winnipeg, Winnipeg, Man.: unpublished observations). When used for radiographic purposes, x-ray radiation is directed toward a target in a focused linear fashion. The diagnostic utility of radiography is based on the varied absorption of radiation by different biologic tissues (i.e., with bone being the most and air the least absorptive structures). Radiation that is not absorbed by the body's tissues passes onto a radiosensitive film or array, producing a 2-dimensional representation of the relative tissue densities. When a CT is used, multiple beams of radiation from different directions are sent toward the target tissues, resulting in a much higher effective dose delivery. Effective doses of radiation delivered for various common procedures are presented in Table 7.

Radiation-induced malignancy (RIM) has been recognized since the early 1900s, and is believed to be caused by alterations in cellular DNA (DNA) and ribonucleic acid (RNA).[58,59] The disruption of nucleotide bonds alters protein synthesis and can result in a cancerous transformation if cellular reproduction is modified.

After the 1945 atomic bombings of the Japanese cities of Hiroshima and Nagasaki, the National Academy of Sciences began collecting data on the approximately 100 000 blast survivors, who had been exposed to various doses of radiation.[60] This long-term cohort study revealed 3 extremely important facts regarding the association between radiation exposure and malignancy. First, RIM from low-dose (diagnostic radiography range) exposures tend to appear at the same age as spontaneous cancers of the same type, but with a higher frequency.[60] The most common of these malignancies involved the bone marrow, stomach, colon, thyroid, lung and breast.[60] Second, a single acute dose of radiation is more important than an equivalent dose given in fractions over time.[60] Finally, younger patients have a higher risk of RIM than older patients who receive an equivalent dose of radiation, and females tend to be more radiosensitive than males.[60]

The increased radio sensitivity in children is likely multifactorial. It is probable that children, who have a higher number of dividing cells, are at greater risk since DNA and RNA alteration is the cornerstone of malignant

Table 7. Estimates of radiation dosage delivered from common radiological procedures

Procedure	Effective dose (mSv)	Equivalent natural background radiation, months
Plain film		
Chest	0.05	0.14
Extremity	0.1	0.3
Abdomen	1.0	2.9
Upper GI series	3.0	8.6
Lower GI series	5.0	14.3
Pelvis	1.6	4.6
Computed tomography		
Head	2.0	5.7
Chest	7.0	20.0
Abdomen	9.0	25.7

GI = gastrointestinal

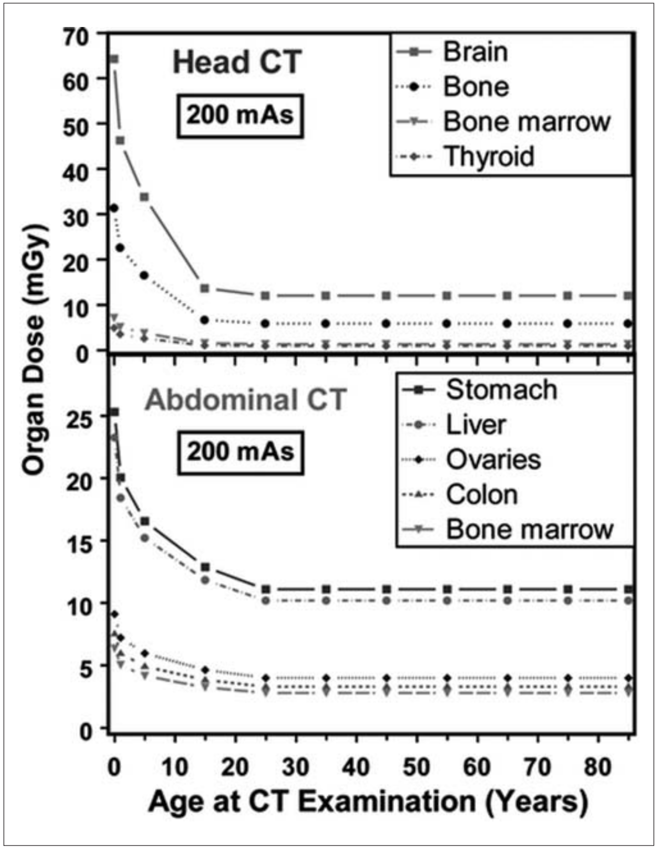

Fig. 1. Age-related organ dosimetry of ionizing radiation during computed tomography. Reproduced with permission from Brenner DJ. Estimating cancer risks from pediatric CT: going from qualitative to the quantitative. Pediatr Radiol 2002;32(4):228–31.[61]

transformation.[61] Moreover, because RIM seems to be a time-dependant phenomena, young age at time of exposure would result in a greater lifespan during which malignant transformation will occur.[61] Finally, the relatively large size of the organs and the lack of shield tissue results in a higher effective organ dose in children, as shown in Fig. 1.[61]

