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REVIEW

Optimizing the role of imaging in appendicitis

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Abstract Acute appendicitis is the most common acute abdominal condition that requires surgical intervention in childhood. From the diagnostic performance perspective, computed tomography (CT) has a significantly higher sensitivity than does ultrasound (US) for diagnosing appendicitis in children; from the safety perspective, however, one should consider the radiation associated with CT, especially in children. There is strong evidence supporting improved patient outcomes in children with suspected acute appendicitis who undergo CT scanning. Nevertheless, we should keep in mind that for a single abdominal CT study in a 5-year-old child, the lifetime risk of radiation-induced cancer would be 26.1 per 100,000 in female and 20.4 per 100,000 in male patients, based on probabilistic models designed with data from atomic bomb survivors. An integrated clinical-imaging approach, applying clinical scores that are able to predict which children with acute abdominal pain do or do not have a high probability of presenting with appendicitis may improve the effectiveness of the imaging diagnosis of appendicitis at the hospital level. Such an approach could avoid exposure of children who at low risk for appendicitis to unnecessary diagnostic tests and eventually, to radiation.

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Evidence-based medicine (EBM) is defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [1]. A requirement for the successful implementation of EBM principles is knowledge related to the hierarchy of evidence and other concepts. The highest level of evidence is produced from prospective, hypothesis-testing research protocols. In medical imaging, the evaluation of diagnostic procedures has focused predominantly on technical performance and simple tests of diagnostic efficacy, with few studies addressing the diagnostic thinking process (diagnostic probabilities and needs for other tests) [2]. Fewer than 10% of imaging studies are supported with respect to specific clinical applications by randomized controlled trials, meta-analyses, or systematic reviews [3].

A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and collect and analyze data from studies included in the review [4]. Statistical methods may or may not be used to analyze and summarize results of the included studies. If statistical techniques are applied in a systematic review, this review is named a meta-analysis [5]. A meta-analysis generates summary estimates of test accuracy measures and summary receiver operating characteristic curves where appropriate [6], with weighting based on the quality of primary studies which can be measured with scales or checklists, or on statistical methods.

Acute appendicitis is the most common acute abdominal condition that requires surgical intervention in childhood

[7, 8]. Despite the relatively high incidence of this entity, its clinical diagnosis is very commonly delayed or missed in children. Because diagnostic delays arise chiefly from the interpretation of the history and physical examination results, diagnostic imaging has become an essential tool in the evaluation of children suspected of having appendicitis. Diagnostic imaging of pediatric appendicitis chiefly involves ultrasonography (US) (Fig. 1) and computed tomography (CT) (Fig. 2). Advantages of US include low cost, the lack of ionizing radiation or need for patient preparation, and the ability to provide dynamic information through graded compression [9]. Advantages of CT include less operator dependency than US; enhanced delineation of the extent of the disease in the case of perforated appendicitis [10, 11]; easier visualization of a retrocecal appendix; unchanged quality of imaging, regardless of the presence of bowel gas, obesity, or severe abdominal pain [12]; and the possibility of multiplanar retrospective data reconstruction [13].

Systematic reviews, meta-analyses and decision-analytic models

Given the variation that exists in practice and research, the uncertainty regarding the quality of the underlying evidence, systematic and quantitative overviews of the diagnostic values of the imaging tests are clearly needed to purport updated diagnostic test results for the assessment of acute appendicitis in the pediatric population. Although several meta-analyses have been conducted on the imaging tests for assessment of appendicitis in adults or in a mixed age-group population [14–19], few have been focused on the pediatric population [20].

