

## ONLINE FIRST

# Early vs Interval Appendectomy for Children With Perforated Appendicitis

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**Objective:** To compare the effectiveness and adverse event rates of early vs interval appendectomy in children with perforated appendicitis.

**Design:** Nonblinded randomized trial.

**Setting:** A tertiary-referral urban children's hospital.

**Patients:** A total of 131 patients younger than 18 years with a preoperative diagnosis of perforated appendicitis.

**Interventions:** Early appendectomy (within 24 hours of admission) vs interval appendectomy (6-8 weeks after diagnosis).

**Main Outcome Measures:** Time away from normal activities (days). Secondary outcomes included the overall adverse event rates and the rate of predefined specific adverse events (eg, intra-abdominal abscess, surgical site infection, unplanned readmission).

**Results:** Early appendectomy, compared with interval appendectomy, significantly reduced the time away from normal activities (mean, 13.8 vs 19.4 days;  $P < .001$ ). The overall adverse event rate was 30% for early appendectomy vs 55% for interval appendectomy (relative risk with interval appendectomy, 1.86; 95% confidence interval, 1.21-2.87;  $P = .003$ ). Of the patients randomized to interval appendectomy, 23 (34%) had an appendectomy earlier than planned owing to failure to improve ( $n = 17$ ), recurrent appendicitis ( $n = 5$ ), or other reasons ( $n = 1$ ).

**Conclusions:** Early appendectomy significantly reduced the time away from normal activities. The overall adverse event rate after early appendectomy was significantly lower compared with interval appendectomy.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00435032

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**A**PPENDICITIS IS THE MOST common gastrointestinal condition that requires urgent surgical treatment in children in the United States.<sup>1</sup> Approximately 30% of these patients present with perforated appendicitis.<sup>2</sup> The universally accepted treatment of acute, nonperforated appendicitis is urgent appendectomy.<sup>3</sup> The optimal treatment of perforated appendicitis, however, is controversial.<sup>4,5</sup> There are 2 commonly used surgical treatment options for children with perforated appendicitis: early appendectomy and interval appendectomy. There has not been an adequately powered randomized trial to compare these 2 treatment strategies.<sup>6</sup>

In both treatment strategies, the patients are resuscitated with intravenous fluids and given broad-spectrum intravenous antibiotics. With early appendectomy, the patient undergoes an urgent appendectomy within

the first 24 hours of hospitalization and any intra-abdominal abscess is drained during the operation. Alternatively, with interval appendectomy, the appendectomy is planned for 6 to 8 weeks after the initial diagnosis, after the patient has been discharged and is back to normal activities. The potential advantage of the interval appendectomy approach is to perform the operation at a time when peritoneal contamination has resolved, potentially resulting in fewer intraoperative and/or postoperative complications. Multiple retrospective studies have reported potential improved outcomes (eg, shorter hospital length of stay) with interval appendectomy.<sup>6-9</sup>

We conducted a randomized trial comparing the effect of early appendectomy with that of interval appendectomy on time away from normal activities in children younger than 18 years with a clinical diagnosis of perforated appendicitis. Children with delayed presentation of perfo-

rated appendicitis who were stable and had a well-formed abscess identified on imaging or a discrete abdominal mass on physical examination could be excluded at the discretion of the attending pediatric surgeon. Although far from conclusive, prior studies support treating this patient subgroup with abscess drainage and interval appendectomy.<sup>10-12</sup> Secondary outcomes included common adverse events known to occur with perforated appendicitis.

## METHODS

### RECRUITMENT, ENROLLMENT, AND RANDOMIZATION

All patients younger than 18 years with a clinical diagnosis of perforated appendicitis were eligible for enrollment. Exclusion criteria were initial treatment at another institution, delayed presentation with a well-formed abscess or mass on examination, family being transient to the area, or inability to complete follow-up. The trial was conducted at a single tertiary-referral urban children's hospital.

