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Comparative Effectiveness of Ceftriaxone plus Metronidazole versus Anti-Pseudomonal Antibiotics for Perforated Appendicitis in Children

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Abstract

Background: Appendicitis is the most common pediatric surgical emergency and one of the most common indications for antibiotic use in hospitalized children. The antibiotic choice differs widely across children's hospitals, and the optimal regimen for perforated appendicitis remains unclear.
Methods: We conducted a retrospective cohort study comparing initial antibiotic regimens for perforated appendicitis at a large tertiary-care children's hospital. Children hospitalized between January 2011 and March 2015 who underwent surgery for perforated appendicitis were identified by ICD-9 codes with confirmation by chart review. Patients were excluded if they had been admitted ≥48 hours prior to diagnosis, had a history of appendicitis, received inotropic agents, were immunocompromised, or were given an antibiotic regimen other than ceftriaxone plus metronidazole (CTX/MTZ) or an anti-pseudomonal drug (cefepime, piperacillin/tazobactam, ciprofloxacin, imipenem, or meropenem) within the first two days after diagnosis. The primary outcome of interest was post-operative complications, defined as development of an incisional infection or abscess within six weeks of hospital discharge.
Results: Of the 353 children who met the inclusion criteria, 252 (71%) received CTX/MTZ and the others received an anti-pseudomonal regimen. A post-operative complication occurred in 37 (14.7%) of the CTX/MTZ group versus 18 (17.8%) of the anti-pseudomonal group. Antibiotic-related complications occurred in 4.4% of children on CTX/MTZ and 6.9% of children on anti-pseudomonal antibiotics ($p = 0.32$). In a multivariable logistic regression model adjusting for sex, age, ethnicity, and duration of symptoms prior to presentation, the adjusted odds ratio for post-operative complications in children receiving anti-pseudomonal antibiotics was 1.25 (95% confidence interval 0.66–2.40).
Conclusion: Post-operative complication rates did not differ for children treated with CTX/MTZ versus a broader-spectrum regimen.

Keywords: antibiotics; antimicrobial stewardship; appendicitis

Appendicitis is the most common surgical emergency in children, with as many as 35% of patients experiencing complicated appendicitis [1]. Children with perforated appendicitis develop post-operative complications including incisional infections and intra-abdominal abscesses in as many as 14% of cases [1]. Standard of care for these children includes an extended course of antibiotics [2].

Among children treated operatively for perforated appendicitis, antibiotic prescribing practices differ in both the regimen and the duration across pediatric institutions [3,4]. Examining the clinical impact of different antibiotic choices for perforated appendicitis will inform anti-microbial stewardship interventions to optimize clinical outcomes while minimizing exposure to unnecessarily broad-spectrum drugs [5–7].

Significant variability in the choice of antibiotic regimen for the treatment of children with perforated appendicitis has been reported in different children's hospitals [4,8,9]. This variability reflects current guidelines, which offer multiple

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options for empiric antibiotic regimens for perforated appendicitis that cover a wide range of gram-positive, gram-negative, and anaerobic bacteria. Some of these regimens are broader spectrum than others, and some provide coverage against *Pseudomonas aeruginosa* whereas the narrower-spectrum regimens do not [2]. The use of anti-pseudomonal antibiotics is an important practical issue for children with perforated appendicitis. However, it must be remembered that broad-spectrum antibiotic use increases the risk of colonization or future infection with a multi–drug-resistant organism [10–12].

Increasing antibiotic resistance in *P. aeruginosa* has led the Centers for Disease Control and Prevention (CDC) to urge judicious use of anti-pseudomonal antibiotics [12], and highlights the importance of investigating whether anti-pseudomonal coverage truly is necessary for treating perforated appendicitis in children. The need for such treatment has been questioned. Because most patients with appendicitis are previously healthy and without unusual antimicrobial drug exposure, most affected children are not considered at risk for invasive infection with *P. aeruginosa* [13]. Nevertheless, microbiologic evaluation of surgical specimens has isolated *P. aeruginosa* in as many as 15% of patients with perforated appendicitis [14–16]. Examining the clinical impact of different antibiotic choices for perforated appendicitis will inform anti-microbial stewardship interventions designed to optimize clinical outcomes while minimizing exposure to unnecessarily broad-spectrum drugs [5–7].

