6 Selection and Timing of Antibiotics for the Management of Appendicitis

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Case Example

A 12-year-old girl presents to the emergency department with 2 days of abdominal pain that began centrally and has migrated to the right lower quadrant. Her mother reports a fever to 38 °C and multiple episodes of vomiting and diarrhea. On physical exam, the patient has focal peritonitis in the right lower quadrant. White blood cell count is 18,000 /uL, and C-reactive protein is 1.8 mg/L. Abdominal ultrasound demonstrates a 9 mm non-compressible, blind-ended tubular structure in the right lower quadrant and a moderate amount of free fluid in the pelvis, consistent with perforated appendicitis. Which antibiotics should be started, and for how long should they be continued?

Introduction

Appendicitis is one of the most common diseases that general surgeons manage. While antibiotic use is widely accepted and is considered current standard of care, there is little consensus regarding which class, route of administration, or duration of antibiotics is best. Furthermore, it is not clear if these choices actually work to resolve the ongoing intra-abdominal infection or reduce post-treatment complications as they are meant to. Many institutions have protocols directing a change in the antibiotic regimen depending on whether the patient's disease is complicated or uncomplicated. Simple or uncomplicated appendicitis typically refers to pathology limited to appendiceal inflammation, while complicated appendicitis generally

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involves appendiceal perforation and/or intra-abdominal abscess formation. However, between these extremes is a spectrum of disease involving other features like gangrene, purulence, and presence of an obstructing appendiceal fecalith or appendicolith. Different studies often distinguish uncomplicated from complicated appendicitis at conflicting points along this spectrum, and sometimes also consider other factors, like delayed return of bowel function or requirement of intensive care, to be complicated. Because the label guides the antibiotic management in most institutions, the lack of universally agreed-upon criteria for complicated appendicitis makes reconciling individual studies and recommendations difficult. The details of antibiotic use in the treatment of appendicitis are not standardized. Herein we discuss the literature supporting common practices.

Current guidelines from multiple experts are similar but still ultimately conflicting. The Infectious Disease Society of America states that the routine use of broad-spectrum antibiotics is unnecessary if there is a high likelihood that the appendicitis is uncomplicated [1]. A recent Cochrane review also recommends narrow-spectrum antibiotics, suggesting that a first-generation cephalosporin with metronidazole or a second-generation cephalosporin alone is sufficient [2]. The Surgical Infection Society (SIS)'s 2017 guidelines on the management of intra-abdominal infection (not specific to appendicitis) specify using cefotaxime, ciprofloxacin plus metronidazole, or ertapenem for community-acquired infection due to a pathogen determined to be at low risk for antibiotic resistance. Recommendations are piperacillin-tazobactam, imipenem-cilastatin, or meropenem for community-acquired infection due to a pathogen at high risk for antibiotic resistance or hospital-acquired infection in children. Interestingly, by those authors' own admission, the definition of high and low risk of antibiotic resistance is vaguely defined and in practice would depend on specific antibiotic resistant patterns at a given institution. These same guidelines suggest a maximum of 5 days for children with adequate source control, but 7 days of intravenous antibiotics for the specific scenario of perforated appendicitis with intra-abdominal abscess [3]. However, the SIS's Study to Optimize Peritoneal Infection Therapy (STOP-IT) from the same year found that continuing antibiotics beyond 4 days made no difference in rates of surgical site infection, intra-abdominal infection, or death at 30 days after source control [4]. This study involved all causes of intra-abdominal infection, although about 10% of the patients included in the trial had appendicitis. Despite these findings, common practice in many institutions is to start broad-spectrum antibiotics, such as piperacillin-tazobactam, immediately at diagnosis, and then make adjustments based on the severity of infection observed at surgery. For uncomplicated appendicitis, the 2017 Pediatric Infectious Disease Journal recommends switching to ampicillin and gentamicin plus metronidazole or clindamycin, or ceftriaxone plus metronidazole until the patient tolerates oral antibiotics, followed by early discharge home on oral amoxicillin-clavulanate. For complicated appendicitis, the same journal recommends continuing piperacillin-tazobactam until the patient tolerates oral antibiotics [5]. At this author's home institution, a pediatric hospital, patients receive broad-spectrum antibiotics upon diagnosis. During appendectomy, the disease is categorized as acute (limited to peri-appendiceal inflammation without gross contamination of the peritoneal cavity), suppurative (contamination of the peritoneal cavity), gangrenous (appendiceal wall necrosis), or gross perforation. These categories are very similar, but not identical, to the American Association of Surgery for Trauma (AAST)'s severity grades for appendicitis, which Hernandez et al. validated and found that increasing grade correlates with increasing complication severity in children [6]. Piperacillin-tazobactam is discontinued for appendectomy demonstrating acute disease or continued for increasing durations correlating to the severity of disease and guided by laboratory data, regardless of oral intake.

