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Is *Pseudomonas* Infection Associated with Worse Outcomes in Pediatric Perforated Appendicitis?

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Abstract

Background: There is little information on the effects of *Pseudomonas* infection on outcomes in perforated appendicitis. As *Pseudomonas* is not covered by many empiric appendicitis antibiotic regiments, we hypothesized that children with *Pseudomonas* would have worse outcomes.

Methods: Patients <18 years old undergoing appendectomy for perforated appendicitis at a tertiary children's hospital 2015-2019 were included and were stratified by presence of *Pseudomonas* on intraoperative culture. The primary outcome was post-operative organ-space infection (SSI).

Results: Intraoperative cultures were collected in 58.4% of patients (n=149/255) with 22.2% (n=33) positive for *Pseudomonas*. SSIs occurred in 21.2% of children with *Pseudomonas* compared to 20.7% of children without *Pseudomonas* (p=0.9). Children with *Pseudomonas* had longer antibiotic duration (9.1 vs. 6.7 days, p=0.03) and LOS (6.7 vs. 5.9 days, p=0.03) than those without, but a similar rate of post-operative interventions (12.2% vs. 19.0%, p=0.4), hospital costs (\$28,860 vs. \$23,945, p=0.3), ED visits (9.1% vs. 19.9%, p=0.3), and readmissions (9.1% vs. 9.5%, p=1).

Conclusion: *Pseudomonas* was identified in 22% children with perforated appendicitis and was associated with longer antibiotic durations and LOS, but similar rates of SSI, post-operative interventions, and readmissions compared to children without *Pseudomonas*. Empiric coverage of *Pseudomonas* may not be necessary.

Keywords

appendicitis; antibiotic stewardship; Pseudomonas; surgical site infection

Level of Evidence: Level III

Declarations of competing Interest None.

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Type of Study: Retrospective comparative study

Introduction

Appendicitis is the most common indication for acute surgical intervention in the pediatric population. Over one-third of patients present with perforated appendicitis [1]. The most common organism isolated on intraoperative culture in perforated appendicitis is *Escherichia coli*, and most empiric antibiotic regimens cover gram negative and anaerobic organisms [2]. However, *Pseudomonas* has been isolated in up to 29% of intraoperative cultures in children with perforated appendicitis [3-8]. In 2019, the Centers for Disease Control and Prevention (CDC) classified *Pseudomonas spp.* as posing a serious threat of antibiotic resistance [9]. Thus, use of antipseudomonal antibiotics are frequently restricted to use in culture-proven cases of *Pseudomonas*.

Antibiotic regimens which do not cover *Pseudomonas* have been found to have comparable surgical site infection rates to antipseudomonal antibiotic regiments in pediatric perforated appendicitis [10]. At our hospital, ceftriaxone and metronidazole are used for the empiric treatment of perforated appendicitis in children, and intraoperative cultures are collected during appendectomy to guide post-operative antibiotic broadening if indicated. In cases where *Pseudomonas* is identified on culture, antibiotics are broadened to cover the microbe. However, as cultures can take several days to result, there is often a delay in antipseudomonal coverage. The effect of *Pseudomonas* on post-operative outcomes in children with perforated appendicitis is not known. One study has evaluated predictors of post-operative infection, finding that resistant *E. coli*, but not *Pseudomonas*, was significantly associated with post-operative infection, but only four children in this study had *Pseudomonas* [5].

Given that *Pseudomonas* is a common gastrointestinal microbe that is not covered by our empiric antibiotic regimen, we hypothesized that post-operative outcomes of children with *Pseudomonas* identified on intraoperative cultures would be worse than children without *Pseudomonas*.