Based on a recent meta-analysis conducted through the assessment of studies of appendicitis in children [20], CT demonstrated a significantly higher pooled sensitivity [94% (95% confidence interval [CI], 92%, 97%)] and specificity [95% (95% CI, 94%, 97%)] than did US [sensitivity, 88% (95% CI, 86%, 90%) and specificity, 94% (95% CI, 92%,

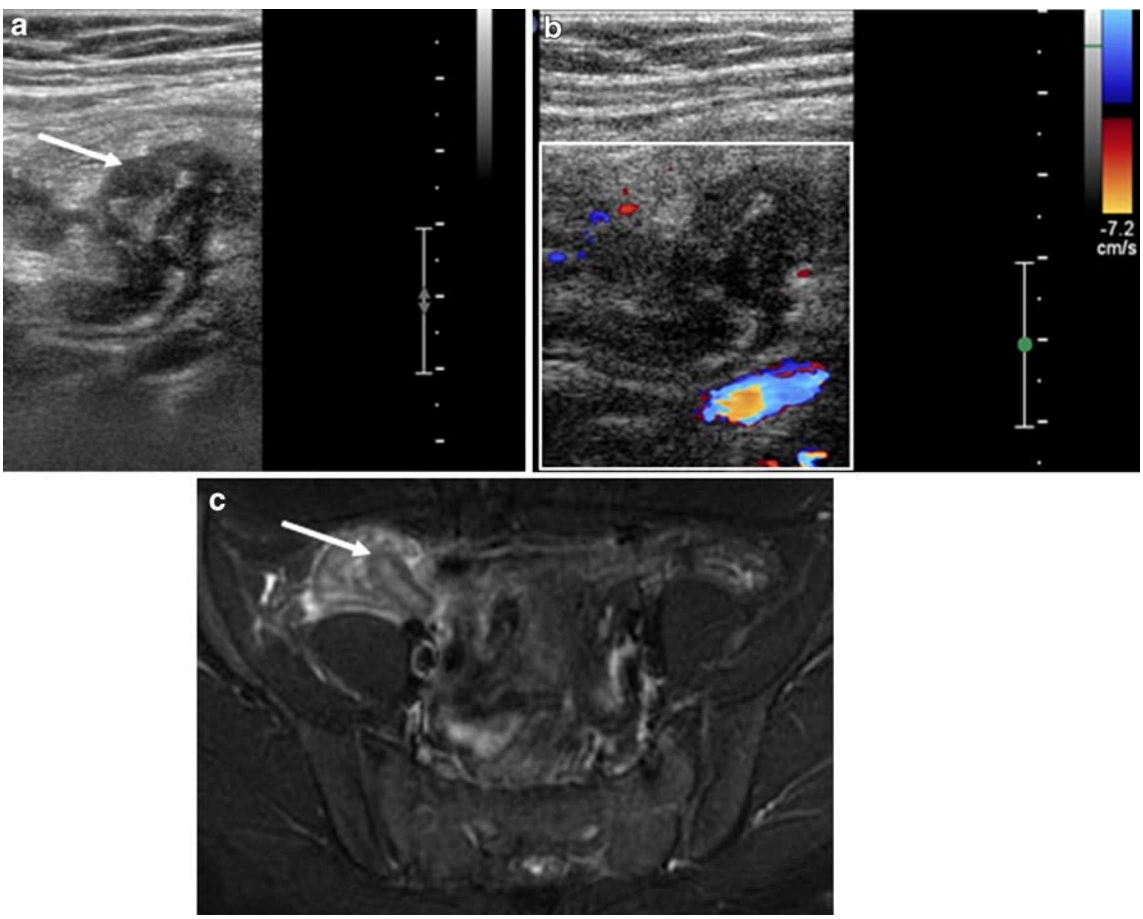

Fig. 1 Gray-scale (**a**) and color Doppler (**b**) sonograms of a child with acute abdominal pain show a distended appendix, folded on itself, measuring 8 mm at its apex (*arrow*) (**a**). The tissue surrounding the appendix has increased echogenicity. No definite abscess or free fluid is noted in the right lower quadrant. Mild hyperemia was appreciated within the appendiceal wall at the time of the examination which was not properly captured on the provided image (**b**). A corresponding axial inversion-recovery MR image of the lower abdomen (**c**) obtained within a short period of time from the sonograms confirms the ultrasound findings with regard to appendiceal distension (*arrow*) and inflammation of adjacent soft tissues. The histologic findings of the appendix confirmed the diagnosis of acute appendicitis