The preoperative diagnosis of perforated appendicitis, for trial participants, was established by the pediatric surgeon just as it is outside of the trial. Medical history, physical examination, laboratory values, and imaging results (116 of the 131 trial patients had an abdominal computed tomographic scan at presentation) were all used. We recently reported<sup>13</sup> that the overall accuracy of the pediatric surgeon's preoperative diagnosis was 92% in children with suspected appendicitis.

After the preoperative diagnosis of perforated appendicitis was established, patients were stratified according to the attending pediatric surgeon (5 surgeons participating) and then randomized to a treatment group using preprinted opaque envelopes. Randomization was done according to a variable blocked design, and the randomization sequence was computer generated and provided by a statistician involved with the trial design. After randomization and treatment group assignment, surgeons were not blinded to treatment assignment, as this was not thought to be feasible.

The institutional review boards of the University of Tennessee Health Science Center and Methodist Le Bonheur Hospital system approved the study. Written informed consent was obtained from the parent or guardian of each participant, and assent was sought for all participants older than 8 years.

### INTERVENTIONS

Patients in both treatment groups received the same initial medical treatment including intravenous fluid hydration, intravenous antibiotics, and narcotic pain management. Cefazidime in 50 mg/kg doses and 10 mg/kg of clindamycin were given every 8 hours. Those in the early appendectomy group underwent appendectomy as soon as the patient was stabilized, as determined by adequate urine output and normalized vital signs. Patients randomized to interval appendectomy had the appendectomy planned for 6 to 8 weeks after diagnosis. These patients ideally returned to normal activities soon after initial discharge and then returned for their appendectomy 6 to 8 weeks later. Both laparoscopic and open appendectomy were allowed.

Criteria for hospital discharge were the same for all patients and included ability to tolerate oral feedings, adequate pain control with oral pain medications, and ability to ambulate without assistance. Criteria for discontinuing intravenous antibiotics included remaining afebrile ( $\leq 38^{\circ}\text{C}$ ) for 48 hours and having a white blood cell count and differential within the

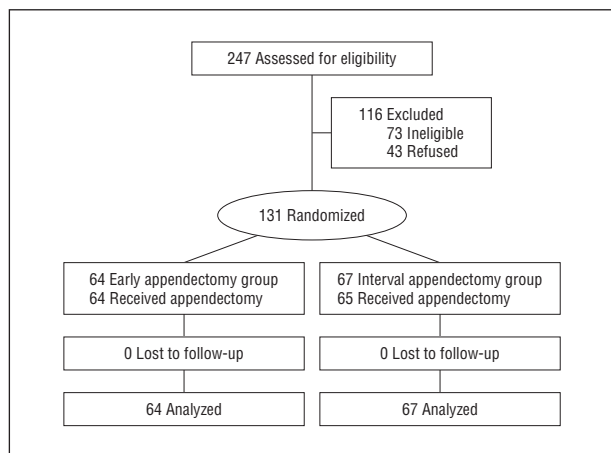
reference range at that time. After stopping intravenous antibiotics, oral antibiotics could be given at the discretion of the pediatric surgeon. Prior studies<sup>14</sup> indicate that specifics regarding use of oral antibiotics after initial intravenous antibiotics were unlikely to effect outcomes.

## STUDY MEASURES

Research nurses who were not involved in the patient's medical care recorded data variables using standardized definitions and forms. The primary outcome was time away from normal activities (days). This outcome is patient-centered, has been used in other surgical trials,<sup>15,16</sup> and is consistent with pragmatic trials in general.<sup>17</sup> As with other pragmatic trials, we attempted to compare the 2 surgical interventions in a "normal practice setting" rather than an ideal setting for trial purposes and did not make extraordinary attempts to control all cointerventions. The time away from normal activities is a combination of objective time periods (hospital length of stay, outpatient status with central venous catheter, and receiving intravenous antibiotics) and more subjective time periods (eg, outpatient with symptoms that limit activity). This was determined by discussion with the patients and their families (via phone follow-up and return visits), by documenting the return to school date during the school year, discussing levels of activity compared with prior to illness, and using activity logs completed by some families or patients. Return visits were scheduled according to our standard clinical practice (ie, 1-2 weeks after discharge for the first return visit and then subsequent visits scheduled according to patient condition). Follow-up phone calls were made as needed for patients for whom the return-to-normal time had not been documented at a clinical visit. The methods used to determine the primary outcome were the same for both treatment groups. When there were discrepancies regarding the primary outcome determination between various data sources, consensus was reached by discussion between the research nurse, research fellow, and nurse practitioner. To decrease bias, the pediatric surgeons responsible for clinical care were not involved in determination of the primary outcome.

