Treatment of suspected acute perforated appendicitis with antibiotics and interval appendectomy

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A B S T R A C T

Background: Initial antibiotics with planned interval appendectomy (interval AP) have been used to treat patients with complicated perforated appendicitis; however, little experience exists with this approach in children with suspected acute perforated appendicitis (SAPA). We sought to determine the outcome of initial antibiotics and interval AP in children with SAPA.

Methods: Over an 18-month period, 751 consecutive patients underwent appendectomy including 105 patients with SAPA who were treated with initial intravenous antibiotics and planned interval AP ≥8 weeks after presentation. All SAPA patients had symptoms for ≤96 hours. Primary outcome variables were rates of readmission, abscess formation, and need for interval AP prior to the planned ≥8 weeks.

Results: Intraabdominal abscess rate was 27%. Appendectomy prior to planned interval AP was 11% and readmission occurred in 34%. All patients underwent eventual appendectomy with pathologic confirmation confirming the previous appendiceal inflammation. White blood cell (WBC) count >15,000, WBC >15,000 plus fecalith on imaging, and WBC >15,000 plus duration of symptoms >48 hours were all significantly associated with higher rates of readmission (p = 0.01, p = 0.04, p = 0.02) and need for interval AP prior to the planned ≥8 weeks (p = 0.003, p = 0.05, p = 0.03).

Conclusions: Treatment of SAPA with antibiotics and planned interval AP is successful in the majority of patients; however, complications such as abscess formation and/or readmission prior to planned interval AP occur in up to one-third of patients. Certain clinical variables are associated with increased treatment complications.

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1. Methods

Optimal management of children with perforated appendicitis continues to be a challenging problem [1,2]. In patients presenting with long-standing symptoms, particularly with mass or abscess, interval appendectomy (interval AP)—antibiotics at diagnosis with operation delayed weeks or months—has frequently been used. The introduction of powerful broad-spectrum antibiotics made the interval pathway a more attractive option and has widened its application to larger groups of patients, including children with clinically diagnosed recent rupture and/or diffuse peritonitis. Despite growing use of such management nationwide, there are few data regarding the outcome of patients with presumed rupture without mass or abscess at diagnosis, what we label suspected acute perforated appendicitis (SAPA), who are systematically treated on an interval AP pathway. We conducted an observational study to determine the efficacy of initial antibiotics and delayed operation in a consecutive series of patients with SAPA.
collect clinical information and recorded data were collated at the end of the study period.

All eligible patients were initially treated with intravenous (IV) fluids, analgesics and the initiation of intravenous antibiotics, with operation planned for approximately 8 weeks after diagnosis. Piperacillin/tazobactam (100 mg/kg/dose) dosed every 6 hours was used primarily; gentamicin (7.5 mg/kg/day) and clindamycin (30 mg/kg/day) were used in combination if the patient had a penicillin allergy. A peripherally inserted central catheter (PICC) was placed for antibiotic administration, and patients were treated with a minimum 7-day course. Patients afebrile for 24 hours, tolerating a regular diet and having adequate pain control with oral analgesics were eligible for home administration of intravenous antibiotics. They were discharged with a PICC and home health care, undergoing reevaluation on an outpatient basis. Criteria for discontinuing antibiotics were absence of tenderness on physical exam, no temperature above 100 °F for 48 hours and a normal WBC.

About 2 weeks after the cessation of antibiotic treatment, patients were seen in the clinic for reevaluation and scheduling of surgery. The interval AP was planned as an outpatient procedure using a single-incision, single-instrument technique [3]. In instances where the single-port technique was not feasible, a standard three-port technique was used. Patients were discharged home from the ambulatory surgery suite unless their operative findings necessitated admission for additional antibiotic therapy (e.g., for residual abscess cavity or exposed fecalith), for pain control or if the operation ended too late in the day for same-day discharge.