1. Methods

1.1. Study Design

Local institutional review board approval was obtained. All patients less than 18 years old undergoing laparoscopic or open appendectomy for perforated appendicitis at a tertiary children's hospital between July 2014 and July 2019 were included. Patients were classified as having perforated appendicitis if the operative report signed by the attending pediatric surgeon described the operative findings or post-operative diagnosis as "perforated appendicitis". Patients were excluded if they were 18 years old, had acute non-perforated appendicitis, or were determined intraoperatively to have a diagnosis other than appendicitis. Patients with perforated appendicitis treated non-operatively with antibiotics or percutaneous drain placement without initial appendectomy and patients undergoing interval appendectomy were also excluded.

Information on patient characteristics, lab and imaging results, operative data, whether intra-operative culture was sent, culture results, antibiotics, length of stay, ED visits,

readmissions, and repeat interventions were recorded. The primary outcome investigated was post-operative organ-space surgical site infection (SSI). Secondary outcomes included antibiotic duration, post-operative interventions, length of stay (LOS), costs, emergency department (ED) visits, and readmissions. Patients were stratified based on presence or absence of *Pseudomonas* on intraoperative culture. This included *Pseudomonas aeruginosa* as well as other *Pseudomonas* species as all are treated with antipseudomonal antibiotics.

To identify the primary outcome, post-operative organ space SSI, all post-operative imaging was evaluated for presence of abscess. Progress notes were evaluated for documentation of peri-incisional cellulitis, incisional fluid collections, or need for antibiotics. Any post-operative drain placement or return to the operating room was recorded.

Over the course of this study period, ten pediatric surgeons performed all of the appendectomies. Open or laparoscopic appendectomy was performed in the standard fashion at the discretion of the operating surgeon. Our institutional protocol is to send intraoperative cultures during appendectomy for perforated appendicitis. Patients are started on ceftriaxone and metronidazole upon diagnosis of perforated appendicitis and continue on this regimen after surgery. Culture results are used to guide broadening of the antibiotic regimen if the results indicate a pathogen which is not covered by the empiric antibiotics. Perioperative care is standardized through departmental practice guidelines. Antibiotic duration is generally determined by obtaining a complete blood count (CBC) with differential when the patient is meeting clinical discharge criteria, which include tolerance of oral intake, minimal pain that is controlled by oral pain medications, and ability to ambulate. Patients with leukocytosis or a left shift are discharged with oral antibiotics to complete a 10-day course and those with normal white blood cell (WBC) counts complete a 5-day course.

1.2. Statistical analysis

Descriptive data is presented using median values and interquartile range (IQR) for non-parametric data. Data were compared using chi-square and Fisher's exact test for categorical data and Mann-Whitney-U test for continuous data. Outcomes of children with *Pseudomonas* on intraoperative culture were compared to those without *Pseudomonas*. Values were considered significant at the level of p < 0.05. Analysis was conducted using statistical software (SAS, version 9.45; SAS Institute Inc).

2. Results

2.1. Overall results

We identified 255 children with perforated appendicitis who underwent operative management at our tertiary children's hospital between January 2015 and July 2019. The median age was 8.5 years old (IQR 5.5-11.3) and ranged from 1.2 to 17.6 years old. The majority of patients were male (63.1%). Most patients underwent laparoscopic appendectomy (n = 210, 82.4%), with 14.9% undergoing open appendectomy and seven patients (3.3%) undergoing exploratory laparotomy with appendectomy. The median length of stay (LOS) was 5.5 days (IQR 3.7-7.4) and the median duration of total antibiotic course was 7.4 days (IQR 5.9-10.3). The overall rate of organ-space SSI was 16.5%. Intraoperative

cultures were sent for 149 of 255 patients (58.4%), with 33 cultures growing *Pseudomonas* (22.2%). Of these 33 patients, all but one grew *P. aeruginosa*; one patient grew another *Pseudomonas* species which was not specified. There was a variety in the frequency of intraoperative cultures by attending surgeon, ranging from 11% of perforated appendicitis cases to 91% (Figure 1). The frequency of intraoperative culture increased over the study period while the rate of *Pseudomonas* on intraoperative culture decreased over time (Figure 2).