The intraoperative diagnosis of perforated appendicitis was assessed by the attending pediatric surgeon and consisted of carefully examining the removed appendix prior to handing the specimen off for pathologic processing. The diagnosis of perforated appendicitis was confirmed if a visible hole in the appendiceal wall could be demonstrated.<sup>18</sup> Intraoperative and preoperative diagnoses were compared to assess accuracy of the preoperative diagnosis.

Prespecified secondary outcome variables included proportion of patients with an intra-abdominal abscess, surgical site infection, total length of hospital stay (days), number of patients receiving a central venous line, number of patients undergoing an interventional radiology procedure (eg, abscess drainage, central venous line placement, pleural effusion drainage), complication rates related to interventional radiology procedures or central venous line placement, and other adverse event occurrences. Definitions of the recorded adverse events are detailed in the eAppendix (<http://www.archsurgery.com>). A detailed assessment documenting adverse events was performed. This consisted of prospective identification and recording of adverse events for each patient from enrollment to last follow-up. Also, a second analysis was done at trial completion by reviewing the electronic medical records of all patients and reaching a final agreement for adverse event recording. This review was completed in a meeting dedicated to this purpose with input from all trial personnel who were blinded to treatment group assignment. Detailed information regarding unplanned readmissions, emergency department visits, and the return admission for interval appendectomy was recorded.



**Figure.** Flow diagram of trial: exclusion, enrollment, randomization, and follow-up.

## STATISTICAL ANALYSIS

Prior to starting our trial, a difference in the time until returning to normal activities between the early and interval appendectomy groups of 5 days was considered clinically significant. Assuming an  $\alpha$  of .05,  $\beta$  of .2, and a standard deviation of 10 (for the primary outcome), 128 total enrolled patients provided 80% power to detect this 5-day difference (hypothesized time away from normal activities, 21 vs 16 days). We anticipated an 80% consent rate for randomization of eligible patients.

Intention-to-treat analyses were performed. Primary outcome data were normally distributed and were analyzed using *t* tests. Prespecified analyses comparing secondary outcomes were analyzed according to data type. Continuous variables were analyzed with *t* tests. The proportions of patients with various complications were compared using  $\chi^2$  analyses or Fisher exact tests. We also documented the number of incorrect diagnoses among all enrollees, the number of patients randomized to interval appendectomy who had an appendectomy earlier than planned, and identified patients randomized to interval appendectomy who did not return.

## RESULTS

Between October 2006 and August 2009, we randomized 131 of 174 (75%) eligible children (**Figure**); 64 were randomized to early appendectomy and 67 to interval appendectomy. Of 247 children assessed for eligibility, 73 were declared ineligible for the following reasons: diagnosis unclear or thought to have acute, nonruptured appendicitis ( $n=45$ ); delayed presentation ( $n=18$ ); bowel obstruction felt to require operation ( $n=2$ ); initial treatment elsewhere ( $n=2$ ); or other reasons ( $n=6$ ). Patients in the early appendectomy group were similar to those in the interval appendectomy group at the time of study enrollment (**Table 1**).