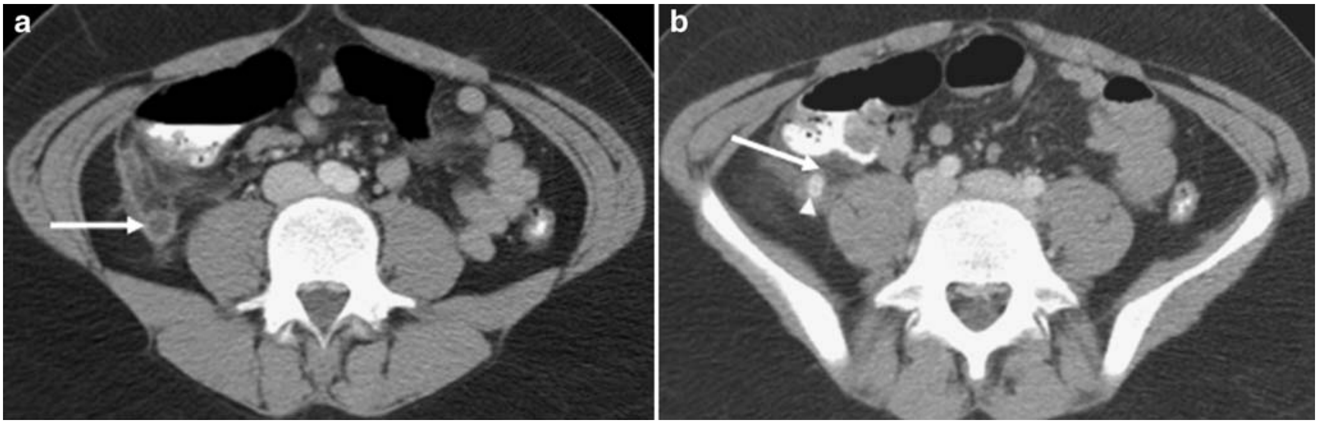

Fig. 2 Oral and intravenous contrast-enhanced axial CT image of the abdomen of a child with surgical-histologic diagnosis of acute appendicitis. The appendix was visualized as a tubular structure with an enhancing wall and a diameter of 15 mm (*arrow*) (**a**). Stranding was apparent in the periappendiceal fat. A small dense structure was seen within the base of the appendix, likely representing a calcified appendicolith (*arrowhead*) (**b**). The cecal bar sign is noted here (*arrow*) helping distinguish between cecal contrast material and a similarly dense, calcified appendicolith [39]

95%)]. From the safety perspective, however, one should consider the radiation associated with CT. Data from atomic bomb survivors have indicated that there is a small but significant risk of developing a radiation-induced malignancy from a single abdominal CT examination [21]. Children are particularly sensitive to the adverse effects of radiation exposure and have longer lifespans during which a radiation-induced cancer can manifest [22]. According to a recent paper that designed a Markov decision model to compare the cost-effectiveness of different imaging strategies in the diagnosis of pediatric appendicitis [23], for a single abdominal CT study in a 5-year-old child, the lifetime risk of radiation-induced cancer would be 26.1 per 100,000 in female and 20.4 per 100,000 in male patients. In this study [23], US followed by CT was the most costly and most effective strategy, CT was the second-most costly and second-most effective strategy, and US was the least costly and least effective strategy. In this study, a Markov decision model was used to predict the overall impact of radiation-induced cancer on a cohort of individuals exposed to radiation at a young age on the basis of their radiation exposure [24] and the estimated risk of cancer from the BEIR VII report [25] (moderate evidence, level of evidence, 2b) [26]. The evidence behind a decision model relies on the quality of the primary studies which depends on the available information in the literature or unpublished scientific material. The results of this decision model confirm the results of a prior prospective cohort study [27] (strong evidence, level of evidence 1c) [26] that showed that limited CT with rectal contrast was highly accurate in the diagnosis of appendicitis in children.

Approximately one-third of children with acute appendicitis have atypical findings [28] which difficults the diagnosis. Morbidity and mortality in acute appendicitis is related almost entirely to appendiceal perforation. Therefore, the surgical aim is to operate in a timely fashion before appendiceal perforation has developed. The reported appendiceal perforation rates are higher in children than in adults [29]. In the meta-analysis conducted by Doria et al. [20], the weighted perforation rate in positive cases of appendicitis was 26.5% in studies of children (n=10) and 18.5% in studies in adults (n=3). The mean sample prevalence of appendicitis calculated on the basis of the data provided by the articles of this meta-analysis was 0.31 for both US and CT in pediatric studies, and 0.44 for US and 0.37 for CT in studies of adults. The relative risk of a false-negative US in a perforated rather than a nonperforated appendicitis was 0.34 in pediatric studies.

