

## **A Clinical Prediction Rule to Identify Children at Low Risk For Appendicitis**

*Kharbanda AB, Dudley NC, Bajaj L, et al. Validation and refinement of a prediction rule to identify children at low risk for acute appendicitis. Arch Pediatr Adolesc Med 2012;166:738-44.*

### **Study Overview**

**Objective.** To validate and improve the sensitivity of a clinical prediction rule to identify children with abdominal pain in a multicenter cohort who are at low risk for appendicitis.

**Design.** Prospective, cross-sectional observational study at 10 geographically diverse pediatric emergency departments (PEDs) from 1 March 2009 to 30 April 2010.

**Setting and participants.** Children aged 3 to 18 years presenting to the PED with abdominal pain < 96 hours and being evaluated for suspected appendicitis. Criteria for suspected appendicitis were considered present when the treating physician obtained blood tests, radiographic studies (CT and/or ultrasonography [US]), or a surgical consultation for the purpose of diagnosing appendicitis. Patients were excluded if they were pregnant, had prior abdominal surgery (eg, abdominal hernia repair), had a history of chronic abdominal illness or pain (eg, inflammatory bowel disease, chronic pancreatitis), sickle cell anemia, cystic fibrosis, or a medical condition affecting the clinician's ability to obtain an accurate history, or if they had any radiographic imaging of the abdomen within 7 days of the PED evaluation.

**Data collection.** A PED attending or fellow completed a standardized history and physical on a structured case report form. All clinicians working in the study PEDs received 1-on-1 standardized training sessions from site investigators on the proper completion of case report forms. Clinicians completed the study forms before knowledge of the CT or US results.

**Methods of measurement.** The primary outcome was the evaluation of a previously published clinical prediction rule to identify patients at low risk for appendicitis [1]. This rule consisted of the following 3 low-risk factors: absolute neutrophil count (ANC) <  $6.75 \times 10^3/\mu\text{l}$  (yes/no), absence of nausea (yes/no/don't know), and absence of maximal tenderness in the right lower quadrant (RLQ) (yes/no/unsure). Outcomes for comparison were the presence of appendicitis for those undergoing surgery, or, for those discharged from the PED, a telephone follow-up within 2 weeks for resolution of signs and symptoms, visits of care to other sites, or need for subsequent surgical intervention. For those not available for follow-up, their medical records were reviewed for 90

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days after the index PED to determine if there were any subsequent radiological studies or surgeries.

Investigators also attempted to refine their original low-risk prediction rule by adding other signs and symptoms including emesis, abdominal pain with walking/jumping or coughing, and white blood cell counts.

**Main results.** Over the study period, a total of 2625 subjects were enrolled from 9 sites (data from 1 site were removed because recruitment rates were less than 40%). A total of 1018 (38.8%) of these were diagnosed as having appendicitis. Of those who had surgery, 95 (8.5%) had no evidence of appendicitis by pathology. The original sensitivity of the prediction rule was 95.5 (95% CI 93.9–96.7) with a specificity of 36.3 (33.9–38.9), negative predictive value of 92.7 (90.1–94.6), and positive predictive value of 48.8 (46.5–51.1). There were no differences in sensitivity analyses for coded responses of “don’t know” or “unsure.”

Investigators were able to refine the sensitivity of their low-risk prediction rule with the following criteria: ANC <  $6.75 \times 10^3/\mu\text{L}$  and no maximal tenderness in the RLQ or ANC <  $6.75 \times 10^3/\mu\text{L}$  with maximal tenderness in the RLQ but no abdominal pain with walking/jumping or coughing. The refined prediction rule sensitivity became 98.1 (95% CI 97.0–98.9), specificity 23.7 (21.7–25.9) with a negative predictive value of 95.3 (92.3–97.0) and positive predictive value of 44.9 (42.8–47.0).

**Conclusion.** Validation of a refined clinical prediction rule with 98% sensitivity in identifying children at low-risk of having appendicitis may be incorporated into clinical practice and potentially reduce the use of radiographic imaging.

