Non-operative Management of Uncomplicated Early Appendicitis in Children

12:15 – 1 p.m.

Dave Lal, MD
I have no relevant financial relationships to disclose.
Objectives

• Understand the current literature regarding the advantages and disadvantages of non-operative management of early appendicitis

• Compare outcomes and quality of life measurements in appendicitis patients treated surgically and medically

• Discuss the multi-institutional, patient choice study for early appendicitis conducted by pediatric surgeons at Children’s Hospital of Wisconsin
Burden of Disease

• Acute appendicitis
  – 300,000 appendectomies annually
  – 11% of pediatric emergency admissions
  – 70,000 children hospitalized annually
Rationale

- Medical dogma
  - appendicitis = appendectomy
- Non-operative management of appendicitis is not new
  - 1959 Coldrey reported non-operative therapy
  - Soldiers in wartime
  - Naval vessels without surgical resources
  - Explorers in remote locations
Non-operative Management of Appendicitis

• Improved diagnostic accuracy

• Effective broad spectrum antibiotics

• Similar abdominal and pelvic infections are treated successfully with antibiotics
  – Diverticulitis
  – Crohn’s disease abscess
  – Tubo-ovarian abscess
  – Perforated appendicitis with abscess

"You're lucky. In my day the doctor beat you with a stick until your appendix fell out."
Non-operative Management of Appendicitis

• Complication rate with appendectomy
  – Minor 5-15%
  – Serious 1-7%
  – Negative appendectomy
    • 5-7%

• Cost
  – Average cost: $7,000

“Well, yes, it’s a routine procedure—if you routinely have someone slice open your body with sharp instruments and then fiddle with your insides.”
Recent Press

• Antibiotics Are Effective in Appendicitis, Study Says, The New York Times, 6/16/2015
• Antibiotics resurfaces as alternative to removing appendix, The New York Times, 5/18/2015
• Surgery not always necessary for appendicitis in kids, FOX News, 4/23/2014
• Appendicitis without surgery may be safe option for some kids, Reuters, 4/22/2014
• Antibiotics may be treatment for appendicitis, NBC News, 4/6/2012
• Hold the knife: Antibiotics may be safe treatment for appendicitis, Yahoo News, 4/6/2012
• Surgery may beat antibiotics for appendicitis, U.S. News and World Report, 5/6/2011
- Adult trials
- Pediatric trials
Non-operative Management of Appendicitis in Adults

• 8 international adult trials in last 15 years
  – Overall success rate at 1 year: 68%
  – No controlling for severity of appendicitis

• No increase in perforated appendicitis

• Identified risk factors for failure:
  – Presence of a fecalith
  – > 48 hours of symptoms
  – Presence of a phlegmon/abscess
  – Elevated WBC count (>18K) or CRP (>4)
### Adult RCT’s

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Age (yrs)</th>
<th># of patients</th>
<th>1 yr Follow-up</th>
<th>Appendectomy rate in Abx group</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrud et al, 2006</td>
<td>Clinical Dx CRP&gt;10 mg/L</td>
<td>&gt;18</td>
<td>Surgery: 124</td>
<td>Not reported</td>
<td>24%</td>
<td>Dx Females excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotic: 128</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansson et al, 2009</td>
<td>Clinical Dx</td>
<td>&gt;18</td>
<td>Surgery: 167</td>
<td>Surgery: 47%</td>
<td>48%</td>
<td>52% antibiotic group crossed over to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotic: 202</td>
<td>Antibiotic: 54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vons et al, 2011</td>
<td>CT Scan</td>
<td>&gt;18</td>
<td>Surgery: 119</td>
<td>Surgery: 87%</td>
<td>37%</td>
<td>Complicated appendicitis Suboptimal abx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotic: 120</td>
<td>Antibiotic: 90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salminen et al, 2015</td>
<td>CT scan</td>
<td>&gt;18</td>
<td>Surgery: 273</td>
<td>Surgery: 272</td>
<td>27%</td>
<td>Open operations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotic: 257</td>
<td>Antibiotic: 256</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Salminen et al, JAMA 2015
Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis
The APPAC Randomized Clinical Trial

- Multicenter RCT Finland

530 Randomized

273 Appendectomy

1 yr. Success Rate
271/272 (99.6%)
(95% CI, 98%-100%)

257 Antibiotics

1 yr. Success Rate
186/256 (72.7%)
(95% CI, 66.8%-78%)

Salminen et al, JAMA 2015
# Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis

## The APPAC Randomized Clinical Trial

<table>
<thead>
<tr>
<th></th>
<th>Surgical Group (n = 273)</th>
<th>Antibiotic Group (n = 257)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall complication rate, % (95% CI)</td>
<td>20.5 (15.3-26.4)(^a)</td>
<td>2.8 (1.0-6.0)(^b)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surgical site infections by type, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ space</td>
<td>1</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Deep incisional</td>
<td>4</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>19</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Incisional hernias, No.</td>
<td>2</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Abdominal, incisional pain, or obstructive symptoms, No.</td>
<td>23</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Length of primary hospital stay, median (25th-75th percentile), d</td>
<td>3.0 (2-3)</td>
<td>3.0 (3-3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VAS score, median (25th-75th percentile)(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At discharge from the hospital</td>
<td>3.0 (2-4)</td>
<td>2.0 (1-2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 1 wk</td>
<td>2.0 (1-3)</td>
<td>1.0 (1-1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 2 mo</td>
<td>1.0 (1-1)</td>
<td>1.0 (1-1)</td>
<td>.40</td>
</tr>
<tr>
<td>Length of sick leave, median (25th-75th percentile), d</td>
<td>19.0 (14-21)</td>
<td>7.0 (7-12)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(^a\) One high-risk patient excluded.
\(^b\) One high-risk patient excluded.
\(^c\) VAS scores for pain at rest.  

Salminen et al, JAMA 2015
Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis
The APPAC Randomized Clinical Trial

• 70/256 (27%) patients randomized to abx underwent surgery
  – 65 appendicitis
  – 5 normal appendix

• Delayed appendectomy
  – No intra-abdominal abscesses
  – No major complications

Salminen et al, JAMA 2015
Non-operative Management of Appendicitis in Children

• Five pediatric studies
  – Selected patients with uncomplicated appendicitis:
    • No fluid collection
    • Localized tenderness
    • Symptoms < 48 hours
# Non-operative Management of Appendicitis in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Success Rate</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abes JPS 2007</td>
<td>81% (13/16)</td>
<td>1 year</td>
</tr>
<tr>
<td>Koike JPS 2014</td>
<td>78% (101/130)</td>
<td>3 years</td>
</tr>
<tr>
<td>Armstrong JPS 2014</td>
<td>75% (9/12)</td>
<td>6 months</td>
</tr>
<tr>
<td>Minneci JACS 2014</td>
<td>76% (28/37)</td>
<td>1 year</td>
</tr>
<tr>
<td>Svensson Ann Surg 2015</td>
<td>62% (15/24)*</td>
<td>1 year</td>
</tr>
</tbody>
</table>

*6 patients underwent appendectomy and had a normal appendix*
Feasibility of a Non-operative Management Strategy for Uncomplicated Acute Appendicitis in Children

- Prospective, Single-center trial of patient/family choice

- 102 patients enrolled
  - 65 operative appendectomy
  - 37 non-operative management

Minneci et al, Journal of the American College of Surgeons, 2014
Hypothesis

Non-operative management with antibiotics alone is a feasible and safe first line therapy in children with uncomplicated appendicitis

• Expected 1 year success rate of 75-80%
Offered treatment choice (n=102)

Minneci et al, Journal of the American College of Surgeons, 2014
Offered treatment choice (n=102)

Chose non-operative management (n=37)
- Received allocated intervention (n=37)

Chose surgery (n=65)
- Received allocated intervention (n=65)

Minneci et al, Journal of the American College of Surgeons, 2014
Offered treatment choice (n=102)

Chose non-operative management (n=37)
- Received allocated intervention (n=37)

Lost to follow-up for secondary outcome analyses (n=5)
- Unable to reach (n=5)

Chose surgery (n=65)
- Received allocated intervention (n=65)

Lost to follow-up for secondary outcome analyses (n=12)
- Unable to reach or withdrew (n=12)

Minneci et al, Journal of the American College of Surgeons, 2014
Study Flow Diagram

Offered treatment choice (n=102)

Chose non-operative management (n=37)
  - Received allocated intervention (n=37)

Lost to follow-up for secondary outcome analyses (n=5)
  - Unable to reach (n=5)

Analyzed:
  - N=37 for primary outcome
  - N=32 for secondary outcome

Chose surgery (n=65)
  - Received allocated intervention (n=65)

Lost to follow-up for secondary outcome analyses (n=12)
  - Unable to reach or withdrew (n=12)