Further evidence of the difficulty of diagnosing appendicitis is the false-negative appendectomy rates of 5% to 25% reported in children [29]. There is strong evidence (level of evidence 1c) [26] supporting improved patient outcomes in children with suspected acute appendicitis who undergo CT scanning [27, 30, 31]. Studies by Garcia-Pena et al., Applegate et al., and Rao et al. [27, 30, 31] have shown a significant decrease in the negative appendectomy rate in children with suspected acute appendicitis who underwent CT before surgery when compared to those who did not.

Although the false-positive rate of clinical and laboratory diagnostic test results, however, has not changed over the last 20 years [6], CT is able to diagnose an alternative condition, such as inflammatory bowel disease, infectious enteritis or colitis, intussusception, pancreatitis, hydronephrosis, pyelonephritis, Meckel's diverticulum, and abdominal neoplasms [10] in up to 50% of pediatric and adult patients with clinically suspected appendicitis who undergo CT (strong evidence, (level of evidence 1c) [26, 30].

Alternative imaging modalities

Besides US and CT as diagnostic tests for evaluating suspected appendicitis in children, few reports are available on the diagnostic value of alternative imaging modalities such as magnetic resonance imaging (MRI) (Fig. 1) and nuclear medicine techniques (poor and strong evidence, levels of evidence 4 and 1a, respectively) [26, 32, 33]. This may in part be explained by the need for sedation in the younger children and low availability of MRI scanners on an emergency clinical setting. In spite of the high (97%) negative predictive value and acceptable sensitivity (91%) and specificity (86%) of 99Tc HMPAO-labeled leukocyte nuclear medicine scans (level of evidence 1a) [26] to diagnose appendicitis in children, the positive predictive value of this technique was relatively low (67%) in this population [33]. The negative laparotomy rate with this technique was 11%. Nevertheless, this technique has drawbacks with regard to radiation exposure and the requirement of blood handling (2-h preparation time prior to imaging) which delays the diagnosis [34].

Economic evaluations and clinical-imaging algorithms

The aim of data synthesis of economic evaluations is to summarize the evidence about the efficiency of health care provision to reduce the uncertainty about relative benefits and costs associated with alternative interventions. Cost-effectiveness analysis assesses technical efficiency and compares alternative approaches to care [5]. A recent cost-effectiveness analysis conducted by Doria et al. [35] (moderate evidence, level of evidence 2b) [26] compared the costs and effectiveness of assessing children with suspected appendicitis who required a laparotomy and had US or CT during an after-hours period (alternative approach) with those assessed during a standard-hours (standard care practice approach) period. The authors concluded that the standard-hours shift was less costly and more effective regardless of whether the calculation included US or CT costs only for DI costing. These results demonstrated that the after-hours shift was more costly considering that more severe cases attend this work shift. However, this was not related to the reasons the authors had initially considered, such as the increased costs associated with premium fees for staff, longer delays between a patient's registration and surgery, and lower diagnostic performance of imaging modalities because of less experienced imagers scanning and/or interpreting imaging in the after-hours shift. A proposed way to decrease the costs and to increase the effectiveness in the after-hours shift was to improve the effectiveness of the after-hours work shifts, providing medical care to children at an earlier stage of their disease. Several clinical pathways have been proposed in the literature to decrease the costs and improve the effectiveness of diagnosis of appendicitis [36–38]. The purpose of these clinical scores is to predict which children with acute abdominal pain do or do not have a high probability of having appendicitis and therefore, optimize the imaging diagnosis of appendicitis. There is strong evidence (level of evidence 1b) [26] that these clinical decision rules can predict accurately the risk of appendicitis in children at different stages of the disease. The application of these clinical-imaging approaches may improve the effectiveness of imaging diagnosis of appendicitis at the hospital level and avoid exposure of children who at low risk for appendicitis to unnecessary diagnostic tests and eventually, to radiation.

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