Results of a Pilot Trial Comparing Prolonged Intravenous Antibiotics With Sequential Intravenous/Oral Antibiotics for Children With Perforated Appendicitis

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Hypothesis: For children with perforated appendicitis, the use of a prolonged course of intravenous (IV) antibiotics is equivalent to a short course of IV antibiotics followed by sequential conversion to oral (PO) antibiotics.

Design: Prospective, randomized, clinical trial.

Setting: Multicenter study in tertiary children’s hospitals.

Patients: Children (aged 5-18 years) with perforated appendicitis found at laparotomy.

Intervention: Children were randomized after appendectomy either to a 10-day course of a combination of IV ampicillin, gentamicin sulfate, and clindamycin (n=10); or to a short course of a combination of IV ampicillin, gentamicin, and clindamycin, followed by conversion to a combination of PO amoxicillin and clavulanate potassium plus metronidazole (n=16).

Main Outcome Measures: The primary outcome measure was clinical success, which was rated as complete, partial, or failure. Secondary outcome measures included return of oral intake, duration of fever, return of normal white blood cell count, and patient charges. Treatment equivalence was determined using confidence interval analysis.

Results: We found treatment equivalence between the IV and IV/PO groups, with 6 (60%) complete and 4 (40%) partial successes for the 10 patients in the IV group and 15 (94%) complete and 1 (6%) partial successes for the 16 patients in the IV/PO group (P<.05). There was no difference in return of oral intake, duration of fever, or return of normal white blood cell count between the groups. Conversion to oral therapy results in savings of approximately $1500 per case.

Conclusion: There is treatment equivalence between prolonged IV therapy and IV therapy followed by conversion to oral antibiotic therapy in children with perforated appendicitis.

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PERFORATED appendicitis is a common condition in children that results in substantial morbidity and cost. Treatment for perforated appendicitis generally involves appendectomy followed by a course of broad-spectrum antibiotics. Antibiotic therapy, usually administered intravenously (IV), traditionally has involved agents directed at gram-negative and obligate anaerobic bacteria. Common drug regimens for perforated appendicitis in children include triple drug therapy (ampicillin, an aminoglycoside, and an anti-anaerobic agent), cephalosporins, carbapenems, or β-lactam/β-lactamase inhibitors. The optimal antibiotic regimen for perforated appendicitis remains poorly defined. In many surgical infections, recent efforts have been directed to limit the use of IV antibiotics through the early conversion to oral (PO) antibiotics. However, to our knowledge, sequential IV/PO therapy for perforated appendicitis in children has not been studied previously in a comparative clinical trial. In a prospective, randomized, pilot trial of antibiotic therapy in children with perforated appendicitis, we compared a prolonged course of IV antibiotics with a short course of IV antibiotics followed by sequential conversion to oral antibiotics.
PATIENTS AND METHODS

STUDY POPULATION

This prospective, randomized, multicenter pilot trial of antibiotic therapy for children with perforated appendicitis was designed to compare a prolonged course of IV antibiotics with a short course of IV antibiotics followed by sequential conversion to PO antibiotics. The study was opened to all children between the ages of 5 and 18 years who were diagnosed as having perforated appendicitis at laparotomy during a 2-year study period.

Inclusion criteria include children noted at laparotomy to have obvious perforation of the appendix accompanied by the presence of purulence or bacteria in the peritoneum. Exclusion criteria included pregnancy, renal failure, neutropenia, drug allergies, or the preoperative use of antibiotics not on the protocol. For consistency, patients were included in the study only if they had an open appendectomy, skin closure of the wound, and no use of external drains. All patients received preoperative administration of a second-generation cephalosporin before the induction of anesthesia.

At the time of appendectomy, the severity of infection was defined as a mild infection localized to the appendix, the presence of a pelvic abscess, or severe diffuse peritonitis. For comparison between treatment groups, routine operative aerobic and anaerobic cultures of peritoneal fluid were obtained for identification and standardized susceptibility testing of organisms. Susceptibility testing was performed in each hospital's clinical microbiology laboratory. Finally, for comparison between treatment groups, all children had a complete blood cell count performed preoperatively, and at 5 and 10 days after surgery.