Patients seen for problems prior to the time of their scheduled interval AP—whether during antibiotic treatment or after termination—were reevaluated using US and/or CT imaging where necessary. Patients with abscess formation underwent aspiration by interventional radiology (IR) with or without drain placement when feasible. If readmission was required for a clinical picture of recurrent appendicitis after the cessation of antibiotics, the initial nonoperative protocol with antibiotics was restarted, and a period of observation was undertaken. Responders to the secondary therapy were taken off antibiotic therapy when the previously outlined criteria were met. Patients then returned at the scheduled time to have their interval AP. Nonresponders with persistent or worsening pain and fever despite the resumption of antibiotic therapy—as determined by the attending pediatric surgeon—underwent early AP and were considered treatment failures. All specimens were examined by a pediatric pathologist.

Primary outcome variables were rates of readmission prior to planned interval AP, development of intraabdominal and/or pelvic abscess, and AP prior to the planned interval AP. Clinical variables studied are listed in Table 1. Analyses were performed to determine whether any measured clinical variables were associated with readmission and the need for early AP. Statistical analysis was completed using SAS software. Associations between categorical variables were evaluated using the Pearson chi-square analysis. The Student’s t-test was used to identify differences between groups regarding quantitative data. All tests of significance were performed with the use of a two-sided type I error rate of 5%.

2. Results

During the 18-month study period, 751 patients underwent AP at our institution. One hundred five patients consecutively diagnosed with SAPA formed the study group. There were 63 males and 42 females with a mean age of 9.8 years (range, 2–18 years). All were started on the nonoperative protocol. Ninety-three (89%) of patients underwent planned interval AP. Twelve children (11%) had early appendectomies. All patients had pathologic confirmation of previous appendiceal inflammation.

SAPA patients had a mean duration of symptoms of 54 hours prior to presentation in the emergency department and none more than 96 hours, and 87 patients (83%) had peritoneal signs (rigidity, involuntary guarding) outside the right lower quadrant on physical examination and all patients had generalized abdominal tenderness. Mean WBC count on admission was 17,500. All SAPA patients underwent diagnostic imaging by either US or CT, and 44 (42%) had findings of an intraabdominal appendicolith.

All SAPA patients were admitted to the hospital for initiation of the nonoperative protocol. The initial length of stay (LOS) until discharge criteria were met was a mean of 6.4 days. We recalculated total LOS for the group, accounting for readmission and the need for admission after interval AP and found a cumulative LOS of 7.5 days. Children were treated with antibiotic therapy for a mean duration of 12.9 days (range 5–29). Ninety-five percent of patients were treated with piperacillin/tazobactam. All clinical data and outcomes are summarized in Tables 1 and 2.

Readmission prior to planned interval AP occurred in 36 patients (34%). All readmitted patients underwent diagnostic imaging. Twenty-eight patients (27% of the study group) were found to have an intraabdominal/pelvic abscess with 12 patients (33% of 36 or 11% of the entire group) being amenable to an IR-guided drainage procedure. All patients ultimately met the criteria for discontinuance of antibiotics after initial or subsequent therapy.

Twelve patients (33% of 36 or 11% of the entire group) presenting for retreatment of appendicitis symptoms after being off antibiotics continued to have pain, fever or worsening clinical symptoms and underwent early AP, a decision made by the attending pediatric surgeon. The remaining 24 readmitted patients (67%) responded to the second course of nonoperative therapy and were brought back at the appropriate time for their interval AP.

