CLINICAL INVESTIGATION

Once Daily Dosing of Ceftriaxone and Metronidazole in Children With Perforated Appendicitis

Ji Yeon Lee, PharmD,¹ Saudia Ally, PharmD,² Brian Kelly, PharmD,³ David Kays, MD,⁴ and Lisa Thames, PharmD³

¹Department of Pharmacy, Texas Children's Hospital, Houston, Texas; ²University of Florida College of Pharmacy, Gainesville, Florida; ³Department of Pharmacy, University of Florida Health Shands Hospital; ⁴Department of Pediatric Surgery, University of Florida Health Shands Hospital, Gainesville, Florida

OBJECTIVES: The aim of this study was to compare hospital length of stay and rate of infectious complications in children with perforated appendicitis based on the postoperative antibiotic administered.

METHODS: This study was a retrospective analysis of children with perforated appendicitis who underwent an appendectomy at a large academic medical center from 2008 to 2013. The primary outcome was hospital length of stay. The secondary outcomes were rates of abscess formation, wound infection, and 30-day readmissions.

RESULTS: One hundred and twenty-three patients were included. Sixty-six patients (53%) were administered ceftriaxone and metronidazole once daily; 57 (47%) were administered other antibiotic regimens, which consisted of single, double, or triple antibiotic therapy with a beta-lactam backbone. There was no difference between the groups in terms of postoperative length of stay (5.7 versus 5.8 days, $p = 0.83$), postoperative abscess rate (8% versus 4%, $p = 0.57$), postoperative wound infection rate (5% versus 2%, $p = 0.73$), and 30-day readmissions (3% versus 11%, $p = 0.19$).

CONCLUSIONS: While there was no statistically significant difference in the outcomes evaluated, the rate of infectious complications was twofold higher in those given ceftriaxone and metronidazole than in others. A larger prospective randomized controlled trial is warranted to better understand the risks of using these agents.

INDEX TERMS: antibiotics, appendectomy, ceftriaxone, metronidazole, pediatrics, perforated appendicitis

J Pediatr Pharmacol Ther 2016;21(2):140–145

INTRODUCTION

Appendicitis is the most common surgical emergency in the pediatric population, accounting for 320,000 appendectomies annually.¹ Studies suggest that antibiotics are not necessary after surgery in patients with non-perforated appendicitis as a result of the low risk of infection and abscess formation.² In contrast, patients with perforated appendicitis require intravenous antibiotics postoperatively to prevent these complications.²

In 2010, the American Pediatric Surgical Association recommended single or double agent antibiotic regimens based on studies showing comparable efficacy and lower cost compared to triple agent therapies.² One study³ cited to support this recommendation included a unique

regimen, ceftriaxone and metronidazole, both dosed once daily. This prospective, single-center trial randomized 98 children with perforated appendicitis to ceftriaxone and metronidazole once daily or to ampicillin, gentamicin, and clindamycin postoperatively. There was no difference in abscess rate (20% versus 16%, $p = 0.6$, respectively) or wound infections (0% versus 2%, $p = 0.99$) between the groups. The ceftriaxone and metronidazole group resulted in a cost savings of \$527 with regard to in-hospital intravenous antibiotic charges ($p < 0.001$).

Based on this evidence, we adopted the once daily ceftriaxone and metronidazole regimen at our institution for children with perforated appendicitis, given the simplicity of the regimen, which facilitated earlier discharge, as patients would receive 24 hours of antimicrobial coverage

Table 1. Antibiotic Regimens

Definition	Regimens Included
Ceftriaxone and metronidazole	Ceftriaxone plus metronidazole once daily Ceftriaxone plus metronidazole TID-QID
Other antibiotic regimens	Imipenem
Beta-lactam single therapy	Piperacillin-tazobactam Ticarcillin-clavulanate
Beta-lactam double therapy	Piperacillin-tazobactam plus metronidazole TID-QID Piperacillin-tazobactam plus clindamycin Ticarcillin-clavulanate plus metronidazole TID-QID Ticarcillin-clavulanate plus clindamycin
Beta-lactam triple therapy	Ampicillin plus gentamicin plus metronidazole TID-QID
Miscellaneous	Ciprofloxacin plus metronidazole TID-QID Gentamicin plus metronidazole TID-QID

QID, 4 times daily; TID, 3 times daily

with one administration. In the current study, we evaluated the efficacy of this antibiotic regimen in comparison to other antibiotic therapies in this population at our institution.