RANDOMIZATION PROTOCOL

All eligible patients and families were approached within 24 hours after appendectomy for possible study enrollment. After complete discussion of the protocol, informed consent was obtained according to each institution's human research institutional review board. Patients who declined enrollment (n=20) were treated with standard clinical practice, and were not included in this study analysis.

Patients in this study were assigned to a study arm with use of a computer randomization program (Figure). After study enrollment, each child was assigned at random on an individual basis to 1 of the 2 treatment arms. The first study arm included patients who underwent prolonged IV therapy for the 10-day treatment period (IV group), with ampicillin, 400 mg/kg per day, administered 4 times daily; gentamicin sulfate, 7.5 mg/kg per day, administered 3 times daily; and clindamycin, 40 mg/kg per day, administered 3 times daily. The second study arm included patients who underwent the same IV triple antibiotic therapy until the return of gastrointestinal function (usually 3-5 days), followed by conversion to PO amoxicillin-clavulanate potassium, 40 mg/kg per day [of amoxicillin], administered 3 times daily, and metronidazole, 40 mg/kg per day, administered 3 times daily, for the remainder of the 10-day treatment period (IV/PO group). All patients in this study had return of gastrointestinal function or a

The 2 treatment groups had similar patient demographics and surgical findings (Table 1). During a 2-year period, 26 children were enrolled in this study; 10 were randomized to the IV group, and 16 were randomized to the IV/PO group. Of these 26 patients, all completed the study. Both treatment groups had a similar distribution of severity of infection, specifically, the rates of mild localized infection found at laparotomy and severe infections as demonstrated by severe diffuse peritonitis. Patients in the IV group received a mean±SD of 10.4±1.3 days of treatment, and patients in the IV/PO group received an average of 4.6±1.8 days of IV antibiotic treatment and 10.1±0.5 days of total treatment.

The organisms encountered in the children with perforated appendicitis were comparable between the treatment groups, and included Escherichia coli, streptococci, and assorted gram-negative and anaerobic bacteria (Table 2). There appeared to be no correlation between the microorganisms isolated and the development of treatment complications. In particular, despite a high incidence of Pseudomonas aeruginosa in the peritoneal cultures of both treatment groups, the use of PO antibiotics that are not directed against P aeruginosa does not seem to increase the risk of treatment complications. Of the patients with P aeruginosa in their peritoneal cultures, only 1 of the 6 in the IV/PO group and 2 of the 3 in the IV group had 1 or more complications of treatment.

The most common reasons for complications of infection were the development of wound infections or pro-

[Diagram: Study protocol for a prospective randomized trial of antibiotic treatment for perforated appendicitis. After appendectomy and trial enrollment, children were randomized by a computer to 1 of 2 treatment groups. Children in treatment arm 1 (intravenous [IV] group) received 10 days of IV antibiotic therapy with ampicillin, gentamicin sulfate, and clindamycin. Children in treatment arm 2 (IV/oral [PO] group) received initial therapy with the same 3 IV antibiotics, and then were converted to sequential PO therapy with amoxicillin-clavulanate potassium and metronidazole at the initiation of PO intake. PICC indicates peripherally inserted central catheter.]

antibiotics followed by sequential conversion to PO antibiotics. The success rates between the IV and the IV/PO group were equivalent, with 6 (60%) complete and 4 (40%) partial successes for the 10 patients in the IV group and 15 (94%) complete and 1 (6%) partial successes for the 16 patients in the IV/PO group. There was no difference in time to return of PO intake, duration of fever, or return of normal white blood cell count between the treatment groups.
favorable clinical response within 5 days after surgery. The choice of a treatment basis of a 10-day course of antibioti-
cics is based on a previously published protocol that is used for clinical management at one study institution.

Patients receiving home IV antibiotics underwent placement of a percutaneously placed IV central catheter for the administration of IV antibiotics. Patients in the IV group received postoperative care for clinical management at one study institution.