Since a third of our SAPA patients were readmitted prior to the planned operation, we looked to identify clinical variables that could be associated with untoward events during nonoperative therapy. We found no statistical difference in the rate of readmission based on admission WBC, presence of an appendicolith on imaging or duration of symptoms longer than 48 hours. Three sets of clinical variables, WBC >15,000 at admission (23.7% vs 4.5%, p = 0.003), WBC >15,000 plus imaging study showing an appendicolith (27.2% vs 7.8%, p = 0.05), and WBC >15,000 plus duration of symptoms more than 48 hours (28.6% vs 8.8%, p = 0.03) were found significantly more frequently in the patients undergoing early AP (Table 3). Pathology specimens in all patients confirmed the previous appendiceal inflammation.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval AP (n = 105)</th>
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<tbody>
<tr>
<td>Age (years), mean</td>
<td>9.84</td>
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<tr>
<td>Duration of symptoms (hours), mean</td>
<td>53.87</td>
</tr>
<tr>
<td>Generalized tenderness, n</td>
<td>87 (83%)</td>
</tr>
<tr>
<td>Temperature (°F), mean</td>
<td>100.19</td>
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<tr>
<td>White blood cell count (103), mean</td>
<td>17.46</td>
</tr>
<tr>
<td>Appendicolith on imaging, n</td>
<td>44 (42%)</td>
</tr>
<tr>
<td>Initial LOS (days), mean</td>
<td>6.41</td>
</tr>
<tr>
<td>Cumulative LOS, mean</td>
<td>7.52</td>
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<tr>
<td>Duration of antibiotics (days), mean</td>
<td>12.96</td>
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</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Event</th>
<th>(n = 105)</th>
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<tbody>
<tr>
<td>Intraabdominal/pelvic abscess</td>
<td>28 (27%)</td>
</tr>
<tr>
<td>Abscess amenable to aspiration or drainage</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>Readmission prior to planned interval AP</td>
<td>36 (34%)</td>
</tr>
<tr>
<td>Appendectomy prior to planned interval AP</td>
<td>12 (11%)</td>
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</table>
During the study period, 37 (6%) of the 646 patients undergoing immediate AP for presumed acute simple appendicitis were found to have perforated appendicitis. These patients were not included in the study cohort but were compared to the SAPA patients. Significant differences existed in duration of symptoms prior to presentation, 54 hours vs 35 hours ($p < 0.001$), and generalized tenderness with peritoneal signs on exam, 87 (83%) vs 9 (24%) ($p < 0.001$). Three developed intraabdominal abscesses (8% vs 28% in the interval management group, $p < 0.001$); additionally, three who had been discharged were readmitted (8% vs 34% on interval management, $p = 0.01$) (Table 4).

3. Discussion

Our institution performs approximately 500 appendectomies per year. Over a 5-year period, one-quarter to one-third were interval appendectomies for patients diagnosed with perforated appendicitis and treated up-front with intravenous antibiotics followed by AP about 2 months later. Most studies employing delayed operation in cases of perforated appendicitis have been conducted in children presenting with a mass on exam or an abscess on imaging studies. We sought to prospectively identify patients with SAPA—perforated appendicitis without mass or abscess—and determine their outcomes on a pathway of interval management. In identifying children with SAPA, all four criteria outlined in the Methods section had to have been met. Any patient with symptoms longer than 4 days or with mass or abscess was excluded from the study.

Multiple studies have identified the characteristics of children more likely to present with ruptured appendicitis; these include younger age, pain longer than 2 to 3 days, generalized abdominal tenderness and fever over 38 °C [4–7]. A prospective cohort study conducted by Williams et al. [8] suggested WBC greater than 19 and fecalith as additional independent preoperative predictors. Importantly, they also found that pediatric surgeons were able to diagnose perforated appendicitis preoperatively with an accuracy of 93.5% and sensitivity and specificity of 96.4% and 83% respectively. Using our definition of SAPA and historical predictors of ruptured appendicitis, we were able to identify 105 patients with SAPA, all of whom were ultimately confirmed to have appendical changes at pathology.