Analyzed:
  - Not part of primary outcome analysis
  - N=53 for secondary outcome
## Results: Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-Operative Management (n=37)</th>
<th>Surgery (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>11.2 (10.2, 14.7)</td>
<td>12.2 (9.9, 14.0)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>24 (65%)</td>
<td>46 (70%)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>25 (69%)</td>
<td>54 (82%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>4 (11%)</td>
<td>2 (3%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Insurance Status</strong></td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Private</strong></td>
<td>25 (67%)</td>
<td>42 (64%)</td>
<td></td>
</tr>
<tr>
<td><strong>Medicaid</strong></td>
<td>11 (30%)</td>
<td>21 (32%)</td>
<td></td>
</tr>
<tr>
<td><strong>No Insurance</strong></td>
<td>1 (3%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Minneci et al, Journal of the American College of Surgeons, 2014
## Results: Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-Operative Management (n=37)</th>
<th>Surgery (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of Abdominal Pain (hours)</strong></td>
<td>13 (8, 23)</td>
<td>15 (9, 24)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>8 (8%)</td>
<td>10 (15.2%)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>18 (49%)</td>
<td>22 (33%)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>4 (11%)</td>
<td>6 (9%)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td>33 (89%)</td>
<td>52 (79%)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>CT scan</strong></td>
<td>11 (30%)</td>
<td>18 (27%)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>WBC count (x 1000)</strong></td>
<td>12.9 (9.0, 14.8)</td>
<td>13.1 (10.0, 14.6)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Minneci et al, Journal of the American College of Surgeons, 2014
Results: Non-operative Success Rate

• Initial hospital stay
  – 35/37 did not require appendectomy
    • 1 acute appendicitis
    • 1 carcinoid tumor
  – Success rate: 94% (95% CI: 78%-99%)

• 30 day follow-up:
  – 33/37 did not require appendectomy
    • 1 normal appendix
    • 1 acute appendicitis
  – Success rate: 89% (95% CI: 79%-99%)
## Results: 30 day Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Non-Operative Management (n=32)</th>
<th>Surgery (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of Stay (hours)</strong></td>
<td>37 (30, 41)</td>
<td>20 (16, 31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Missed School (days)</strong></td>
<td>3 (2, 5)</td>
<td>5.0 (3, 8)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Return to Normal Activities (days)</strong></td>
<td>4 (3,10)</td>
<td>20 (14, 27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Guardian Return to Normal Schedule (days)</strong></td>
<td>2 (1.0, 3.0)</td>
<td>3 (1.0, 9.0)</td>
<td>0.17</td>
</tr>
</tbody>
</table>
## Results: 30 day Complications

<table>
<thead>
<tr>
<th></th>
<th>Non-Operative Management (n=32)</th>
<th>Surgery (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment related complications</td>
<td>1 (3%)</td>
<td>4 (6%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Post-treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fevers</td>
<td>3 (8%)</td>
<td>3 (5%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>8 (21%)</td>
<td>19 (29%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3%)</td>
<td>3 (5%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (8%)</td>
<td>6 (9%)</td>
<td>0.83</td>
</tr>
<tr>
<td>ED visit</td>
<td>3 (8%)</td>
<td>4 (6%)</td>
<td>0.69</td>
</tr>
</tbody>
</table>
## Results: 30 day QOL & Satisfaction

<table>
<thead>
<tr>
<th></th>
<th>Non-Operative Management (n=32)</th>
<th>Surgery (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child QOL questionnaire</strong></td>
<td>93.5 (87.0, 96.7)</td>
<td>87.0 (80.4, 92.4)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Parent proxy for child QOL questionnaire</strong></td>
<td>95.7 (88.0, 98.9)</td>
<td>89.1 (80.4, 95.7)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Parent Healthcare Satisfaction</strong></td>
<td>99.0 (94.8, 100.0)</td>
<td>99.0 (95.8, 100.0)</td>
<td>0.63</td>
</tr>
</tbody>
</table>
1 year Results: Non-operative Group

- Overall: 76% success rate (95% CI: 59%-88)
  - 28/37 did not require appendectomy
  - 5 recurrences after 30 days
    - 3 acute appendicitis
    - 2 normal appendix
Comparison of expected outcomes for non-operative management and surgery at 1 year

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Non-operative management</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent undergoing surgery</td>
<td>24%</td>
<td>100%</td>
</tr>
<tr>
<td>Percent with surgical complications</td>
<td>2.5%</td>
<td>7%</td>
</tr>
<tr>
<td>Median disability days for child</td>
<td>8 days</td>
<td>21 days</td>
</tr>
<tr>
<td>Median cost to treat appendicitis</td>
<td>$4,219</td>
<td>$4,992</td>
</tr>
</tbody>
</table>

