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Single daily dosing ceftriaxone and metronidazole vs standard triple antibiotic regimen for perforated appendicitis in children: a prospective randomized trial

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Abstract

Introduction—Appendicitis is the most common emergency condition in children. Historically, a 3-drug regimen consisting of ampicillin, gentamicin, and clindamycin (AGC) has been used postoperatively for perforated appendicitis. A retrospective review at our institution has found single day dosing of ceftriaxone and metronidazole (CM) to be a more simple and cost-effective antibiotic strategy. Therefore, we performed a prospective, randomized trial to compare efficacy and cost-effectiveness of these 2 regimens.

Methods—After internal review board approval (IRB no. 04 12-149), children found to have perforated appendicitis at appendectomy were randomized to either once daily dosing of CM (2 total doses per day) or standard dosing of AGC (11 total doses per day). *Perforation* was defined as an identifiable hole in the appendix. The operative approach (laparoscopic), length of antibiotic use, and criteria for discharge were standardized for the groups. Based on our retrospective analysis using length of postoperative hospitalization as a primary end point, a sample size of 100 patients was calculated for an α of .5 and a power of 0.82.

Results—One hundred patients underwent laparoscopic appendectomy for perforated appendicitis. On presentation, there were no differences in sex distribution, days of symptoms, temperature, or leukocyte count. There was no difference in abscess rate or wound infections between groups. The CM group resulted in significantly less antibiotic charges then the AGC group.

Conclusions—Once daily dosing with the 2-drug regimen (CM) offers a more efficient, cost-effective antibiotic management in children with perforated appendicitis without compromising infection control when compared to a traditional 3-drug regimen.

Keywords

Antibiotic regimen; Perforated appendicitis; Children

Triple antibiotic therapy providing broad-spectrum coverage of gram-positive, gram-negative, and anaerobic bacteria has been the standard treatment of perforated appendicitis

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in children. This therapy usually uses ampicillin, gentamicin, and clindamycin. These medications are individually inexpensive; however, each is administered multiple times per day creating a complex dosing schedule. Gentamicin is an aminoglycoside with known renal and ototoxic side effects that requires the measurement of serum levels. Although this regimen has been safe and reliably effective, contemporary antibiotics allows a large selection of drugs that do not require laboratory monitoring.

We have retrospectively showed that a 2-drug regimen consisting of ceftriaxone (Rocephin, Roche Pharmaceuticals, Nutley, NJ) and metronidazole (Flagyl, Pharmacia Corporation, Chicago, Ill) can be used in a single daily dosing regimen for perforated appendicitis with some clinical benefits including cost [1]. In this study, we used once-a-day dosing for both medications.

To verify the findings of our retrospective review, we conducted a definitive, prospective, randomized trial comparing single daily dosing with ceftriaxone and metronidazole (CM) to a standard triple antibiotic regimen of ampicillin, gentamicin, and clindamycin (AGC).

1. Methods

Approval was obtained from the Children's Mercy Hospital internal review board (IRB) (IRB no. 04 12-149) before enrolling patients in this study. Patients were subsequently enrolled only after obtaining consent from the patient's legal guardian. The consent forms and consent process were carefully evaluated by the IRB on a continual basis.

1.1. Participants

The study population consisted of children with perforated appendicitis. Inclusion criteria required the presence of perforation. *Perforation* was defined as an identifiable hole in the appendix, which was not iatrogenic. In cases where this was not obvious at laparoscopic appendectomy, the extracted specimen was carefully inspected for the presence of hole.

Exclusion criteria included patients with a documented allergy to any of the medications in the trial. Those with an abscess identified by computed tomographic (CT) scan before surgery were not included in the study. These patients were excluded from the study because, at the time of this study, the standard management in our institution for children with perforated appendicitis with abscess was abscess drainage followed by interval laparoscopic appendectomy.

1.2. Interventions

After determination of perforation, patients were randomized to receive either ceftriaxone and metronidazole or triple antibiotic therapy as the postoperative antibiotic regimen. Triple antibiotic therapy consisted of ampicillin, gentamicin, and clindamycin. Resuscitation fluid in all cases was normal saline because of the FDA concerns about the use of lactated Ringers solution in combination with ceftriaxone.