### Table 3

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ruptured appendicitis, we were able to identify 105 patients with
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When nonoperative management of perforated appendicitis was studied using appropriately matched controls, lower complication rates (19% vs 43%, $p < 0.01$), fewer abscesses (4% vs 24%, $p < 0.01$) and a trend for shorter length of hospital stay (6.5 vs 8.8 days, $p = 0.08$) were found in a subset of patients presenting with a 7-day duration of pain [9]. Another study evaluated the safety and efficacy of initial nonoperative management for perforated appendicitis not accompanied by a palpable mass in 77 adult patients [10]. All had localized abdominal tenderness and none had a palpable abdominal mass. Initial nonoperative management was successful in 95% of patients, a figure similar to our 89% in this pediatric cohort. Complications occurred in 12% of their patients, while 34% in our series had adverse events while on the pathway. Other retrospective data also show lower complication rates and lower or similar LOS in nonoperatively treated patients with interval AP for perforated appendicitis [11–14]. It is difficult to compare studies, however, because significant variability exists between the criteria for diagnosing perforation, making it impossible to ascertain optimal management strategy. Almost 90% of our patients completed the protocol and underwent AP at about 8 weeks postoperatively, 74% of these (69 of 93) following the pathway without complication. Patients requiring operation—because of deteriorating clinical picture—prior to the time for interval AP (11% in our study) were considered treatment failures. Other published series have demonstrated similar success rates, from 62% to 95%, following interval AP protocols [9,10,15,16]. About one-third (36 patients) of SAPA patients had untoward events during treatment or the interval between stopping the antibiotics and operation, of which 27% (28 patients) formed intraabdominal and/or pelvic abscesses. Only 11% (12 patients) of SAPA patients required an IR procedure for drainage.

Comparison of clinical characteristics of SAPA patients to published reports of ruptured appendicitis presenting with mass or abscess and treated on an interval management pathway reveals that SAPA patients tended to have a shorter duration of symptoms and lower temperature on admission. SAPA patients otherwise were similar in terms of admission WBC, location of tenderness and presence of appendicolith on initial imaging. Most patients with SAPA respond well to nonoperative management and interval AP with a small number needing early AP.

The role of early AP in perforated appendicitis is evolving as seen in two recent randomized prospective trials. St. Peter et al. [17] evaluated children who over a 2-year span presented with a well-defined abdominal abscess by CT scan. Forty patients were enrolled and randomized to either immediate AP or nonoperative medical management after abscess drainage followed by interval AP. No significant differences existed between the groups at time of admission. While this study was small, 20% of patients in the nonoperative cohort required early AP. The two groups did not differ significantly with regard to operative times (though slightly longer in early AP), total LOS, recurrence of abscess (20% early AP vs 25% for interval management) and total charges. A significantly greater number of CT scans, however, were used in the interval group (2.1 scans vs 1.5 for immediate operation). We routinely use US as the initial imaging modality in all patients with suspected appendicitis. Recent data [18] reveal that sonography compares favorably with CT with respect to sensitivity and specificity (98.7% and 95.4%) in the diagnosis of appendicitis and minimizes radiation exposure. The authors concluded that there was no clear benefit to either pathway, but pointed out that technical laparoscopic expertise and IR resources must be available.

A recent randomized clinical trial by Blakely et al. [19] looked at early (64 patients) versus delayed AP (67 patients) in those patients with acute perforated appendicitis who did not have a well-formed abscess or mass on exam. These patients were similar to our SAPA patients; however, 35% of their patients in each arm had an imaging diagnosis of an intraabdominal abscess at initial presentation. While

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval AP (n = 105)</th>
<th>Early AP (n = 37)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean</td>
<td>9.84</td>
<td>11.52</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of symptoms (hours), mean</td>
<td>53.87</td>
<td>34.86</td>
<td>ns</td>
</tr>
<tr>
<td>Generalized tenderness, n</td>
<td>87 (83%)</td>
<td>9 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature (°F), mean</td>
<td>100.19</td>
<td>99.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White blood cell count (103), mean</td>
<td>17.46</td>
<td>17.69</td>
<td>ns</td>
</tr>
<tr>
<td>Appendicolith on imaging, n</td>
<td>44 (42%)</td>
<td>15 (41%)</td>
<td>ns</td>
</tr>
<tr>
<td>Initial LOS (days), mean</td>
<td>6.41</td>
<td>5.22</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of antibiotics (days), mean</td>
<td>12.96</td>
<td>11.54</td>
<td>ns</td>
</tr>
<tr>
<td>Intraabdominal/pelvic abscess, n</td>
<td>28 (27%)</td>
<td>2 (5.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Readmission prior to planned interval AP, n</td>
<td>16 (34%)</td>
<td>3 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appendectomy prior to planned Interval AP, n</td>
<td>2 (11%)</td>
<td>n/a</td>
<td></td>
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</table>
there were no significant differences in operative times or total duration of antibiotic therapy, there was a 34% treatment failure rate in the interval AP group, with all these patients undergoing early AP. Our treatment failure rate was lower at 11%. The interval group also had an overall adverse event rate of 55% versus 30% in the early AP group (p = 0.003). Patients on the interval management pathway were more likely to have intraabdominal abscess subsequent to admission [37% vs 19% for the early surgery cohort (p = 0.02)], small bowel obstruction during treatment [10% vs 0% (p = 0.01)], unplanned readmission [31% vs 8% (p = 0.01)] and recurrent appendicitis [9% vs 0% (p = 0.01)]. Their primary outcome, measure of time away from normal activity, was significantly shorter in the early AP group, 13.8 days vs 19.4 days (p < 0.001). Early AP was shown to have lower adverse event rates overall, notably lower occurrence of intraabdominal abscess. Hospital charges and costs were significantly lower for early AP when compared with interval AP [20].