The objective of this study was to compare the clinical outcomes of children with perforated appendicitis who were treated with ceftriaxone and metronidazole (CTX/MTZ) versus a broader-spectrum, anti-pseudomonal regimen.

Patients and Methods

Study population

We performed a retrospective cohort study at Children's Hospital of Philadelphia (CHOP) enrolling patients <19 years old hospitalized between January 2011 and March 2015 who underwent surgery for perforated appendicitis. Potentially eligible patients were identified from the electronic health record using the ICD-9 CM codes for appendicitis (540, 540.0, 540.1, 540.9, 541, 542, 543.9, 558.9, 646.80, and 787.99) and a length of stay (LOS) greater than one day. We included patients who received either CTX/MTZ or an anti-pseudomonal regimen (cefepime, ceftazidime, piperacillin/tazobactam, ciprofloxacin, imipenem, or meropenem) within the first two days after admission. Because aminoglycosides generally are considered inferior as monotherapy for *P. aeruginosa* infections, aminoglycoside-containing regimens were not included in either group. We also excluded children without a confirmed diagnosis of perforated appendicitis by intra-operative or histopathologic findings (on manual chart review), those who had been admitted for ≥48 hours prior to surgery, those having a history of appendicitis, who received inotropic agents, or who were immunocompromised. We had planned to perform a sensitivity analysis excluding any patients who crossed over between the two treatment groups during the first two days; however, no such patients were enrolled.

Exposures

For our primary analysis, we compared children who received CTX/MTZ with those who received an anti-pseudomonal regimen (cefepime, ceftazidime, piperacillin/tazobactam, ciprofloxacin, imipenem, or meropenem) within the first two days after admission. The general practice for perforated appendicitis at our institution is for antibiotics to be started pre-operatively and continued post-operatively.

Outcomes

The primary outcome of interest was a post-operative complication, defined as development of an incisional infection or abscess within six weeks of discharge from the hospital. The occurrence of such an infection was determined by review of daily physician notes and radiographic study results throughout the hospitalization. An abscess was determined to be present if the radiographic study report included the terms ''abscess,'' ''fluid collection,'' or ''phlegmon.'' Secondary outcomes were LOS (in days, as a continuous variable) and the proportion of patients with antibiotic-related complications, including hypersensitivity reactions, *Clostridium difficile* infection, and thrush.

Data collection

Patient demographic and clinical data were extracted electronically from the electronic health record (EpicCare, Epic Systems, Inc., St. Louis, MO) by two study investigators (DD and ES). For any exposures or outcomes not clearly defined by documentation in the medical chart, the data were adjudicated by two pediatric infectious disease physicians (RFH and LKH). Data abstracted through manual chart review included the presence of co-morbidities, pre-admission antibiotic therapy, laboratory data, surgical/drainage procedures, antibiotics received in hospital (choice, route, and duration of therapy), and primary and secondary outcomes. Data were collected and managed using REDCap electronic data capture tools hosted at CHOP [17]. This study was approved by the Institutional Review Board of CHOP.

Statistical analysis

Descriptive counts and percentiles were provided for patients prescribed CTX/MTZ or an anti-pseudomonal regimen. Univariable logistic regression was conducted between the outcome of a post-operative complication and potential risk factors including sex, age (as a continuous variable), race (as a binary variable: black vs. non-black), ethnicity (as a binary variable: Hispanic vs. non-Hispanic), presence of a chronic medical condition (as a binary variable: any underlying condition vs. none), duration of symptoms prior to diagnosis (categorized as ≤1 day, 2–3 days, or >3 days based on distribution), and initial white blood cell count (categorized as <5, 5–14.9, 15–19.9, or ≥20/mm^3 based on distribution). We constructed a multivariable logistic regression model for the odds of a post-operative complication, adjusting for clinically important variables selected a priori including age, sex, and duration of symptoms prior to presentation, in addition to any additional variables that were noted to be associated with a post-operative complication in univariable analysis at $p < 0.20$ [18]. [18]. Data were analyzed using Stata version 13.1 (StataCorp, College Station, TX).