Patients in the early appendectomy group underwent appendectomy at an average of 1 day after admission. Fifty-five of them had laparoscopic appendectomy; 6, open appendectomy; and 3, laparoscopic converted to open appendectomy. The average time of appendectomy in the interval group was 51 days after diagnosis. Sixty of these had laparoscopic appendectomy, 3 had an open appen-

**Table 1. Baseline Characteristics of Trial Participants (n=131)**

Characteristic	No. (%)		P Value
	Early (n=64)	Interval (n=67)	
Age, mean (range), y	10.5 (1.8-16.6)	9.9 (2.6-17.3)	.29
Male sex	40 (63)	33 (49)	.13
Race			.60
Black	30 (47)	28 (42)	
Hispanic	13 (20)	12 (18)	
White	20 (31)	26 (39)	
Other	1 (2)	1 (1)	
Duration of symptoms, mean (range), d	3.4 (1-14)	3.4 (1-17)	.93
ED temperature, mean (range), °C	38.0 (36.2-39.8)	38.4 (36.2-40.2)	.01
Admission WBC count, mean (range), No. $\times 10^3/\mu\text{L}$	17.6 (5.2-34.3)	16.8 (5.6-28.7)	.38
Abdominal CT performed at initial assessment	55 (87)	61 (91)	.49
IAA at admission	25 (39)	26 (39)	.98
ICU admission	2 (3)	3 (4)	>.99

Abbreviations: CT, computed tomography; ED, emergency department; IAA, intra-abdominal abscess; ICU, intensive care unit; WBC, white blood cell.

dectomy, and 2 had a laparoscopic converted to open appendectomy. Two patients assigned to the interval appendectomy group did not have an appendectomy because they failed to return for this treatment. Twenty-three patients assigned to interval appendectomy (34%) had an appendectomy earlier than planned, according to the interval protocol, owing to small bowel obstruction ( $n=10$ ), persistent symptoms ( $n=5$ ), recurrent appendicitis ( $n=6$ ), unresolved intra-abdominal abscess ( $n=1$ ), and parental demand ( $n=1$ ).

A diagnosis other than perforated appendicitis was identified intraoperatively in 7 patients in the early appendectomy group (11%) and in 1 patient in the interval appendectomy group. Conditions other than perforated appendicitis detected were acute, nonperforated appendicitis ( $n=5$ ), ileal volvulus ( $n=1$ ), primary peritonitis with normal appendix ( $n=1$ ), and a benign ovarian teratoma ( $n=1$ ). All of these patients had a presentation (including imaging) consistent with perforated appendicitis.

The primary outcome of time away from normal activities (days) was measured in 100% of randomized children and was significantly different according to treatment group (mean [SD], 13.8 [7.5] days for early vs 19.4 [8.7] days for interval appendectomy;  $P < .001$ ). The total length of hospital stay (mean) for early appendectomy patients was 9.0 days (range, 2.6-23.9 days) compared with 11.2 days (range, 3.3-40 days) for patients who received interval appendectomy ( $P = .03$ ). The total duration of intravenous antibiotic therapy was 13 days for early

vs 15 days for interval appendectomy groups ( $P=.10$ ). The rates of other prespecified secondary outcomes are shown in **Table 2**.

The overall adverse rate event was 30% (18 of 64 persons) in the early appendectomy group vs 55% (35 of 67 persons) for interval appendectomy ( $P=.003$ ). As shown in **Table 3**, patients treated with interval appendectomy were significantly more likely to have an intra-abdominal abscess subsequent to admission, a small bowel obstruction during treatment, an unplanned readmission, and recurrent appendicitis during the trial period.

## COMMENT

Despite the frequency of perforated appendicitis in children, treatment for this condition is quite controversial. In a survey of pediatric surgeons, almost no consensus was demonstrated on most aspects of surgical treatment for perforated appendicitis.<sup>4</sup> There are few prospective comparisons of these 2 treatment options available in the literature. One pilot randomized trial restricted to patients with well-formed intra-abdominal abscesses ( $n=40$ ) found no major differences in outcomes when comparing early appendectomy vs interventional radiology drainage of the abscess with interval appendectomy.<sup>19</sup> Some pediatric surgeons have proposed initial nonoperative treatment and no interval appendectomy.<sup>20</sup> In selected patient subgroups, when appendectomy is not done, the recurrent appendicitis rate is approximately 5% to 8%.<sup>20,21</sup> This treatment option has not been studied prospectively (or retrospectively) in unselected populations of patients with perforated appendicitis and is not commonly used. As is true with much of pediatric surgery, there is a lack of high-quality evidence to inform this treatment decision.