Since early AP has shown to have benefits of lower recurrent abscess rate, we compared our SAPA patients on interval management with the 37 excluded patients who were initially operated on for suspected acute simple appendicitis but who were found to have perforation upon appendectomy. As expected, the early AP patients had favorable clinical criteria compared to SAPA patients for all clinical characteristics but significantly lower duration of symptoms and less generalized tenderness with peritoneal signs. These patients with perforated appendicitis, who were treated with early AP, also showed a significantly decreased intraabdominal abscess and readmission rates (Table 4) compared to our SAPA cohort treated on the interval management pathway. Though the groups were clinically different based on the examining surgeon’s opinion, the role of early AP in patients relegated to the SAPA pathway may prove to be beneficial.

We analyzed our clinical and imaging data to see if any variables identified which patients would be delayed responders or treatment failures or return before scheduled operation with recurrent appendicitis. Nadler et al. [10] found no difference between patients who went through the interval management pathway with no untoward events and all others, when examining age, gender, initial WBC, percent bands, percent neutrophils or duration and type of presenting symptoms. Event-free patients, however, were more likely to have a phlegmon without abscess on CT scan compared to all others. In this latter group, patients were twice as likely to undergo drainage of an abscess by IR. The authors concluded that treatment could be directed appropriately to those patients who had pretreatment variables that predicted complication during nonoperative therapy.

Whyte et al. [16] determined that the admission band count, temperature response in the first 24 hours and CT findings were most helpful in predicting problems with initial nonoperative therapy. As in our study, while the presence of a fecalith alone was not a significant predictor of adverse event on the delayed operation pathway, patients with certain clinical factors—higher band count, prolonged fever, and CT finding of disease spread beyond the right lower quadrant—had more problems with interval management. We found that WBC greater than 15,000, especially when accompanied by appendicolith or symptoms longer than 48 hours duration led to a significantly greater likelihood of an AP prior to planned interval AP. Ein et al. [21], on the other hand, showed in a retrospective review that if a there was a fecalith in the ruptured appendix (with an associated inflammatory mass or abscess) that was initially treated nonoperatively, there was a 72% recurrence rate of appendicitis, usually within 3 months.

In conclusion, we attempted to identify a group of patients with SAPA without mass or abscess and outline their outcomes as no data exist for this subgroup of patients. We believe that the majority of patients with SAPA can be successfully treated on an interval management protocol; however, readmission rate is significant. While 85% of children did complete the pathway and underwent planned interval AP, certain clinical features such as WBC over 15,000 when accompanied by feotalith or symptoms longer than 2 days were associated with treatment failure. Our study adds to the growing body of complex and conflicting literature on the application of interval management in the treatment of childhood appendicitis. Further work needs to be done to identify patients who will benefit from early intervention in the face of perforated appendicitis, whether with mass or diffuse perforation, separating them clinically from children best suited to early antibiotic treatment and delayed surgery. Though a great body of literature exists supporting the use of interval management in perforated appendicitis, evidence may be swinging toward the more frequent use of early AP.

References