TABLE 1. BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES BY TREATMENT GROUP

	Total (n = 353)	*Anti-pseudomonal antibiotic[a] within 2 d of diagnosis (n = 101)*	*Ceftriaxone/ metronidazole (n = 252)*
Male sex (%)	222 (62.9)	63 (62.4)	155 (61.5)
Median age (y) (IQR)	9.9 (7.5–13.0)	9.8 (7.8–13.1)	10.0 (7.5–12.9)
Black race (%)	73 (20.0)	19 (18.8)	53 (21)
Hispanic ethnicity (%)	53 (15.0)	21 (20.8)	32 (12.7)
Chronic medical condition (%)	16 (4.5)	5 (5.0)	11 (4.4)
Median duration of symptoms prior to diagnosis (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
Median admission temperature (°) (IQR)	37.6 (37.1–38.3)	37.6 (37–38.3)	37.5 (37.1–38.3)
Median white blood cell count/mm^3 (IQR)	15.3 (11.8–20.4)	15.2 (11.7–20.2)	15.5 (11.9–20.5)
Treatment failure (%)	55 (15.6)	18 (17.8)	37 (14.7)
Incision infection	2 (0.6)	0	2 (0.8)
Abscess, medical management	36 (10.2)	14 (13.9)	22 (8.7)
Abscess, drained	22 (6.2)	7 (6.9)	15 (6.0)
Antibiotic-related complication (%)	25 (7.1)	9 (8.9)	16 (6.4)
Catheter-related complication (%)	5 (1.4)	4 (1.6)	1 (1.0)
Mean length of stay (d) (SD)	6.3 (3.9)	6.0 (4.6)	6.4 (3.5)

[a]Anti-pseudomonal antibiotics were piperacillin/tazobactam (n = 36) or ciprofloxacin (n = 68).
IQR = interquartile range; SD = standard deviation.

Results

Study population

A total of 1,576 children were identified as having appendicitis via ICD-9 codes during the specified time period. Of these, 382 were found to have perforated appendicitis verified by intra-operative or pathologic findings. The following patients were excluded: seven each were hospitalized for >48 hours prior to diagnosis, were immunocompromised, or received inotropic agents; two had a previous diagnosis of appendicitis; and 17 received an initial antibiotic regimen other than CTX/MTZ or an anti-pseudomonal drug. Children