1.3. Sample size

The power calculation was based on the length of hospitalization for patients treated with the 2 different antibiotic regimens in our previously mentioned retrospective study. A sample size of 50 patients in each arm with α of .05 provided a power of 0.82.

1.4. Assignment

An individual unit of randomization was used in an unblocked, nonstratified sequence. Perforation was defined by the surgeon at the time of the operation after which the family

was approached for consent. The randomization sequence was accessed to identify the next allotment after the consent was signed.

1.5. Protocol

Appendectomies were performed by one of the 7 institutional staff surgeons as dictated by the call schedule. Abdominal CT scans were obtained as clinically necessary to make the diagnosis of appendicitis. All of the appendectomies were initiated laparoscopically. Nasogastric tubes were not used after the operation [2].

Postoperative orders were controlled via a standard electronic order set for all operations. All patients received a 5-day course of intravenous antibiotics. A white blood cell count was drawn on postoperative day 5 in all patients. If this was normal, the patient was not febrile and was tolerating a regular diet, they were discharged home without oral antibiotics. If leukocytosis was found, the patient received 2 additional days of antibiotics, and the white blood cell count evaluation is repeated. If the white blood cell count remained elevated, they received another 3 days of antibiotics, and a CT scan was obtained to evaluate for the presence of an abscess. In addition, CT scans were obtained if the patient's clinical condition suggested an abdominal abscess at any time after 7 days. All patients who developed postoperative abscesses were treated with intravenous antibiotics consisting of the CM regimen that allowed for more efficient home administration. Drainage and length of treatment of abscesses were dictated by the individual treating surgeons.

The group allotted to the 2-drug regimen received once-a-day dosing of ceftriaxone (50 mg/ kg) and metronidazole (30 mg/kg). The group randomized to the 3-drug regimen received ampicillin (50 mg/kg per dose) every 6 hours, gentamicin (2.5 mg/kg per dose) every 8 hours, and clindamycin (10 mg/kg per dose) every 6 hours. In this group, serum gentamicin peak and trough levels were drawn after the third dose.

1.6. Data collection

All data were collected prospectively. At the time of presentation, the patient's age, weight, sex, days of symptoms, maximum temperature, and white blood cell count were collected.

Operative variables collected included the operative approach, operative, and all intraoperative complications including conversion to the open approach.

The outcome variables included maximum daily temperatures for each of the first 5 postoperative days, time to initial oral intake, time to regular diet, length of hospitalization, length of antibiotic therapy, total medication charges, antibiotic charges, abscess rate, wound infection rate, and any abnormal findings during the postoperative or follow-up visits.

1.7. Statistical analysis

Continuous variables were compared using an independent sample, 2-tailed Student's *t* test. Discrete variables were analyzed with Fisher's Exact test with Yates correction where appropriate. Significance was defined as *P* value ≤ .05. Descriptive statistics were calculated as mean ± SD.

2. Results

From April 2005 to November 2006, 100 patients were enrolled in the study. Two patients were dropped from the study. One was because of surgical failure because of a retained fecalith not removed at the initial operation. The other was because of an urgent family need

to transfer the patient to a facility closer to their home before the postoperative course was complete.

2.1. Demographics

The mean maximum temperature was 37.8°C in both groups. The mean duration of symptoms at presentation was 3.2 ± 2.2 days in the CM group compared to 3.0 ± 1.9 days in the AGC group ($P = .70$). The sex distribution was 57% male in the CM group compared to 65% in the AGC group ($P = .60$). Mean age in years was 9.9 ± 4.0 in the CM group compared to 7.3 ± 4.2 in the AGC group ($P = .02$). Mean weight in kilograms was 39.0 ± 22.2 in the CM group compared to 29.9 ± 20.1 in the AGC group ($P = .04$). Thus, the CM patient's were slightly older and, subsequently, heavier because of a few outliers, which did reach statistical significance.