In this prospective, randomized trial comparing early appendectomy with interval appendectomy, we found that those treated with early appendectomy return to normal activities an average of 5 days earlier ( $P<.001$ ). Because a child's time away from normal activities limits parents' abilities to work, we believe it is an important outcome from a patient and family perspective. It is readily measured and, as used in this trial, it is a composite of objective (eg, hospital length of stay) and subjective measures. As was true in our trial (no deaths), mortality in children with perforated appendicitis is rare, and essentially all patients return to their pre-illness levels of activity. Once families are reassured that their child will return to normal at some point, the next concern is usually how quickly this will occur.

Perforated appendicitis is a significant childhood illness with an overall length of hospitalization in our study of 10 days. The length of hospitalization was significantly reduced with early appendectomy (9.0 vs 11.2 days;  $P=.03$ ), which has major implications for use of hospital beds. The overall complication rates reported in most studies ranges from 3% to 30%.<sup>8,10,22-26</sup> Most of these adverse events result from the disease process and occur much less commonly after appendectomy for nonperforated appendicitis. Measuring the adverse event rates in each treatment group was a secondary objective of this

**Table 2. Health Care Use After Early Appendectomy or Interval Appendectomy**

Outcome	Early (n=64)	Interval (n=67)	P Value
Received central venous catheter, No. (%)	28 (44)	58 (87)	<.001
Discharged with central venous catheter, No. (%)	6 (9)	29 (43)	<.001
Underwent IR procedure, No. (%)	13 (21)	15 (23)	.77
Total antibiotic duration, mean (range), d	13 (3-30)	15 (6-33)	.10
Operative time, mean (range), min	113 (39-213)	112 (48-295)	.95
CT scans during study period, mean (range), No.	1.3 (0-5)	1.7 (0-6)	.06
Hospital length of stay, mean (range), d	9 (2.6-23.9)	11.2 (3.3-40)	.03

Abbreviations: CT, computed tomography; IR, interventional radiology.

trial, and the power to detect small differences was low. However, our study found significant differences in the adverse event rates in the 2 treatment groups. Most of patients treated with interval appendectomy (55%) had at least 1 predefined adverse event compared with 30% of those in the early appendectomy group ( $P=.003$ ). The most frequent adverse events in the interval group, accounting for the increased rate overall, were intra-abdominal abscesses during the treatment period, development of a small bowel obstruction, unplanned readmission, and recurrent appendicitis. Reporting of adverse events in surgical studies is known to be highly variable, and there is no uniformity in the definitions of adverse events used.<sup>27,28</sup> There are promising ongoing efforts to reduce the variability of pediatric surgical adverse reporting.<sup>29</sup>

A concern with early appendectomy is the difficulty of performing it during the acute phase immediately after diagnosis of perforated appendicitis. We found that the duration of the operation was not significantly longer with early (113 minutes) vs interval (112 minutes) appendectomy. Intraoperative complications were uncommon. There were none in the early group and 1 in the interval group. The complication (intestinal injury necessitating resection with reanastomosis) occurred in a patient randomized to interval therapy but who required an earlier operation owing to bowel obstruction. In our trial, most operations were done laparoscopically in both treatment groups, and conversion rates from laparoscopic to open operation were not different. These data illustrate the feasibility of early appendectomy when performed by experienced pediatric surgeons trained in minimally invasive techniques. Generalizability to other practice types is unknown.