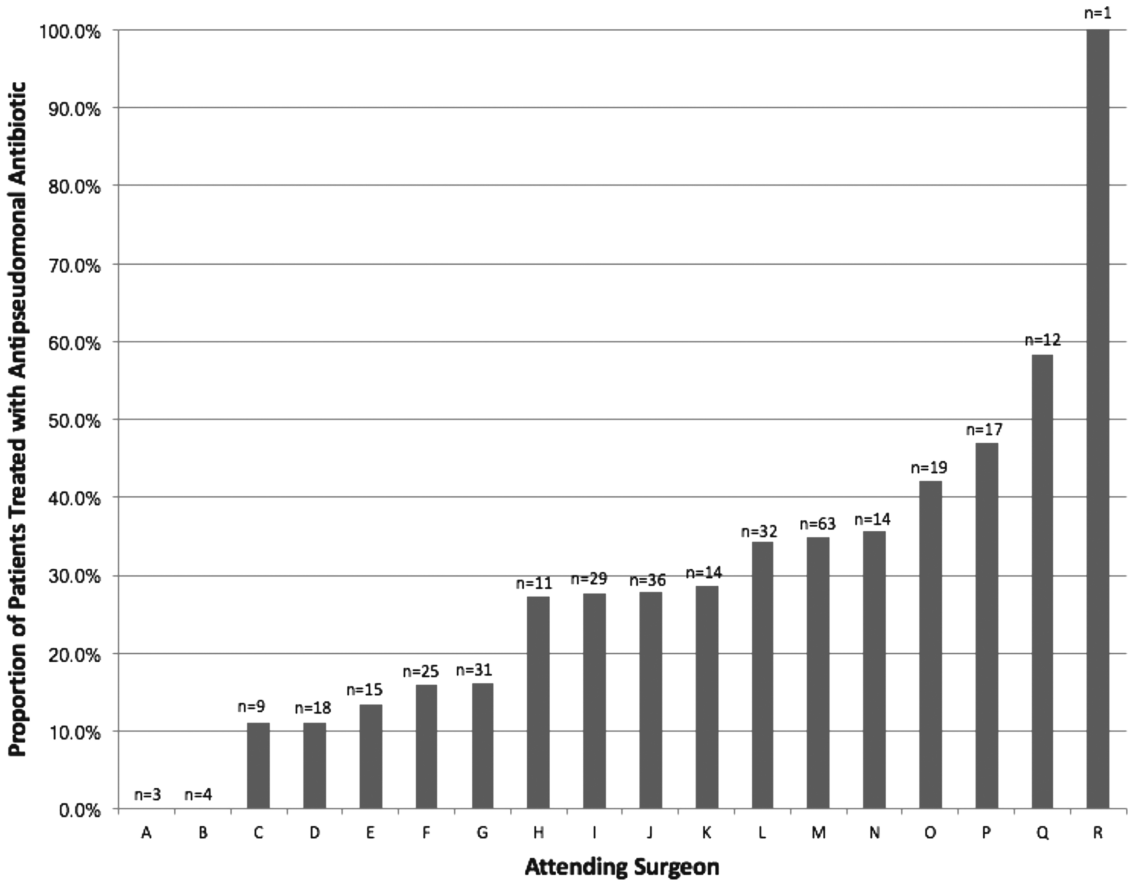

FIG. 1. Proportion of patients treated with anti-pseudomonal antibiotics, by attending surgeon.

may have met more than one exclusion criterion, resulting in a final cohort of 353 children.

Of the accepted children, the median age was 9.9 years (interquartile range [IQR] 7.5–13.0), 222 (62.9%) were male, 73 (20.7%) were black, and 16 (4.5%) had a chronic medical condition. The median duration of symptoms prior to diagnosis was two days (IQR 1–3 days), and the median white blood cell count was 15.3/mm^3 (IQR 11.8–20.4). The baseline characteristics and outcomes are summarized in Table 1. Only 32 patients (9%) had any bacterial culture data available. Of these, 21 were blood cultures, and 11 were intra-operative cultures. All blood cultures were negative, and only one intra-operative culture (obtained by drainage by an interventional radiology procedure) was positive (*Streptococcus anginosis*).

Primary analysis: Antibiotic regimen

A large percentage of patients (252; 71.4%) were treated with an initial regimen of CTX/MTZ, the others receiving anti-pseudomonal drugs. The most common anti-pseudomonal regimen was parenteral ciprofloxacin and metronidazole (68/101; 67.3%) followed by piperacillin/tazobactam (36; 35.6%). A documented beta-lactam allergy was identified in 22 of the 68 children receiving ciprofloxacin (32.3%). Overall, a medication change attributable to treatment failure or an antibiotic-related complication occurred in 53 patients: 35 (13.9%) in the CTX/MTZ group and 18 (17.8%) in the anti-pseudomonal group. Medication changes caused by treatment failure were to a broader-spectrum antibiotic regimen. The proportion of children treated with anti-pseudomonal antibiotics differed for the 18 surgeons from 0 to 100%; among those surgeons who had performed at least 10 appendectomy procedures, the proportion ranged from 11.1% to 58.3% (Fig. 1).

Of the 353 patients, 55 (15.6%) experienced a post-operative complication: 18 (17.8%) in the anti-pseudomonal group and 37 (14.7%) in the CTX/MTZ group. Of those with a post-operative complication, 2 (0.6%) had a wound infection, 36 (10.2%) developed an abscess that was managed medically, and 22 (6.9%) developed an abscess that was drained either surgically or by an interventional radiology technique. Among the 55 patients, 49 had the complication during the initial hospitalization (four of whom also experienced a complication post-discharge), and six suffered a complication post-discharge. Among the 304 children who did not experience a post-operative complication as an inpatient, 46 (15.1%) were discharged on intravenous antibiotics, whereas 258 (84.9%) were transitioned to oral antibiotics at the time of discharge. In univariable analysis, male sex, non-Hispanic ethnicity, and duration of symptoms prior to presentation were associated with a post-operative complication (Table 2).