In 2001, Brenner and colleagues compared atomic bomb survivor data to current radiation exposures experienced by patients undergoing CT and calculated the increased risk of fatal RIM based on the patient's age at the time of CT (Fig. 2).[61] A one-year-old child undergoing abdominal CT would have an increased lifetime risk of fatal RIM of 0.18%, but only 0.11% if they were 15 years of age at the time of exposure, suggesting that for every 555 abdominal CT scans performed on 1-year-old children, 1 child would develop a fatal RIM in his or her lifetime. Nearly twice as many 15-year-olds would need to be scanned to result in a fatal RIM. On an individual basis, the immediate benefits of CT could be argued to outweigh the possibility of adverse outcome later in life. However, it is when one considers the increased number of CT scans being performed on younger patients with non-specific abdominal pain or clinically obvious appendicitis, that the cumulative increased lifetime risk of fatal RIM becomes important. For example, if we assumed that each of the annual 70 000 pediatric cases of appendicitis were imaged with CT, and that an equal number of patients without appendicitis were imaged to exclude the diagnosis, then we could expect that there would be between 150 and 250 of those patients whose eventual death would be as a result of this imaging.

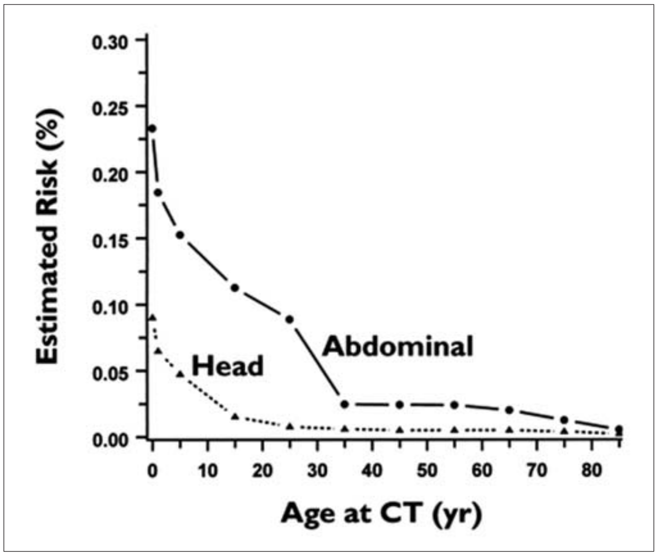

Fig. 2. Estimated risk of fatal radiation-induced malignancy by age at time of computed tomography. Reproduced with permission from Brenner DJ. Estimating cancer risks from pediatric CT: going from qualitative to the quantitative. Pediatr Radiol 2002; 32(4):228–31.[61]

To reduce the risk of RIM, 2 options are available. The first encourages manufacturers of CT scanners to develop technologies that allow for comparable image quality with less ionizing radiation. The second implores clinicians to use alternative diagnostic approaches. In 1999, Garcia Pena and colleagues evaluated 139 children with suspected appendicitis, all of whom were initially investigated with ultrasound. Using their protocol, only the 108 patients with negative or equivocal ultrasounds were imaged further with CT. This protocol resulted in a sensitivity, specificity and overall accuracy of 94%, and a negative appendectomy rate of 10.7%.[37] They subsequently compared their rates of negative appendectomy before and after the implementation of this imaging protocol and found that they had decreased from 14.7% to 4%.[62] Another centre reported an overall accuracy of 93.3% and a negative appendectomy rate of 6% using a similar protocol.[44]

Conclusion

The evaluation of suspected appendicitis in the pediatric population has become facilitated with new imaging modalities but remains challenging because of the limitations of current tests. The appropriate application of CT and ultrasound is as important as a good history and physical examination in the assessment of patients with abdominal pain. CT scanning is superior to ultrasound in terms of diagnostic accuracy for appendicitis. However, the dose of ionizing radiation and resulting increased risk of fatal malignancy warrant careful consideration. In light of this, the most reasonable approach described to date is to use ultrasonography as the primary means of imaging children with suspected appendicitis, and to reserve CT for those patients with negative or equivocal results.

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