TREATMENT OUTCOME ANALYSIS

To compare a prolonged course of IV antibiotics with a short course of IV antibiotics followed by sequential conversion to PO antibiotics in children with perforated appendicitis, we measured various treatment outcome criteria, including clinical success, duration of fever, duration of hospitalization, and length of antibiotic therapy. Clinical success was defined as complete success (clearance of infection without any complications), partial success (clearance of infection with ≥1 complication of infection), or failure (no clearance of infection). We defined treatment complications as abscess formation, wound infection, prolonged fe-

londed fevers, and 3 of the 10 children in the IV group and 1 of the 16 children in the IV/PO group required anti-

Table 3

Table 2. Microorganisms Encountered in Patients
With Perforated Appendicitis*

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>IV Group (n = 10)</th>
<th>IV/PO Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Other gram-negative organisms</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>β-Hemolytic streptococi</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data are given as number of patients. The microorganisms were identified from cultures of peritoneal fluid by routine aerobic and anaerobic techniques. The intravenous (IV) group was treated with prolonged IV therapy, and the IV/oral (PO) group was treated with IV therapy followed by conversion to PO antibiotic therapy. The specific drugs administered are described in the “Randomization Protocol” subsection of the “Patients and Methods” section.

Perforated appendicitis results in substantial morbidity and cost. Treatment for perforated appendicitis in-
cludes operative therapy followed by broad-spectrum anti-

microbial therapy directed against gram-negative and anaerobic organisms. Throughout the United States and Canada, many antibiotic regimens are used, including triple agents (ampicillin, an aminoglycoside, and an an-
tianerobic agent), cephalosporins, carbapenems, or β-lac-

CHARGE ANALYSIS

To compare patient charges between the treatment groups, we calculated the difference in patient charges for postop-
erative care. The patient charges for postoperative care be-
tween the 2 treatment groups were equivalent up to the time of hospital discharge. The difference in patient charges af-
after hospital discharge was compared between the 2 treat-
ment groups based on medication and administration charges of $250 per day for IV triple antibiotics for each child in the IV group and medication charges of $22 per day for PO antibiotics for each child in the IV/PO group. We also calculated patient charges based on the placement of the peripherally inserted central catheter line of $250 for each child in the IV group. These charges were equivalent between the participating institutions, and all patients discharged from the hospital with home IV anti-

biotics received home health care services.

Table 1. Comparison of Treatment Groups by Demographic Characteristics and Surgical Findings*

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV Group (n = 10)</th>
<th>IV/PO Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-male ratio</td>
<td>4.6</td>
<td>5.11</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>12.5 ± 3.7</td>
<td>11.9 ± 3.9</td>
</tr>
<tr>
<td>Surgical findings, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized infection</td>
<td>8 (80)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Pelvic abscess</td>
<td>1 (10)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Diffuse peritonitis</td>
<td>1 (10)</td>
<td>3 (19)</td>
</tr>
</tbody>
</table>

*The intravenous (IV) group was treated with prolonged IV therapy, and the IV/oral (PO) group was treated with IV therapy followed by conversion to PO antibiotic therapy. The specific drugs administered are described in the “Randomization Protocol” subsection of the “Patients and Methods” section.
tam/β-lactamase inhibitors. Various protocols are followed regarding the length of antibiotic therapy, and range from a defined short course of antibiotics, to tailoring the IV or PO antibiotic course to clinical response, or to a defined prolonged course of broad-spectrum IV antibiotics. Despite the extensive literature on perforated appendicitis, the optimal antibiotic therapy remains poorly defined.

Recent interest in surgical infections has led to efforts to limit the use of IV antibiotic therapy through early conversion to PO antibiotic therapy for certain infections. The conversion from IV to PO antibiotics can limit hospital costs, minimize unnecessary treatment, and ease patient care. However, to our knowledge, sequential IV/PO therapy for perforated appendicitis in children has not been studied previously in a comparative clinical trial. In this prospective, randomized, multicenter pilot trial of antibiotic therapy for children with perforated appendicitis, we found treatment equivalence between a prolonged course of IV antibiotics and a short course of IV antibiotics followed by sequential conversion to PO antibiotics.

The 2 PO agents used in this study, amoxicillin-clavulanate and metronidazole, were chosen because they are used commonly in children, are directed against the organisms commonly encountered in patients with perforated appendicitis, and have well-studied pharmacokinetics. Amoxicillin-clavulanate has activity against gram-negative facultative and anaerobic organisms, is absorbed well from the gastrointestinal tract, has a large volume of distribution, and penetrates into the peritoneum. Metronidazole is an anaerobic agent that is well absorbed when taken orally, penetrates into the peritoneum, and is frequently used for colonic surgery. Oral metronidazole has been shown in children with nonperforated appendicitis to achieve bactericidal plasma levels and reduce infectious complications.