MATERIALS AND METHODS

A retrospective review of patients less than 18 years of age with perforated appendicitis was conducted. Patients were identified using procedure codes for appendectomy (470.0, 470.1, 470.9, 471.1, or 471.9) and concomitant ICD-9 codes for appendicitis (540.0, 540.0, or 540.9). Procedures executed at the University of Florida Health Shands Hospital from January 2008 to July 2013 were included. Patients were excluded if diagnosed with non-perforated appendicitis or treated with a prolonged course of antibiotics prior to surgery (i.e., underwent an interval appendectomy). Patients were also excluded if diagnosed with a condition (e.g., leukemia on chemotherapy) or infection (e.g., shunt infection) not related to the appendectomy that might influence antibiotic selection and duration. Additionally, patients were excluded if documentation was inadequate.

A group of patients treated with ceftriaxone and metronidazole was compared with a cohort of patients treated with other antibiotic regimens. Patients were given ceftriaxone (50 mg/kg/day up to 2000 mg/dose) every 24 hours and metronidazole (30 mg/kg/day up to 1000 mg/dose) divided every 6, 8, or 24 hours. Patients receiving other antibiotic (Table 1) were dosed using recommendations for intra-abdominal infections,

as outlined in standard pediatric drug references.

Baseline characteristics were obtained at admission and included age, sex, weight, leukocyte count, and maximum temperature. Operative details were collected, including operative approach and administration of preoperative antibiotic treatment. The postoperative duration of intravenous antibiotics was calculated based on duration of activity (i.e., 1 dose of an antibiotic dosed every 6 hours would result in 0.25 day of therapy; every 8 hours in 0.33 day of therapy; every 24 hours in 1.00 day of therapy). Postdischarge antibiotic treatments and readmissions that occurred within 30 days of discharge to our institution were reported. Intraoperative cultures, susceptibility of the pathogens in patients, and postoperative antibiotic were assessed in those who developed an abscess.

The primary outcome variable was the postoperative length of stay. It was anticipated that patients receiving the once daily ceftriaxone and metronidazole would have a shorter postoperative hospital stay as patients could receive 24 hours of antimicrobial coverage with a single dose of each agent. The secondary outcomes were total length of intravenous antibiotic treatment, rate of wound infection, and abscess formation.

Continuous variables were compared using an independent sample, 2-tailed Student's *t*-test. Binary outcomes were compared using exact logistic regression. The statistical analysis was performed using SAS software (Durham, NC). Significance was defined as $p \leq 0.05$. Descriptive statistics were reported as mean $\pm$ standard deviation.

Table 2. Patient Demographics

Demographics	Ceftriaxone and Metronidazole (n = 66)	Other Antibiotic Regimens* (n = 57)	p-Value
Age, yr†	9.0 ± 3.9	9.8 ± 4.3	0.27
Weight, kg†	41.1 ± 22.1	42. ± 20.6	0.73
Male, No.	48 (73%)	43 (74%)	0.73
Maximum temperature (°C) on admission†	38.5 ± 0.88	38.2 ± 0.89	0.07
Leukocyte count on admission (10 ³ leukocytes)†	18.9‡	17.4§	—

* See Table 1

† mean ± SD

‡ Data analyzed for 62 patients

§ Data analyzed for 53 patients

RESULTS

From January 2008 to July 2013, 756 patients under 18 years of age underwent an appendectomy for appendicitis. Of these, 531 (70.2%) had non-perforated appendicitis. Of the 225 patients with perforated appendicitis, 52 were excluded as a result of pretreatment with antibiotics and 50 for other exclusion criteria. A total of 123 patients met our inclusion criteria and were evaluated.

There was no difference between the 2 groups in terms of age, weight, sex, leukocyte count, or maximum temperature on admission (Table 2). The majority of patients given ceftriaxone and metronidazole (97%) or other antibiotics (88%) underwent laparoscopic surgery, and all 123 patients received intraoperative antibiotics prior to incision. Intraoperative antibiotics may have differed from the postoperative regimen.

Postoperatively, 66 (53%) patients were administered ceftriaxone and metronidazole. Of these patients, 53 and 13 patients were administered metronidazole divided every 24 hours and every 6 or 8 hours, respectively. Fifty-seven (47%) patients received other antibiotics. Of these patients, 26 were administered beta-lactam alone, 26 received double therapy with beta-lactam, and 3 were given triple beta-lactam therapy. Two patients with documented allergies to beta-lactams received miscellaneous therapies.

Postoperative duration of intravenous antibiotic treatment (Table 3) was not different between the groups (6 versus 5.9 days, $p = 0.96$). Approximately two-thirds of the patients were discharged on an oral antibiotic, which they received for a mean duration of 7 days. When including both intravenous and oral antibiotic

therapies, there was no difference between the 2 groups in duration of total antibiotic treatment (10.7 versus 9.9 days, $p = 0.83$).