2.2. Intraoperative culture results

The most common organism cultured at the time of appendectomy was *Escherichia coli* (66.4%) followed by *Streptococcus anginosus* (58.4%) and *Bacteroides fragilies* (52.0%). The fourth most common organism was *Pseudomonas* at 22.2% (n = 33). Less than 10% of cultures grew the following organisms or species: *Streptococcus viridans, Peptostreptococcus, Enterococcus avium, Parvimonas micra, Clostridium* species, *Parabacteroides* species, *Gemella species, Klebsiella* species, *Actinomyces* species, *Fusobacterium* species, *Eikenella corrodens, Eggerthelci* species, *Lactobacillus* species, *Citrobacter freundii, Comamonas* species, *Enterococcus faecium, Aeromonas* species, *Bifidobacterium* species.

In all but three of the 33 cases, *Pseudomonas* was susceptible to all tested antibiotics (cefepime, ceftazidime, gentamicin, levofloxacin, piperacillin/tazobactam, tobramycin); in the remaining three cases resistance was detected to piperacillin/tazobactam (n=1) or to meropenem, (n=2) respectively. Two patients had intraoperative cultures without evidence of *Pseudomonas* but then developed an intraabdominal abscess requiring percutaneous drainage, and cultures of the abscess grew out *Pseudomonas*. These patients are not included in the 33 patients with initial cultures positive for *Pseudomonas*. Of note, in six cases, *E. coli* was resistant to multiple antibiotics and qualified as an extended-spectrum beta-lactamase (ESBL) producing bacteria.

2.3. Outcomes of patients with and without intraoperative culture sent

Children who had intraoperative cultures sent had higher rates of SSI (20.8% vs. 10.4%, p = 0.027) and a longer LOS (6.0 days vs. 4.5 days, p < 0.00001) (Table 1). They also had higher rates of post-operative interventions (17.5% vs. 5.7%, p = 0.005). In the group of children with intraoperative cultures sent, 17 had post-operative drains placed by interventional radiology (IR), 5 had abscess aspiration or attempted aspiration, and 7 patients returned to the operating room for the following indications: small bowel obstruction requiring lysis of adhesions (n=3), lysis of adhesions and abscess washout (n=2), washout of abscess not accessible by percutaneous drainage (n=1), and abdominal compartment syndrome (n=1).

In the group of children without intraoperative cultures sent, 3 had post-operative drains placed by IR, 2 had aspiration or attempted aspiration of an abscess, and 1 returned to the operating room for incision and drainage of a superficial wound incision with serial negative pressure dressing changes. The median antibiotic duration was similar between the group of patients with intraoperative culture and those without (7.9 days vs. 7.1 days, p = 0.12). Total

hospital costs were significantly higher in the children with cultures sent (median \$24,659 vs. \$18,879, p < 0.0001), and antibiotic costs were higher as well (\$806 vs \$558, p = 0.002). Children with cultures sent had a higher 30-day ED visit rate (16.8% vs. 8.5%, p = 0.055) which trended toward significance, but readmission rates were not different between the groups (9.5% vs. 4.7%, p = 0.16).

2.4. Characteristics and outcomes of patients with Pseudomonas on intraoperative culture

When compared to children without *Pseudomonas* on intraoperative culture, children with *Pseudomonas* had a similar duration of symptoms prior to presentation (median 3 vs. 2 days, p = 0.45) and a similar WBC on admission (median 16.8 vs. 17.75, p = 0.20). Children with *Pseudomonas* had a 21.2% organ-space SSI rate compared to 20.7% of children without *Pseudomonas* (p=0.9) (Table 2). Children with *Pseudomonas* had a longer antibiotic duration than those without (9.1 days vs. 6.7 days, p = 0.03), and a longer LOS (6.7 days vs. 5.9 days, p = 0.03) and same rate of post-operative interventions (12.5% vs. 18.0%, p=0.6). Post-operative interventions in the children with *Pseudomonas* included 2 percutaneous drains, 1 re-operation for bowel obstruction, and 1 abscess aspiration. In the children without *Pseudomonas* infection, post-operative interventions included 12 percutaneous drains, and 6 returns to the operating room for bowel obstruction or recurrent abscess. Total hospital costs were similar between groups (\$28,860 vs. \$23,945, p=0.3), as were antibiotic costs (\$789 vs. \$822, p = 1.0). There were no differences in ED visits (9.1% vs. 19.0%, p = 0.3) or readmissions (9.1% vs. 9.5%, p = 1.0).