### Commentary

Clinical prediction rules (CPRs) are tools devised to assist clinicians in their evaluation of patients and provide a probability of the patient having (or not having) an outcome. The tools are based on clinical variables that can be obtained from the history, physical exam, and/or complementary tests. By reducing uncertainty and standardizing the interpretation of clinical data, they can be most useful in complex decision making or high-risk situations for health cost reduction [2,3]. For some conditions, such as appendicitis, the use of such rules may also reduce unnecessary use of and exposure to radiation

with CT scans. This study by Kharbanda et al both validated in a multicenter setting and further improved the sensitivity of a previously published CPR to identify children who were at low risk for appendicitis. The original prediction rule when validated in a multicenter setting had 95.5% sensitivity and consisted of (1) low ANC count (<  $6.75 \times 10^3/\mu\text{L}$ ), (2) the absence of nausea, and (3) the absence of maximal tenderness in the RLQ [1]. A refined rule with 98% sensitivity consisted of the low ANC count and no maximal tenderness in the RLQ or the low ANC count with maximal tenderness in the RLQ but no abdominal pain with walking/jumping or coughing.

Despite the original validated prediction rule for identifying children at low risk of appendicitis having been published more than 7 years ago, use of this rule and most pediatric CPRs have been slow to gain acceptance. This may be due to the fact that there are fewer CPRs for children than adults [4]. Few of these rules have undergone formal impact analysis to determine whether or not they are used in clinical practice and improve outcomes [5]. Per criteria published by the Evidence-Based Medicine Working Group (EBMWG), clinical decision rules can be ranked based on whether or not the rules have been validated (level 4—lowest level of evidence), prospectively validated in a single sample (level 3), broadly validated in multiple settings (level 2), or had impact analyses performed and demonstrated impact on clinician behavior with beneficial consequences (level 1) [3]. Using these standards, the most recently multicenter validation study Kharbanda et al would now be considered a level 2 decision rule.

A distinction should be noted between clinical prediction rules and clinical decision rules. CPRs are meant to provide diagnostic probabilities but do not actually recommend decisions or tell clinicians what to do [5]. Whether or not the additional information provided by clinical prediction rules impact final decisions made by clinicians is not known and is recommended as a final step in establishing a rule as a decision making one [6,7]. Interestingly, the Kharbanda study was published concurrently with a clinical practice guideline that incorporated early surgical consultation for high-risk patients and staged imaging first with US and then with CT scan if the US was indeterminate [8]. Unlike the Kharbanda study, which attempted to identify low-risk appendicitis patients and thus sought high sensitivity, this study by Santillanes et al sought to determine which patients were at high risk of appendicitis and thus

required high specificity. For patients who followed their clinical guideline stratification for low risk (ALL of the following:  $WBC \leq 10,000/mm^3$ ,  $PMN \leq 67\%$ , bands  $< 5\%$ , absence of guarding or focal tenderness in RLQ or periumbilical area), medium risk (patients not meeting ALL high or low risk criteria), and high risk (ALL of the following:  $WBC > 10,000/mm^3$ ,  $PMN > 67\%$ , presence of guarding and/or focal tenderness in RLQ or periumbilical area, abdominal pain  $> 13$  hours), their study achieved specificity rates of 99% with US imaging and 98% using CT scan. While the study was conducted at a single institution and has not yet been validated in a multicenter setting, it does provide complementary and overlapping support to clinicians implementing Kharbanda's clinical prediction rule in practice. Use of a combination of both the clinical prediction rule for identifying those at low risk and further stratification with a clinical guideline for those at medium and high risk of appendicitis allows for a reasonable approach on whether or not to use radiological imaging on children.

Limitations of the Kharbanda study include patients lost to follow-up (12%) and whether or not they may or may not have had appendicitis. While authors attempted to review all medical records at the centers of study, it is not known if these patients may have presented to other local or regional hospitals and what their outcomes were. Additionally, while this was a multicenter validation study, the generalizability of the rules may remain limited as enrollment occurred exclusively in PEDs.

### Applications for Clinical Practice

The results of this study by Kharbanda et al (and a concurrent one by Santillanes et al) provide guidance for clinicians in how they can utilize patient histories, physical exam findings, and test result data to assist in their evaluation of children with abdominal pain and suspected appendicitis. Low-risk patients may be predicted by ANC count ( $< 6.75 \times 10^3/\mu l$ ) and no maximal tender-

ness in the RLQ, or ANC count ( $< 6.75 \times 10^3/\mu l$ ) with maximal tenderness in the RLQ but no abdominal pain with walking/jumping or coughing. These patients may be observed or discharged with observation. High-risk patients may be identified as those with ALL of the following:  $WBC > 10,000/mm^3$ ,  $PMN > 67\%$ , presence of guarding and/or focal tenderness in RLQ or periumbilical area, and abdominal pain  $> 13$  hours. These patients should have early surgical consultation involvement with decision making. Medium-risk patients (those meeting neither low- nor high-risk criteria) may follow a stepped approach of US imaging and then CT scan if the US is considered indeterminate.

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