There was no statistically significant difference between the ceftriaxone and metronidazole and other antibiotic group in terms of postoperative length of stay (5.7 versus 5.8 days, $p = 0.83$), postoperative abscess rate (8% versus 4%, $p = 0.57$), postoperative wound infection (5% versus 2%, $p = 0.73$), and 30-day readmissions (3% versus 11%, $p = 0.19$) (Table 4). While the difference in infectious complications between the 2 groups was not statistically significant, the twofold greater risk in the ceftriaxone and metronidazole group may be worth reexamining in future clinical trials; the trend toward increased 30-day readmissions in those receiving other antibiotics should be examined as well. An evaluation of intraoperative culture results in patients who developed an abscess did not suggest inadequate susceptibility as the cause as the pathogens were sensitive to the postoperative antibiotic administered.

DISCUSSION

To date, the studies³⁻⁵ reporting the use of once daily ceftriaxone and metronidazole in children with perforated appendicitis originated from a single center. The abscess rates reported in these studies were significantly higher (9%-20%), bringing into question the external validity of these studies. In light of this observation, we devised our current study to better understand outcomes with this regimen at our institution.

The baseline characteristics of our patient population and the outcomes observed were similar to those reported in the literature.³⁻⁸ While the

Table 3. Intervention Details

Intervention	Ceftriaxone and Metronidazole (n = 66)	Other Antibiotic Regimens* (n = 57)	p-Value
Laparoscopic surgery, No.	64 (97%)	50 (88%)	0.10
Administered intraoperative antibiotic treatment, No.	66 (100%)	57 (100%)	1.00
Postoperative duration of intravenous antibiotic treatment (days)†	6.0 ± 3.1	5.9 ± 2.4	0.96
Discharged on oral antibiotic treatment, No.	45 (68%)	33 (58%)	0.24
Duration of oral antibiotic treatment (days)†	7.0 ± 3.6‡	7.0 ± 3.5§	—
Total duration of intravenous and oral antibiotic (days)†	10.7 ± 5.0	9.9 ± 5.3	0.83

* See Table 1

† mean ± SD

‡ Data analyzed for 45 patients

§ Data analyzed for 33 patients

difference in infectious complications between the 2 groups was not statistically significant, the twofold greater risk in those receiving ceftriaxone and metronidazole was concerning.

One possible source for this difference may be inadequate antimicrobial coverage. The most apparent deficiency in Gram-negative coverage with ceftriaxone and metronidazole is *Pseudomonas aeruginosa*, as neither agent has intrinsic activity against this pathogen. While clinical practice guidelines do not recommend coverage for this organism in patients undergoing appendectomy for uncomplicated appendicitis and other intra-abdominal surgeries, it is worth noting that *P aeruginosa* is a commonly isolated pathogen from peritoneal cultures obtained from this population.⁹⁻¹² An analysis⁹ of 296 intraoperative cultures in children with perforated appendicitis reported *P aeruginosa* as one of the top 3 isolated organisms found in 23% of cultures.

In our study, intraoperative cultures in those who developed an abscess did not suggest inadequate susceptibility as the pathogens were sensitive to the postoperative antibiotic administered. The usefulness of intraoperative cultures is debatable, as studies^{9,10} report a discordance between outcomes and antibiotic therapy tailored to these culture results. It is unclear if empiric coverage of *P aeruginosa* is necessary in this population based on the current practice guidelines and literature. One may postulate that in the setting of perforation, bacteria isolated from peritoneal fluid intraoperatively have the potential to be a causative organism for postoperative

infectious complications.

In surveys,^{6,7,13} many institutions report use of broad-spectrum agents with anti-pseudomonal properties (e.g., piperacillin-tazobactam) in children with perforated appendicitis. In our study, no patients on piperacillin-tazobactam monotherapy had an abscess. Studies published in the literature and our current study support the use of monotherapy with an anti-pseudomonal beta-lactam for this specific indication. Institutions should use their local antibiogram to determine the best postoperative antibiotic therapy.

Another possible cause for the increase in postoperative infectious complications in those given ceftriaxone and metronidazole may be the metronidazole dosing regimen. There is limited evidence supporting the efficacy of once daily dosing of metronidazole, as the majority of studies use traditional dosing (i.e., 3 to 4 times daily) for most infectious indications. However, *in vitro* data suggest that metronidazole administered in a pulse-dosing fashion achieves high activity against both susceptible and resistant strains of *Bacteroides fragilis*.¹⁴ Unfortunately, we were unable to conduct a meaningful subset analysis of those patients who received metronidazole divided every 24 hours versus those divided every 6 to 8 hours because of the low number of patients receiving the latter regimen in our study, a limitation of our findings.