2.2. Operation

There was no difference in operating time between the groups (Table 1). One patient in the CM group had an ileal injury with circumferential deserosalization, which was managed conservatively. This patient recovered well from the operation but subsequently was readmitted with partial bowel obstruction also managed conservatively. A single patient required conversion from the laparoscopic approach to an open procedure, and he was in the AGC group.

2.3. Outcome

No difference existed in time to full oral intake, the length of the postoperative hospitalization, or abscess rate between the 2 groups (Table 1). There was no difference in the fever curves for the first 5 postoperative days between the 2 groups (Fig. 1). One patient in the AGC group developed a wound infection compared to no wound infections in the CM group. Significantly higher antibiotic charges were incurred by the AGC group (Table 2).

In patients who developed an abscess, those in the CM group received an additional 11.7 ± 7.0 days of intravenous antibiotics and 2 patients received an additional 10 days of oral antibiotics without additional intravenous therapy. Those abscess patients from the AGC group received an additional 14.1 ± 4.3 days of intravenous antibiotics, 1 patient received another 10 days of oral antibiotics, and 2 patients took oral antibiotics for 7 days. The difference in days of additional intravenous therapy was not significant ($P = .4$).

In the AGC group, no clinically useful gentamicin levels were available in 8 patients because of error or inadequate specimen collection. The recorded gentamicin serum levels were persistently below the therapeutic window in an additional 10 patients. Therefore, only 31 patients (63%) receiving gentamicin ever achieved therapeutic level. Of these, only 17 patients (35%) were found to have a therapeutic level from the outset, whereas the remainder spent a portion of their hospital stay below the therapeutic level. Regarding serum analysis, a mean of 3 draws per patient was required for monitoring. This resulted in a mean charge of $482 per patient for gentamicin tests.

3. Discussion

Triple antibiotic therapy for perforated appendicitis is still common practice in pediatric surgery despite several reports of simpler antibiotic regimens [3–5]. Monotherapy with newer broad-spectrum agents such as piperacillin/tazobactam for intraabdominal infections has recently been shown to be equally efficacious as traditional triple therapy [3,4]. Similarly, cefotaxime, a cephalosporin with a similar profile to ceftriaxone, has been shown to be equal to the aforementioned monotherapy schedule of piperacillin/tazobactam in

children with complicated perforated appendicitis when combined with metronidazole [5]. Monotherapy seems more advantageous than a dual regimen. However, the expenses of most of the newer broad-spectrum medications are increased by 1 or 2 levels of magnitude over the medications in this trial. Perhaps overlooked and most important, independent of health care cost, the charges to the patient are inseparably linked to dosing schedule. This impact of decreased dosing on antibiotic expenses has been emphasized by several authors [6–11]. In particular, a dramatic decrease in expense has been shown with once daily dosing of ceftriaxone compared to broad-spectrum monotherapeutic agents in the penicillin and cephalosporin families in several studies [6,9–16].

It has been shown that ceftriaxone and metronidazole provide comprehensive coverage for most enteric organisms in prophylactic studies as well as traumatic and surgical contamination studies [6,17–23]. However, the novel contribution of the regimen used in our study is the institution of once-a-day dosing of metronidazole. Previously, once daily dosing of ceftriaxone and metronidazole has been shown to be superior to ampicillin, netilmicin, and metronidazole for the treatment of bacterial peritonitis in a prospective, controlled clinical trial in adults [21].

On the basis of this evidence, we began using a once-a-day dosing schedule of ceftriaxone and metronidazole nearly 4 years ago. We retrospectively reviewed our experience of once daily dosing of metronidazole and found it to be more cost-effective than triple antibiotic therapy [1]. In addition, we identified a shorter length of hospitalization and more rapid defervescence with the CM regimen. However, several flaws mandated this study to be verified by a prospective, randomized trial. First, that study was retrospective with most comparison group not occurring concurrently, thus creating a historical comparison. In addition, during the time frame of the current study, there has been a general trend to get patients home sooner, which may have contributed to a shorter length of hospitalization that was not found in our prospective trial. Second, far more operations in the retrospective CM group were done laparoscopically. This is the likely reason we identified different temperature curves in the retrospective series but not in this prospective trial.