2.5. Antibiotic selection

Overall, the initial antibiotic regimen was ceftriaxone and metronidazole in 97.7% of patients, with two patients started on piperacillin-tazobactam (n=2), two started on levofloxacin and metronidazole (n=2), and two started on ceftriaxone, metronidazole, and vancomycin (n=2).

Fifty-five patients had their antibiotics changed (21.6%), the vast majority of whom were in the cohort with intraoperative cultures sent (n=50, 33.6%). Of these, all but one patient with *Pseudomonas* on intraoperative culture had antibiotics adjusted to an antipseudomonal regimen (n=32/33). The one patient who did not have antibiotics adjusted met clinical criteria for discharge prior to receipt of culture results, and thus was not changed to an antipseudomonal antibiotic. For patients with antibiotic changes, these occurred at a median of two days post-operatively (IQR 2-3, range 1-5) and patients received antipseudomonal coverage for a median of four days (IQR 2.5-6.5, range 1-16).

An additional 18 patients in the intraoperative culture cohort had antibiotics changed, with 83% of these changed to include antipseudomonal coverage. The remainder had antibiotics adjusted due to sensitivities reported on intraoperative culture (n=2) or allergic reaction to initial regimen (n=1). Of the changes to antipseudomonal coverage (n=15), two were due to *Pseudomonas* growth on post-operative drainage cultures. Eight others were due to intraoperative culture results: growth of *Citrobacter freundii* (n=2), resistant *E. coli* (n=2), ESBL (n=4). Three patients had coverage broadened due to failure to improve clinically,

and one had no reason stated. One patient had coverage broadened due to presumptive *Pseudomonas* species on intraoperative culture which was determined to be absent on final culture results.

Only five patients without intraoperative cultures sent had antibiotics changed (4.7%). Four of the five were broadened to antipseudomonal coverage. Of these, two were due to failure to improve clinically, one due to positive blood cultures while awaiting speciation, one due to allergic reaction to initial antibiotics. The fifth patient was initially started on piperacillin-tazobactam in the emergency department but transitioned to ceftriaxone and metronidazole post-operatively.

3. Discussion

In the largest study to date examining the microbiology of pediatric perforated appendicitis, we found that 22% of children with intraoperative cultures sent for perforated appendicitis grew *Pseudomonas*. This rate was consistent with reported rates from other smaller studies. Furthermore, children with *Pseudomonas* on culture did not have worse outcomes than children without *Pseudomonas* infection. Aside from longer total antibiotic duration, rates of surgical site infections, post-operative interventions, ED visits, and readmissions were similar to children without *Pseudomonas* infection. We did note that surgeons at our institution had varying practices of sending intraoperative cultures, ranging from 11% of cases to 91% of cases.

There have been few studies aimed at identifying the most common organisms isolated on intraoperative culture for perforated appendicitis in children. Three studies examined intraoperative cultures from perforated appendicitis, and one opened the appendix on the back table and swabbed the lumen for culture; however, 73% of patients in that study had non-perforated appendicitis. Studies of intraoperative culture findings have had sample sizes ranging from 47-69 children per study, with one study of 117 combined pediatric and adult patients. Rates of *Pseudomonas* isolated on intraoperative culture during appendectomy have commonly ranged from 0-12% [3,5,6], with one study in children and adults reporting a 15% rate of *Pseudomonas* [4] and one small study of 42 pediatric patients alone finding a 29% rate of *Pseudomonas* [8]. The true rate of *Pseudomonas* remains unknown as only 60% of patients in our study had cultures sent.