P<0.001

© Children’s Specialty Group. All rights reserved.
Conclusions

• Single center results suggest that nonoperative management:
  – Feasible with a high success rate
  – Patients return to school and activities faster
  – Higher quality of life scores
  – Lower costs at 1 year
  – No increase in rates of complicated appendicitis
MWPSC Multi-Institutional Study

- Midwest Pediatric Surgery Consortium
  - Children’s Hospital of Wisconsin, Milwaukee
  - Cincinnati Children’s Hospital, Cincinnati
  - Children’s Mercy Hospital, Kansas City
  - Comer Children’s Hospital, U of Chicago
  - C.S. Mott Children’s Hospital, Ann Arbor
  - JW Riley Hospital for Children, Indianapolis
  - Kosair Children’s Hospital, Louisville
  - University of Wisconsin, Madison
  - Lurie Children’s Hospital, Northwestern
  - Nationwide Children’s Hospital, Columbus
  - St. Louis Children’s Hospital, St. Louis
Study Design

• Prospective, multi-center trial of patient/family choice
  – Previous studies provide evidence for efficacy and safety in selected patients
  – Assess the effectiveness of treatment options in a “real world” setting to facilitate generalizability and rapid adoption
  – Non-operative management should be offered to families as an alternative to surgery
Primary Outcome

- Success rate of non-operative management:
  - Success rate defined as: percent of patients who do not undergo an appendectomy
  - Analyzed at 30 days and 1 year
Secondary Outcomes

• Group comparisons
  – Disability days
    • Patients: reported days off of school and activities
    • Caregivers: reported days to return to normal schedule
  – Quality of life (QOL): patient and caregiver
  – Healthcare satisfaction
  – Length of stay
  – Treatment related complications
Inclusion Criteria

• Age: 8-17 years
• Uncomplicated early appendicitis
  – US or CT confirmed uncomplicated appendicitis:
    • ≤1.1 cm diameter
    • No abscess, perforation, phlegmon or fecalith
  – WBC >5,000 or < 18,000
  – Focal abdominal pain ≤ 48 hours prior to receiving antibiotics
Study Protocol

• Non-operative Pathway:
  – In hospital observation (minimum of 24 hours)
  – IV antibiotics (minimum of 24 hours)
  – NPO (minimum of 12 hours)
  – Improving
    • Advance diet, transition to oral antibiotics
    • Discharge with oral antibiotics to complete 7 days
  – No improvement at 24 hours or worsen
    • Appendectomy

• Surgery:
  – Appendectomy with routine post-operative care
• Criteria for failure of non-operative pathway:
  – After 12 hours of IV abx (clinical worsening in 1)
    • Increasing abdominal pain (2 point higher pain score)
    • Diffuse abdominal pain (spreading to 1 additional quadrant or becoming generalized)
    • Higher temperature (≥1 F) than documented on presentation
    • Increase in HR (≥20 bpm) from admission with pain control

  – At any time
    • Diffuse abdominal pain (spreading to 1 additional quadrant or becoming generalized)
    • Signs of progressive sepsis (hypotension, altered MS)
Study Protocol

• Short Term follow-up:
  – 2-5 days and 10-14 days: Non-op only
    • Symptom resolution and completion of antibiotics
  – 30 days: All patients
    • Treatment related complications
    • Return to activities
    • PEDSQL Quality of Life Inventory and Satisfaction

• Long term follow-up:
  – 6 months: Non-op only
    • Recurrence
  – 1, 2 and 3 years: All patients
    • Treatment related complications
Children’s Hospital of Wisconsin

• 13 patients enrolled
  • 8 operative
  • 5 non-operative
    – 1 failure persistent pain
    – Pathology normal appendix
Non-operative Management of Uncomplicated Early Appendicitis in Children

• Optimal management remains controversial

• Data supportive of non-operative management

• Await results of multi-institutional trial
“The time has come to consider abandoning routine appendectomy for patients with uncomplicated appendicitis. The operation served patients well for more than 100 years. With development of more precise diagnostic capabilities like CT and effective broad-spectrum antibiotics, appendectomy may be unnecessary for uncomplicated appendicitis, which occurs in the majority of acute appendicitis cases.”
Contact Information

Dave R. Lal, MD, MPH
(414) 266-6553

Physician Consultation and Referral: (800) 266-0366

© Children’s Specialty Group. All rights reserved.