Previous studies have examined the use of PO antibiotics in patients with perforated appendicitis. In children with perforated appendicitis, the conversion of IV ampicillin-sulbactam to PO amoxicillin-clavulanate was compared with the conversion of a combination of IV benzopenicillin, netilmicin sulfate, and metronidazole to PO metronidazole, with the findings of no clinical difference between the treatment groups. Banani and Talei examined the use of PO metronidazole in children with perforated appendicitis and found comparable treatment success to a control group receiving broad-spectrum IV antibiotics. Although these studies establish a role for PO antibiotics in patients with perforated appendicitis, the risk of treatment failure or complications from the conversion from IV to PO therapy is not clearly defined. The present study demonstrates that early conversion from IV to PO therapy can be performed without increasing the risk of treatment failure or complications.

The high prevalence of *P. aeruginosa* in peritoneal fluid cultures of children with perforated appendicitis raises several clinical issues. The finding of a 30% rate of *P. aeruginosa* in our series correlates with the finding in previously reported series of children with perforated appendicitis. However, most antibiotic protocols used in North America for perforated appendicitis do not include coverage directed against this organism, suggesting that in most of these patients, *P. aeruginosa* is not a clinically important pathogen. We have shown that the presence of *P. aeruginosa* does not seem to increase the incidence of infectious complications in children receiving PO antibiotics that are not directed against *P. aeruginosa*, and suggest that the presence of *P. aeruginosa* is not a contraindication to the conversion of IV to PO antibiotics.

The main limitation of this study is the low number of children enrolled. The reasons for the low enrollment are numerous, and include the strict inclusion criteria and difficulty gaining parental consent for a random choice of treatment arms. The low enrollment resulting in a relatively low statistical power of the study, which is based on the construction of confidence intervals between the treatment groups. Although we were able to demonstrate treatment equivalence between the treatment arms, a larger study would offer greater statistical power to demonstrate the superiority of one treatment arm. Therefore, we have classified our project as a pilot study, and suggest that future clinical trials in appendicitis therapy be constructed to address the need for large, randomized, clinical trials. This will require a large, multicenter, clinical study group, similar to the style used for the study of cancer protocols in pediatric centers.

Given the range of protocols to treat perforated appendicitis in North America, it may be argued that the use of an empirical 10-day course of antibiotics in both treatment arms examined in this trial may overtreat the underlying infection. The choice of this treatment is based on a previously published protocol that is our practice at one study institution. Although other antibiotic treatment protocols with shorter courses of therapy may report similar rates of success, it is the purpose of our trial to demonstrate in a strict fashion that conversion from IV to PO therapy can be performed without reducing the efficacy of a single well-studied treatment protocol. Future clinical outcome trials should be designed in a fashion to further define the proper course of antibiotic treatment that will maximize efficacy while minimizing unnecessary treatment, ease patient care, and limit treatment costs.

### Table 3. Specific Processes Resulting in Treatment Failure

<table>
<thead>
<tr>
<th>Process</th>
<th>IV Group (n = 10)</th>
<th>IV/PO Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>1 (10)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Persistent fever (temperature, &gt;38.5°C) for &gt;3 d</td>
<td>3 (30)</td>
<td>0</td>
</tr>
<tr>
<td>Persistent bacteremia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Need for additional antibiotics</td>
<td>3 (30)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Surgical reintervention</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. The intravenous (IV) group was treated with prolonged IV therapy, and the IV/oral (PO) group was treated with IV therapy followed by conversion to PO antibiotic therapy. The specific drugs administered are described in the “Randomization Protocol” subsection of the “Patients and Methods” section.*
In summary, in a prospective, randomized, pilot trial of antibiotic therapy in children with perforated appendicitis, we found treatment equivalence between a prolonged course of IV antibiotics and a short course of IV antibiotics followed by sequential conversion to PO antibiotics. This study has demonstrated that the early use of PO antibiotics does not limit the efficacy of IV antibiotics, does not increase the rate of treatment failure or complications, and results in substantial charge savings.

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REFERENCES