Numerous studies have been performed to elucidate best practice patterns for the treatment of pediatric appendicitis. Over the past 20 years, surgeons have shifted from prescribing triple antibiotic therapy to prescribing a more narrow regimen, most commonly ceftriaxone and metronidazole [2]. One retrospective cohort study examined outcomes of children treated empirically with ceftriaxone and metronidazole compared to those treated with an anti-pseudomonal antibiotic and found no difference in SSI rates between groups [10]. However, intraoperative cultures were only available for 9% of patients, so it is unknown whether those receiving antipseudomonal therapy has *Pseudomonas* infection.

In our cohort, nearly all patients with *Pseudomonas* on intraoperative cultures had their antibiotics broadened for coverage. This may account for the unchanged rates of SSIs and

post-operative interventions between patients with and without Pseudomonas. An additional twelve patients had antibiotics changed in response to microbial sensitivities from initial intraoperative culture. Thus, nearly one-third (29.5%) of patients with intraoperative cultures sent had a change in management as a result. Additionally, the similar rate of SSIs between patients with and without Pseudomonas may indicate that the potential delay in starting antipseudomonal antibiotics necessitated by waiting for intraoperative culture results, on average 2-3 days, does not impact clinical outcomes. This further supports published work that empiric antipseudomonal coverage does not reduce SSI rates, and our findings do not support empiric antipseudomonal coverage. It is worth noting that only five patients of the 106 without intraoperative cultures had antibiotics changed and only two of these were for clinical decompensation. Additionally, one patient with Pseudomonas on intraoperative culture never received antipseudomonal antibiotics due to meeting clinical discharge criteria prior to culture speciation. Future studies may be warranted examining the outcomes of patients with Pseudomonas on culture who do not have their antibiotic coverage broadened unless clinically indicated. If they do not have worse outcomes than children with antibiotic coverage broadened solely due to culture results, this may reduce unnecessary exposure to broader spectrum antibiotics and result in decreased costs, as sending intraoperative cultures may be unnecessary.

Lastly, the worse outcomes noted in patients with intraoperative cultures sent, in conjunction with the range of adherence to our institutional protocol of sending cultures, indicate that surgeons may choose to send intraoperative cultures when the abdomen looks particularly contaminated with purulent spillage from the perforated appendicitis. There are no studies in the literature examining outcomes of children with and without intraoperative cultures sent. Ideally, with higher rates of intraoperative cultures we will be able to identify the true rate of *Pseudomonas* infection in the pediatric population of perforated appendicitis.

3.1. Limitations

Our study has several limitations. It is a single-center retrospective review, and our results may not be generalizable to the larger population of all children with perforated appendicitis. Some patients may have been missed in creating our cohort due to coding errors. 40% of patients with perforated appendicitis did not have intraoperative cultures sent, so the true rate of *Pseudomonas* infections may be higher or lower than that reported here. Patients with more severe perforated appendicitis may have been more likely to have cultures sent and may be over-represented in our results. Additionally, individual surgeons within our group had variation in their rates of sending intraoperative cultures. However, we have provided here the largest cohort of children with perforated appendicitis with intraoperative culture results, thus adding to the evidence base in guidelines for treating pediatric appendicitis.

4. Conclusion

Pseudomonas was identified in nearly a quarter cases of perforated appendicitis in children. Children with *Pseudomonas* had longer antibiotic durations and hospitalizations, but similar rates of SSI, post-operative interventions, and readmissions compared to children without *Pseudomonas*. Empiric coverage of *Pseudomonas* may not be necessary.