Regarding charges, we used calculated charges in the retrospective comparison to compensate for the historical, nonconcurrent comparison of the 2 groups. We found the CM regimen to be significantly more cost-effective. In this prospective trial, we used actual billing charges to the patient. These billing numbers confirm the retrospective experience that charges for intravenous antibiotics during the hospital stay were significantly less for the CM regimen. The additional antibiotic charges for the patients who developed an abscess were, on average, $8000 less in the CM group. This did not reach significance because of the small number of patients with an abscess and the wide variation of charges per individual case as reflected by the large SD. There may be a suggestion from these data that abscesses were more virulent in the AGC group because both groups were treated with the same antibiotics. However, the mean time of additional intravenous antibiotics for abscess treatment was only 3 days less in the CM group, which did not reach significance.

In this study, we had a slightly older and heavier patient population in the CM group. This is an unusual but possible event in a prospective randomized trial even when the randomization process was strictly followed with no mistakes in the order. This difference in weight (39 vs 29 kg) or age (9 vs 7 years), was statistically significant, but only a few very heavy teenagers in the CM group account for this difference. This patient base has a theoretically increased risk of postoperative abscess because of obesity. Indeed, 4 of the 6 patients in the CM group more than 70 kg did develop an abscess. In spite of this finding, the overall data were in favor of the CM group.

It is important to understand the difficulty establishing therapeutic levels of gentamicin. In this study, we had a prospective protocol in place, a standard computerized order set, a surgical floor with nurses experienced in managing these patients and medications, and a research coordinator that followed the database daily. Despite these strengths, only one third of the patients had therapeutic levels of gentamicin throughout the antibiotic course. From our experience, we can only assume that most patients receiving gentamicin treatment as part of the antibiotic regimen for perforated appendicitis around the world are not uniformly receiving adequate therapy. This finding in our study may also be interpreted as a suggestion that gram-negative coverage is not the critical component of this regimen, given infectious complications were not higher in this group despite the inadequate gentamicin levels.

Any comparative antibiotic trial should not only offer its current findings but at least contemplate the possibility of microbial resistance changing the efficacy of the regimen with time. There are no published data regarding the propensity of microbial resistance between the 2 regimens compared in this trial. However, neither combination holds a great deal of double coverage for individual strains. Therefore, the expected resistance rates should not differ discernibly.

We conclude that once daily dosing of both ceftriaxone and metronidazole is equal to standard triple antibiotic therapy for infection control in the treatment of perforated appendicitis in children. However, the 2-drug regimen is more cost-effective and easier for patients and caregivers. Until a more superior regimen is identified, we recommend that single day dosing of ceftriaxone and metronidazole be used in all patients with perforated appendicitis.

Acknowledgments

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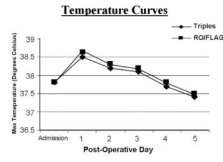
Fig. 1.
Maximum recorded temperature for the 2 groups on admission and each of the first 5 postoperative days.

Table 1

Clinical outcomes

	CM (n = 49)	AGC (n = 49)	P
Mean operating time (min-s)	40:56 ± 17:33	48:28 ± 25:29	.09
Mean time to regular diet (h-min)	75:56 ± 47:40	78:03 ± 39:27	.82
Mean length of stay after operation (h-min)	154:50 ± 68:56	151:59 ± 81.01	.85
Postoperative abscess (%)	20	16	.60
Wound infection (%)	0	2	.99

Table 2

Financial comparison

	CM (n = 49)	AGC (n = 49)	*P*
Inhospital intravenous antibiotic charges ($)	1413 ± 782	1940 ± 633	<.001
Abscess intravenous antibiotic charges ($)	9224 ± 8424	17,308 ± 11,697	.10
Mean % of medication charge for antibiotics	4.5	6.1	<.001