One of the main controversies in appendicitis treatment protocols is the adequacy of narrow-spectrum antibiotics versus the necessity of broad-spectrum antibiotics. General principles for antibiotic use allow initial narrow-spectrum antibiotics if there is a historically likely causative bacteria with known susceptibilities. If the offending pathogen is unknown or the infection is severe, treatment begins with broad-spectrum antibiotics and is narrowed based on later culture results. However, cultures are not routinely performed for appendicitis. Furthermore, causative bacteria may be quite similar in the vast majority of cases. In a South Korean study of appendicitis, Song et al. found that 64.6% of the bacteria isolated from appendiceal lumens and intra-abdominal abscesses grew *E. coli* susceptible to most cephalosporins, ciprofloxacin, and broad-spectrum penicillins. Only 16.4% of isolated bacteria were *P. aeruginosa* resistant to cefotaxime and broad-spectrum penicillins, and these were associated with increased risk of superficial surgical site infections [7]. A worldwide study by Coccolini et al. corroborated that most bacteria isolated from appendicitis patients are gram-negative, specifically *E. coli*. Gram-positive bacteria were less prevalent, the most common being *Streptococcus*. Only 6.3% of gram-negative and 0.1% of gram-positive bacteria demonstrated notable resistance to narrow-spectrum antibiotics [8]. Taken together, these studies suggest that the causative bacteria are often similar, and antibiotic resistance requiring broad-spectrum antibiotics is less common in patients with appendicitis.

In addition to resolving the primary appendiceal infection, antibiotics are most often used to reduce or prevent post-treatment complications, i.e. surgical site infections and intra-abdominal abscesses. For uncomplicated appendicitis, Cameron et al. compared three antibiotic regimens: cefoxitin, ceftriaxone plus metronidazole, or piperacillin-tazobactam. They found no difference in incisional or organ-space surgical site infections, returns to the hospital, readmissions, or cost within 30 days of operation [2]. It seems reasonable to assume that complicated appendicitis – involving perforation and gross intra-abdominal contamination seen at the time of operation – would be more likely to result in post-treatment complications and therefore benefit from longer and broader-spectrum antibiotic treatment. Upon investigating this idea, however, Kronman et al. found that with regard to 30-day hospital readmission or requirement of additional abdominal procedures, broad-spectrum antibiotics (i.e., piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime, cefepime, or carbapenem in this study) offered no advantage over narrower-spectrum antibiotics (not specifically named) in post-appendectomy patients with uncomplicated or complicated appendicitis. Unlike most other studies, this one expanded its definition of "complicated appendicitis" to include a hospital stay greater than 3 days, requirement for central venous access, major or severe illness, or admission to an intensive care unit [9]. Another source of controversy that exists around antibiotic selection is the addition of an agent specifically targeting anaerobes. Shang et al. compared outcomes of perforated appendicitis treated with broad-spectrum antibiotics with and without the addition of metronidazole. This study found that metronidazole made no difference in the rate surgical wound infection, intra-abdominal abscess, or 30-day readmission when compared to broad-spectrum antibiotics alone. Additional outcomes that were unchanged by metronidazole included duration of intravenous antibiotics, hospital length of stay, and inflammatory markers on post-operative day 5 [10]. Taken together, these data suggest that narrow-spectrum antibiotics without anaerobic coverage are an adequate choice in the treatment of both uncomplicated and complicated appendicitis (Table 6.1). Regardless, it is difficult to overcome the intuition that more severe infections warrant broader-spectrum antibiotics. This author's home institution is a tertiary pediatric referral center that cares for a disproportionately higher percentage of complicated appendicitis. Current protocol directs all patients, except those with the mildest category of disease, to receive broad-spectrum antibiotics for at least 12 hours post-operatively.