In a multivariable logistic regression model adjusting for age, sex, ethnicity, and duration of symptoms prior to presentation, the adjusted odds of a post-operative complication with anti-pseudomonal antibiotics was 1.25 (95% confidence interval [CI] 0.66–2.40) compared with treatment with CTX/MTZ (Table 3).

Table 2. Univariable Analyses of Variables Associated with Treatment Failure

	Post-operative complication (%)	*Odds ratio (95% CI)*	p
Age (y)			
≤5	5/ 42 (11.9)	[Ref]	
6–11	31/205 (15.1)	1.32 (0.48 –3.62)	0.59
≥12	19/106 (17.)	1.62 (0.56 –4.65)	0.37
Sex			
Female	14/135 (10.4)	[Ref]	
Male	41/218 (18.8)	2.00 (1.05 –3.83)	0.036
Race			
Non-black	43/281 (15.3)	[Ref]	
Black	12/ 72 (16.7)	1.11 (0.55 –2.23)	0.78
Ethnicity			
Not Hispanic	52/300 (17.3)	[Ref]	
Hispanic	3/ 53 (5.7)	0.29 (0.086–0.95)	0.041
Underlying co-morbidities			
None	54/337 (16.0)	[Ref]	
Yes (any)	1/ 16 (6.3)	0.35 (0.045–2.70)	0.31
Duration of symptoms prior to diagnosis (d)			
≤1	9/ 92 (9.8)	[Ref]	
2–3	33/201 (16.4)	1.81 (0.83 –3.96)	0.14
>3	13/ 60 (21.7)	2.55 (1.01 –6.41)	0.047
Initial white blood cell count/mm^3[a]			
<5	0/ 3		
5–14.9	12/ 66 (18.2)	[Ref]	
15–19.9	5/ 57 (8.8)	0.43 (0.14 –1.31)	0.14
≥20	11/ 61 (18.0)	0.99 (0.40 –2.44)	0.98
Antibiotic regimen			
CTX/MTZ	37/252 (14.7)	[Ref]	
Anti-pseudomonal	18/101 (17.8)	1.26 (0.7 –2.3)	0.46

[a]Includes initial count obtained prior to or on day of surgery.
CI = confidence interval; CTX/MTZ = ceftriaxone plus metronidazole.

Table 3. Multivariate Logistic Regression Analysis for Odds of Post-Operative Complication (N = 353)

	Odds ratio (95% CI)	p
Anti-pseudomonal antibiotic	1.25 (0.66 –2.40)	0.49
Male sex	1.99 (1.02 –3.85)	0.042
Patient age[a]	0.98 (0.90 –1.06)	0.60
Hispanic ethnicity	0.28 (0.081–0.95)	0.041
Duration of symptoms[a]	1.12 (0.95 –1.31)	0.17

[a]Included in the model as a continuous variable.
CI = confidence interval.

Secondary outcomes

Length of stay. A multivariable linear regression model examining LOS as a continuous outcome found no significant difference by treatment group ($\beta = -0.25$; 95% CI −1.36–0.86) adjusting for age, sex, and duration of symptoms prior to diagnosis.

Antibiotic-related complications. A complication associated with the antibiotic occurred in 4.4% of the children on CTX/MTZ and 6.9% of the children on anti-pseudomonal antibiotics ($p = 0.32$). An additional multivariable logistic regression analysis adjusting for age, sex, and duration of symptoms prior to diagnosis found no difference in the odds of antibiotic-related complications between treatment groups (adjusted odds ratio for the anti-pseudomonal group of 1.41; 95% CI 0.60–3.33). No patient in either group developed *C. difficile* infection during the study period.

Discussion

In this retrospective cohort study of children with perforated appendicitis, after adjusting for potential confounders, we found no difference in post-operative complication rates among children treated with an initial regimen of CTX/MTZ compared with those treated with an anti-pseudomonal regimen. The groups also were similar in their LOS and likelihood of antibiotic-related complications.