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Table 1:

Demographic breakdown and comparison of outcomes, children with intraoperative culture sent vs. children without intraoperative culture sent

	Intraoperative culture n = 149	No culture n = 106	p-value
Age, years – median (IQR)	8.1 (5.4-11.4)	8.8 (6.1-11.2)	0.65
Female sex – n (%)	53 (36)	41 (38)	0.74
LOS, days – median (IQR)	6.0 (4.3-8.3)	4.5 (3.0-6.3)	< 0.0001*
OR length, minutes – median (IQR)	61.0 (51-72)	56.5 (45-74)	0.06
Total antibiotic duration, days – median (IQR)	7.9 (6.0-11.1)	7.1 (5.9-9.7)	0.12
Post-operative imaging – n (%)			
CT scan	38 (25.5)	32 (30.2)	0.41
Ultrasound	19 (12.8)	10 (9.4)	0.41
Post-operative intervention – n (%) ^{λ}			
Any	26 (17.5)	6 (5.7)	0.005*
Drain	17	3	0.017*
Abscess aspiration/attempt	5	2	0.47
Surgery	7	1	0.09
Surgical site infection – n (%)	31 (20.80)	11 (10.4)	0.027*
Costs, dollars - median (IQR)			
Total hospitalization	\$24,659 (\$18,112-34,543)	\$18,870 (\$13,941-25,751)	< 0.0001*
Antibiotic costs	\$806 (\$486-1165)	\$558 (\$344-881)	0.002*
30-day ED visit – n (%)	25 (16.8)	9 (8.5)	0.055
30-day readmission – n (%)	14 (9.5)	9 (4.7)	0.16

 $^{\Lambda}$ Note, post-operative intervention subtypes add up to more than the total number of patients with post-operative interventions because some patients had more than one intervention.

IQR: interquartile range; LOS: length of stay; OR: operating room; CT: computed tomography; ED: emergency department

Table 2:

Demographic breakdown and comparison of outcomes, children with *Pseudomonas* on intraoperative culture vs. children without *Pseudomonas*

	Pseudomonas positive n = 33	<i>Pseudomonas</i> negative n = 116	p-value
Age, years – median (IQR)	7.5 (4.2-11.2)	8.3 (5.6-11.5)	0.4
Female sex – n (%)	11 (33.3)	42 (36.2)	0.8
Duration of symptoms, days - median (IQR)	3 (2-3)	2 (2-4)	0.5
Initial WBC count – median (IQR)	16.8 (12.25-20.5)	17.75 (14.8-21.1)	0.2
LOS, days - median (IQR)	6.7 (4.9-8.9)	5.9 (4.1-7.7)	0.03*
OR length, minutes – median (IQR)	60 (49-65)	61 (52-77)	0.2
Total antibiotic duration, days – median (IQR)	9.1 (7.6-11.4)	6.7 (5.7-10.7)	0.03*
Post-operative imaging – n (%)			
CT scan	9 (27.3)	29 (25.0)	0.8
Ultrasound	3 (9.1)	16 (13.8)	0.6
Post-operative intervention – n (%) ^{$^{^{^{^{^{^{^{^{^{^{^{^{^{^{^{^{^{^{^{$}			
Any	4 (12.2)	22 (19.0)	0.4
Drain	2 (6.1)	14 (12.1)	
Abscess aspiration or attempt	1 (3.0)	4 (3.4)	
Surgery	1 (3.0)	7 (6.0)	
Surgical site infection – n (%)	7 (21.2)	24 (20.7)	0.9
Costs, dollars – median (IQR)			
Total hospitalization	\$28,860 (\$19,114-36,333)	\$23,945 (\$17,697-34,210)	0.3
Antibiotic costs	\$789 (\$525-1188)	\$822 (\$484-1161)	1.0
30-day ED visit – n (%)	3 (9.1)	22 (19.0)	0.3
30-day readmission – n (%)	3 (9.1)	11 (9.5)	1.0

^ANote, post-operative intervention subtypes add up to more than the total number of patients with post-operative interventions because some patients had more than one intervention.

IQR: interquartile range; WBC: white blood cell; LOS: length of stay; OR: operating room; CT: computed tomography; ED: emergency department.