Aside from the spectrum of coverage, the other main variable in an antibiotic regimen is the duration of treatment. As previously mentioned, the SIS suggests giving antibiotics for 4–5 days in a patient with source control and up to 7 days in a patient without source control [3, 4]. However, these recommendations are for general intra-abdominal infections. To determine the necessary antibiotic duration

Table 6.1 Summary of findings regarding antibiotic selection

First author, year	Treatment groups	Demographic, disease severity	Primary outcomes	Conclusion
Cameron D, 2017	Pip-tazo vs cefoxitin vs CTX + metronidazole	Pediatric, uncomplicated	30-day SSI (superficial, deep, organ space), returns to ED, hospital readmission	Extended spectrum not associated with decreased outcomes
Kronman M, 2016	Pip-tazo vs ticarcillin-clavulanate vs ceftazidime vs cefepime vs carbapenem	Pediatric, complicated and uncomplicated	30-day readmission for SSI or additional abdominal procedures	Extended spectrum offers no advantage
Shang Q, 2017	Broad-spectrum alone vs broad-spectrum + metronidazole	Pediatric, perforated	Postoperative antibiotic duration, POD5 WBC/CRP, LOS, intra-abdominal abscess, wound infection	Metronidazole has no beneficial clinical effects

Pip-tazo piperacillin-tazobactam, *CTX* ceftriaxone, *SSI* surgical site infection, *ED* emergency department, *POD* postoperative day, *WBC* white blood cell count, *CRP* C-reactive protein, *LOS* length of stay

Table 6.2 Summary of findings regarding antibiotic duration

First author, year	Treatment groups	Demographic, disease severity	Primary outcomes	Conclusion
Sawyer R, 2015	Abx for 4 ± 1 day vs abx until 2 days after resolution of fever, leukocytosis, and ileus (maximum 10 days)	Adult, not specific to appendicitis	30-day SSI, recurrent intra-abdominal infection, death	No significant difference
van Rossem C, 2016	3 vs 5 days of postoperative abx	Pediatric and adult, complicated	SSI, intra-abdominal abscess, postoperative ileus	5 days not associated with reduced infectious complications
Kim D, 2015	Postoperative abx vs no postoperative abx	Adult, gangrenous and perforated	Wound complications, LOS, hospital readmission	Postoperative abx associated with increased LOS but not decreased wound complications

Abx antibiotics

specifically for pediatric appendicitis, van Rossem et al. compared the rate of infectious complications including surgical site infection, intra-abdominal abscess, and post-operative ileus in children with complicated appendicitis who received 3 versus 5 days of postoperative antibiotics, whether entirely intravenous or combined intravenous-oral. Their definition of "complicated" appendicitis included patients whose surgeons prescribed post-operative antibiotics for greater than 24 hours for any reason, which suggests a subset of patients thought to have more severe infection than average. They found no difference in infectious complications in groups receiving 3 days of postoperative antibiotics compared to 5 [11]. Taken together, these studies suggest that following appendectomy, antibiotics should not be continued after postoperative day 5 and may be stopped as early as postoperative day 3 (Table 6.2).

Other questions related to antibiotic spectrum and duration include whether antibiotics are necessary after discharge from the hospital, and if the oral or intravenous route is superior. Generally, oral antibiotics are narrower spectrum and are given after control of the infectious source. In uncomplicated appendicitis, this typically means immediately post-operatively, after appendectomy. Patients with complicated appendicitis may receive oral home antibiotics or may require intravenous home antibiotics (the latter is especially common if source control was not possible due to degree of perforation). In a study comparing rates of complications after discharge home on oral versus intravenous antibiotics for perforated appendicitis in post-appendectomy patients, Rangel et al. found that treatment failure (defined as organ-space infection requiring percutaneous or operative drainage) and all-cause hospital revisits or admissions (e.g., wound complications, bowel obstruction, intravenous catheter complications) were more frequent in patients receiving intravenous home antibiotics [12]. This may have resulted from selection bias, since the patients determined likely to benefit from intravenous home antibiotics are usually those with more severe infections as determined by clinical criteria, such as intra-operative findings, persistent fever, or leukocytosis during post-operative monitoring. Although those authors minimize this disease severity-based confounding by matching patients with similar severity-associated characteristics, they acknowledge the potential for residual effects. Importantly, the study did not show that intravenous home antibiotics reduced the rate of post-operative complications in perforated appendicitis, which suggests that even in very severe disease, systemic treatment with broad-spectrum antibiotics may not make a difference in complication rate.