Clinical practice guidelines released by the Surgical Infection Society and the Infectious Diseases Society of America published in 2010, which were the most recent at the time of this study, recommend treating complicated community-acquired intra-abdominal infections in children with broad-spectrum antimicrobial regimens that target gram-positive, gram-negative, and anaerobic pathogens. These guidelines include several options, such as an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a beta-lactam/beta-lactamase-inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanic acid), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole [19], although without clear evidence supporting any drug or drugs. Because these regimens differ in anti-bacterial spectrum, ease of administration, and cost, evidence for equivalence or superiority would be helpful for clinical decision-making. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection, published in 2017, offer a risk-stratified approach, reserving broader-spectrum antibiotics for higher-risk patients, including those with signs of septic shock, those who have been hospitalized in a healthcare facility for >48 hours in the preceding months, and those having a high Acute Physiology and Chronic Health Evaluation II score [20]. These high-risk factors were exclusion criteria for our study results support the narrower spectrum antibiotics for patients not identified as high risk.

Approximately 13% of the 51,000 healthcare-associated *P. aeruginosa* infections occurring annually in the United States are caused by multi–drug-resistant strains [12]. These alarming statistics have led the CDC to designate resistant *P. aeruginosa* a ''serious threat'' to public health and to urge judicious use of anti-pseudomonal antibiotics in order to slow the development of antibiotic resistance [12]. Studies evaluating the characteristics of organisms isolated in cases of acute appendicitis have identified *P. aeruginosa* in 0–15% of cases [14–16]. Nevertheless, previous studies showed similar outcomes in children treated with either anti-pseudomonal regimens or narrower-spectrum agents [5,6,9,21], and the results of our study confirm these findings. The largest project was a retrospective cohort study of children with appendicitis using administrative data from 23 freestanding children's hospitals comparing outcomes of those who received broader-spectrum antibiotics, including drugs with anti-pseudomonal activity, with those who received narrower-spectrum antibiotics and concluded that extended-spectrum antibiotic exposure offered no advantage [9]. Our study adds to this body of literature by confirming these findings with more granular information, including medication administration and laboratory, individual surgeon, and pathology data for confirmation of the perforated appendicitis diagnosis. This enabled a multivariable analysis adjusting for potentially confounding factors.

Previous studies that have sought to identify risk factors for the development of post-operative complications in children with perforated appendicitis have noted that older age [22], higher weight or body mass index [22], longer duration of symptoms prior to presentation [23], and diarrhea on presentation [22,24] were associated with complications. In the present study, we found that post-operative complications were significantly more common in male and non-Hispanic patients. These associations have not been reported previously in studies that have evaluated risk factors for complications in children with perforated appendicitis [23,24]. Although the difference was not statistically significant, our study did find that, perhaps not surprisingly, complications were more common in patients with a longer duration of symptoms prior to presentation, an association that has been noted in the literature [23].

Our study has several limitations. First, patients may have been more likely to receive broader-spectrum antibiotics because of the severity of their illness. To minimize this, we restricted our cohort to patients without immunocompromised status or hemodynamic instability requiring inotropic support, and we adjusted for potential confounding factors, including the white blood cell count, in our multivariable analysis. The degree of contamination and operative time also are important potentially confounding factors [25,26] that were not adjusted for in our analysis. Second, because we categorized treatment groups by initial antibiotic therapy (given within the first 48 hours after admission), patients may have received alternative regimens after this time; however, this happened in a minority of our patients. We chose this method of categorization a priori because we hypothesized that the initial antibiotic regimen would have a greater impact on outcome and to minimize the risk of confounding by

indication. Third, we did not explore the effect of the duration of antibiotic administration, which in theory could have affected the outcome, although a recent randomized controlled trial evaluating the duration of antibiotics after surgery for intra-abdominal infections showed that the outcomes after approximately four days of therapy were similar to those after approximately eight days [27]. As our study was limited to review of records at our institution, there is a risk that patients who developed a complication after discharge did not present to our institution so the outcome would not have been captured. Finally, this is a single-center study, and the results may not be generalizable, as pathogen distribution differs geographically, and surgical practice varies among centers.

In summary, this study does not support a need for antipseudomonal antibiotics in the treatment of children with perforated appendicitis. Given the frequency of this condition, hospitals should consider these data when determining the optimal antibiotic regimen for children with this condition.

Author Disclosure Statement

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