In this trial, 8 of the 131 patients (6%) were misdiagnosed as having perforated appendicitis and, in fact, had some other condition. Most of these incorrect initial diagnoses were due to nonperforated acute appendicitis (63% of all incorrect diagnoses). Other actual diagnoses included a benign ovarian teratoma, an ileal volvulus, and primary peritonitis. Our ability to define a diagnostic ac-

**Table 3. Adverse Events After Early or Interval Appendectomy**

Event	No. (%)			RR Associated With Interval Appendectomy (95% CI)	P Value
	Early (n=64)	Interval (n=67)			
Any adverse event	19 (30)	37 (55)		1.86 (1.21-2.87)	.003
Intra-abdominal abscess	12 (19)	25 (37)		1.99 (1.10-3.62)	.02
Small bowel obstruction	0	7 (10.4)			.01
Wound infection	6 (9.4)	6 (9.0)		0.94 (0.32-2.76)	.91
Unplanned readmission	5 (8)	21 (31)		3.94 (1.59-9.84)	.01
CVL-related adverse event	1 (1.6)	4 (6.0)		0.88 (0.21-3.72)	1
IR procedure-related adverse event	0	1 (1.5)			1
Recurrent appendicitis	0	6 (9)			.01

Abbreviations: CI, confidence interval; CVL, central venous line; IR, interventional radiology; RR, relative risk.

curacy rate differed greatly between the 2 treatment groups. In the 64 patients who had early appendectomy, the correct diagnosis was made in 89% of cases (57 of 64 cases). Most patients with an incorrect diagnosis are likely to have acute, nonperforated appendicitis and can be treated more simply with an early appendectomy. Inherent in the interval appendectomy treatment strategy is the inability to definitively exclude alternate diagnoses on abdominal exploration. In the interval appendectomy group, our ability to comment on diagnostic accuracy is limited. At the time of appendectomy, 6 to 8 weeks after diagnosis, the typical findings are inflammatory adhesions in the periappendiceal region. While this supports an initial diagnosis of appendicitis, it does not prove prior rupture. There is no compelling reason to believe that the diagnostic accuracy rate would differ according to treatment group. We believe the possibility of inaccurate initial diagnoses should promote caution when using the interval appendectomy treatment protocol. We have recently reported that the accuracy of distinguishing acute nonperforated appendicitis from perforated appendicitis is approximately 90% in our center.<sup>13</sup>

A limitation of this trial is the single-center design, which may affect the generalizability of our findings. Other centers use different antibiotic regimens in their interval appendectomy treatment plans, as well as various criteria for discontinuing antibiotics, and these may compare differently with early appendectomy. However, most data support the concept that the exact antibiotic regimen would not significantly alter our findings.<sup>30,31</sup> Also, patient populations may differ between various clinical sites. Another limitation is the lack of a well-accepted, standardized method by which to determine when a child has returned to normal activities. Although imperfect, our trial did assess this important outcome using the same measurement for each treatment group. Despite limitations, this trial represents the only randomized trial comparing early and interval appendectomy in nonselected children with a preoperative diagnosis of perforated appendicitis and definitively favors early appendectomy.

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**Author Contributions:** Dr Blakely had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Blakely, Dassinger, Eubanks, Hester, Streck, and Langham. *Acquisition of data:* Williams, Dassinger, Eubanks, Paton, Culbreath, Hester, Streck, Hixson, and Langham. *Analysis and interpretation of data:* Blakely, Williams, Eubanks, Fischer, Huang, Streck, and Langham. *Drafting of the manuscript:* Blakely and Williams. *Critical revision of the manuscript for important intellectual content:* Blakely, Williams, Dassinger, Eubanks, Fischer, Huang, Paton, Culbreath, Hester, Streck, Hixson, and Langham. *Statistical analysis:* Williams, Eubanks, Fischer, and Langham. *Obtained funding:* Blakely. *Administrative, technical, and material support:* Eubanks, Huang, Paton, Culbreath, Hester, Streck, and Langham. *Study supervision:* Blakely, Dassinger, Hixson, and Langham.

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**Online-Only Material:** The eAppendix is available at <http://www.archsurg.com>.

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