While predetermined, evidence-based protocols for antibiotic selection and timing are useful starting points, an often-employed adjunct is to allow patients' clinical features to guide development of individualized antibiotic regimens. For example, a patient with post-operative fever and/or leukocytosis may be deemed still acutely ill and thus receive a longer antibiotic duration. Evidence supporting use of persistently elevated serum inflammatory markers such as white blood cell count (WBC) and the acute phase reactant C-reactive protein (CRP) are conflicting. The previously mentioned STOP-IT trial suggests that a prolonged systemic inflammatory response syndrome after 4 days may be reflective of simply ongoing immune activity and not necessarily indicative of ongoing bacterial presence [4]. However, other studies, including work from Assarsson et al., found a significant correlation between improvement in WBC and CRP within 24 hours of starting antibiotics and improvement of clinical disease. The correlation between resolution of fever and resolution of disease was not significant ($p = 0.06$) [13]. Procalcitonin (PCT) is another acute phase reactant that has shown promise as a marker of specifically bacteria-induced inflammation and systemic shock. There is especially a fast-growing support for use of elevated serum PCT levels as an indicator to continue antibiotics in lower respiratory bacterial infections like bronchitis and pneumonia, while de-escalating or stopping antibiotics based on decreasing PCT levels improves respiratory and ICU outcomes [14]. Theoretically, PCT levels could also aid in tailoring individualized antibiotic regimens for intra-abdominal bacterial infections, but existing data in this context is new and therefore meager. Assarsson et al. compared PCT levels in appendicitis patients who were clinically responding to antibiotics versus PCT levels in patients who were deemed antibiotic non-responders, but they found no difference in these groups, concluding that PCT is not a useful predictor of antibiotic response [13]. Similarly, Slieker et al. queried whether elevated serum PCT levels might help identify patients with peritonitis who are likely to develop postoperative complications but found that PCT levels did not correlate to differences in required antibiotic duration, hospital length of stay, rate of postoperative complications, or death [14]. However, conclusions about PCT levels in the specific context of intra-abdominal infections and appendicitis are at best undefined, and this topic may be of interest for future study. Meanwhile, despite a lack of definitive supporting evidence, post-operative fever, leukocytosis, and elevated CRP remain widely trusted indicators of ongoing infection. If the patient in the case study were a current patient at this author's home institution and had a WBC greater than 15 on post-operative day 3, she would receive further intravenous antibiotics.

If she were still febrile on the evening of post-operative day 2, her WBC would not be checked until she had been afebrile for 24 hours.

Because appendicitis is an inflammatory condition with associated infection, antibiotics have long been commonplace in the care of patients with this disease, prompting continued debate over the details. These details include the previously discussed broadness of coverage, route of administration, and duration. However, with current efforts to decrease bacterial development of antibiotic resistance by reducing antibiotic usage, it is interesting to consider whether the diagnosis of appendicitis really warrants antibiotic treatment at all. In a randomized controlled trial, Park et al. treated computed tomography-verified, uncomplicated appendicitis in adults with either intravenous second-generation cephalosporin plus metronidazole or supportive care and intravenous vitamins for 4 days. This study found that between treatment groups, there was no difference in requirement of drainage, surgery, or further antibiotics within 1 month. Additionally, patients in the supportive care group had decreased length of hospital stay and overall cost [15]. However, in 2017, a meta-analysis involving pediatric patients with uncomplicated appendicitis found that non-operative management with antibiotics resulted in increased hospital readmissions, concluding that appendectomy at the time of index admission is still the treatment of choice in this population [16]. Interestingly, a study investigating the necessity of post-operative antibiotics for complicated appendicitis in adults by Kim et al. also found no difference in hospital readmission or superficial or deep surgical site infection. The finding of decreased length of hospital stay for patients not receiving antibiotics continued to hold true for the adult complicated appendicitis cohort [17]. Similar studies are currently ongoing at major academic centers in the United States.

Conclusions

Although appendicitis is considered a classic surgical diagnosis, and the frequency at which surgeons encounter it makes its management one of the foremost items in training surgeons' repertoires, there still exists wide, often institution-specific variation in its treatment. Regardless of the antibiotic regimen or protocol used, the guiding principle remains to reduce broadness of coverage, invasiveness of administration, and duration as much as possible while still minimizing these patients' post-operative morbidity. Despite sometimes conflicting or unclear data, our best recommendation based on the available literature is to treat all appendicitis, regardless of severity, with narrower-spectrum antibiotics for 3 days postoperatively, unless persistently elevated WBC and/or CRP suggest the patient may benefit from extending the treatment for a maximum of 5 total days.

Clinical Pearls

- Initiate antibiotics in a timely fashion following diagnosis.
- Reduce the broadness and duration of antibiotics as much as possible.
- WBC and/or CRP level may aid in deciding when to discontinue antibiotics.

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