In our study, the cost associated with each regimen was not assessed. The literature suggests a decrease in cost with a decrease in dosing frequency, specifically with once daily ceftriaxone

Table 4. Outcomes

Outcomes	Ceftriaxone and Metronidazole (n = 66)	Other Antibiotic Regimens* (n = 57)	p-Value
Postoperative length of stay (days)†	5.7 ± 2.96	5.8 ± 2.46	0.83
Postoperative abscess rate, No.	5 (8%)	2 (4%)	0.57
Postoperative wound infection rate, No.	3 (5%)	1 (2%)	0.73
Complication requiring readmission, No.	2 (3%)	6 (11%)	0.19

* See Table 1

† mean ± SD

compared to other more frequently administered regimens.³ Each institution should review contract prices and dispensing and administration billing practices to better understand the cost implications of each regimen.

Lastly, the threefold increase in 30-day readmission rate in those receiving other non-ceftriaxone and metronidazole antibiotics may be worth examining in future clinical trials.

While there are plausible reasons for the difference in complications observed in our patients, there are many limitations that compromise the applicability of our study. There were only 123 patients included, with a small group developing an abscess (n = 6). The twofold higher abscess rate observed in those given ceftriaxone and metronidazole may have been found by chance. A power calculation based on a rate of 4% in the control arm (i.e., non-ceftriaxone and metronidazole arm) in abscess rate suggested 350 patients would be needed in each arm, with an α of 0.05 and power of 0.8. Additionally, the retrospective nature of this study relied on each surgeon's assessment and classification of a patient as having perforated appendicitis and documentation of complications. Other confounding variables including surgical sterilization practices may have influenced the outcomes observed.

CONCLUSION

There were no statistically significant differences in the outcomes evaluated. A prospective, randomized, controlled trial is warranted to better understand the benefits and risks of this regimen, including the rate of infectious complications such as abscess formation.

Disclosure The authors declare they have no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Correspondence Ji Yeon Lee, PharmD, Department of Pharmacy, Texas Children's Hospital, 6621 Fannin Street, WB1-120, Houston, TX 77030, email: jylee@texaschildrens.org

REFERENCES

1. Muehlstedt SG, Pham TQ, Schmeling DJ. The management of pediatric appendicitis: a survey of North American pediatric surgeons. *Pediatr Surg.* 2004;39(6):875-879.
2. Lee SL, Islam S, Cassidy LD, et al. Antibiotics and appendicitis in the pediatric population: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. *J Pediatr Surg.* 2010;45(11):2181-2185.
3. St Peter SD, Little DC, Calkins CM, et al. A simple and more cost effective antibiotic regimen for perforated appendicitis. *J Pediatr Surg.* 2006;41(5):1020-1024.
4. St Peter SD, Tsao K, Spilde TL, et al. Single daily dosing ceftriaxone and metronidazole vs. standard triple antibiotic regimen for perforated appendicitis in children: a prospective randomized trial. *J Pediatr Surg.* 2008;43(6):981-985.
5. Fraser JD, Aguayo P, Leys CM, et al. A complete course of intravenous antibiotics vs. a combination of intravenous and oral antibiotics for perforated appendicitis in children: a prospective, randomized trial. *J Pediatr Surg.* 2010;45(11):1198-1202.
6. Fishmann SJ, Pelosi L, Klavon SL, et al. Perforated appendicitis: prospective outcome analysis for 150 children. *J Pediatr Surg.* 2000;35(6):923-926.

7. Nadler EP, Reblock KK, Ford HR, et al. Monotherapy versus multi-drug therapy for the treatment of perforated appendicitis in children. *Surg Infect.* 2003;4(4):327-333.
8. Adibe OO, Barnaby K, Dobies J, et al. Post-operative antibiotic therapy for children with perforated appendicitis: long course of intravenous antibiotics versus early conversion to an oral regimen. *Am J Surg.* 2008;195(2):141-143.
9. Kokoska ER, Silen ML, Tracy TF, et al. The impact of intraoperative culture on treatment and outcome in children with perforated appendicitis. *J Pediatr Surg.* 1999;34(5):749-753.
10. Mosdell DM, Moris DM, Fry DE. Peritoneal cultures and antibiotic therapy in pediatric perforated appendicitis. *Am J Surg.* 1994;167(3):313-316.
11. Curran TJ, Mueuchow SK. The treatment of complicated appendicitis in children using peritoneal drainage: results from a public hospital. *J Pediatr Surg.* 1993;28(2):204-208.
12. Bratzler DW, Dellinger EP, Olsen KM, et al. American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health-Syst Pharm.* 2013;70(3):195-283.
13. Goldin AB, Sawin RS, Garrison MM, et al. Aminoglycoside-based triple-antibiotic therapy versus monotherapy for children with ruptured appendicitis. *Pediatrics.* 2007;119(5):9059-9111.
14. Ibrahim KH, Gunderson BW, Hermensen ED, et al. Pharmacodynamics of pulse dosing versus standard dosing: in vitro metronidazole activity against *Bacteroides fragilis* and *Bacteroides thetaiotaomicron*. *Antimicrob Agents Chemother.* 2004;48(11):4195-4199.