Infectious Causes of Appendicitis

Laura W. Lamps, MD

The pathologic spectrum of the inflamed appendix encompasses a wide range of infectious entities, some with specific histologic findings, and others with nonspecific findings that may require an extensive diagnostic evaluation. The appendix is exclusively involved in some of these disorders, and in others may be involved through extension from other areas of the gastrointestinal (GI) tract. The numerous viral, bacterial, fungal, and parasitic organisms that may infect the appendix are summarized in Table 1.

VIRAL INFECTIONS OF THE APPENDIX

Adenovirus

Adenovirus is one of the more common viruses described in the appendix.1–5 It is also associated with ileal and ileocecal intussusception, particularly in children.1–4 The virus is believed to cause intussusception by producing lymphoid hyperplasia, altering intestinal motility, or a combination of both. Most patients do not have symptoms of appendicitis, and adenovirus is usually found after segmental resection for intussusception.1–4 There is no specific antiviral therapy for treatment of enteric adenovirus, but most patients do well following surgery for intussusception.

Pathologic features

Morphologic changes are subtle, including lymphoid hyperplasia (Fig. 1) and overlying disorderly proliferation and degeneration of surface epithelium.1–7 In the appendix, inclusions are reportedly found on routine stains in only one-third of patients with intussusception in which adenovirus is detected by other methods, such as immunohistochemistry, polymerase chain reaction (PCR), and in situ hybridization.1–4 The most common adenovirus inclusions, known as smudge cells, have enlarged, basophilic nuclei without a clear nuclear membrane (Fig. 2).2,4,6,7 Homogenous, eosinophilic inclusions surrounded by halos with distinct nuclear membranes (Cowdry A-type) are less common. Adenovirus inclusions are exclusively intranuclear, and fill...
<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
<th>Fungi</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td><em>Salmonella</em> sp (both typhoid and nontyphoid)</td>
<td>Mucormycosis</td>
<td><em>Enterobius vermicularis</em> (pinworm)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td><em>Shigella</em> sp</td>
<td>Histoplasmosis</td>
<td><em>Entamoeba histolytica</em></td>
</tr>
<tr>
<td>CMV</td>
<td><em>Yersinia</em> (both <em>Y. enterocolitica</em> and <em>Y. pseudotuberculosis</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td><em>Actinomyces</em> sp</td>
<td><em>Balantidium coli</em></td>
<td><em>Strongyloides stercoralis</em></td>
</tr>
<tr>
<td></td>
<td><em>Campylobacter</em> sp</td>
<td></td>
<td><em>Toxoplasma</em></td>
</tr>
<tr>
<td></td>
<td><em>Clostridium</em>, including <em>Clostridium difficile</em></td>
<td></td>
<td><em>Cryptosporidium</em></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>(tuberculosis and atypical)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rickettsia rickettsii</td>
<td></td>
<td><em>Echinococcus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Trichuris</em> sp ( whipworms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Ascaris</em> sp (roundworms)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1.** Marked lymphoid hyperplasia with overlying ulceration and luminal narrowing in an appendix infected with adenovirus. Hematoxylin and eosin (H&E), original magnification ×40. To see full-color versions of all figures in this article, please go to [http://www.id.theclinics.com/](http://www.id.theclinics.com/).
the entire nucleus; however, the cell itself is not enlarged. Inclusions are most often seen in areas with epithelial degenerative changes; inclusions may be widely scattered, with many apparently uninfected cells in between.

Useful aids in the diagnosis of adenovirus infection include immunohistochemistry (Fig. 3), stool and/or tissue examination by electron microscopy, and viral culture.¹⁻⁴ Positive serologies or fecal identification of the virus do not necessarily represent current infection, because viral shedding and increased serologic titers may persist for months.⁵

**Differential diagnosis**
The differential diagnosis of adenovirus infection is primarily with other viral infections, particularly cytomegalovirus (CMV). Adenovirus inclusions lack the owl’s eye morphology of CMV, and are found primarily within epithelial rather than endothelial and stromal cells. In addition, the entire cell is enlarged in CMV infection, but not in adenovirus infection.

**CMV**
CMV is the most common GI pathogen in patients with AIDS. CMV is described in the appendix with increasing frequency in this population,⁸⁻¹³ and it has been suggested

---

**Fig. 2.** Adenovirus inclusions, known as smudge cells, are seen within the nuclei of epithelial cells within the inflammatory debris. The smudge cells have homogenous basophilic nuclei with peripheral chromatin margination. H&E, original magnification ×100.

**Fig. 3.** Immunohistochemical stain for adenovirus highlights infected epithelial cells in the appendix. Adenovirus immunostain, original magnification ×200.
that CMV appendicitis should be suspected in any human immunodeficiency virus (HIV)-positive patient who presents with localized right lower quadrant tenderness. Patients typically present with a more prolonged prehospital course than that of immunocompetent patients with appendicitis, consisting of several weeks of fever, diarrhea, and abdominal pain and tenderness that ultimately localizes to the right lower quadrant. Perforation is a common complication. In addition to surgical intervention for acute appendicitis, specific antiviral therapy (usually gancyclovir) is available, and GI CMV infection generally responds well.

**Pathologic features**

Histologic findings include variably ulcerated appendiceal mucosa with a transmural mixed inflammatory infiltrate, including numerous histiocytes, plasma cells, and lymphocytes, in addition to neutrophils. The characteristic owl’s eye inclusions (Fig. 4), as well as basophilic granular inclusions (Fig. 5), are typically seen in epithelial, endothelial, histiocytic, and stromal cells, either in intranuclear or intracytoplasmic locations.

Useful diagnostic aids include immunohistochemistry, viral culture, PCR assays, in situ hybridization, and CMV serologic studies/antigen tests. However, isolation of CMV in culture does not imply active infection, as virus may be excreted for months.
to years after a primary infection. The differential diagnosis is primarily that of other viral infections, particularly adenovirus (see earlier discussion).

**Measles (Rubeola Virus)**

Measles infection occasionally produces appendicitis and mesenteric lymphadenitis.\textsuperscript{15–17} Histologic findings in measles-related appendicitis include lymphoid hyperplasia and multinucleate Warthin-Finkeldey giant cells (Fig. 6), predominantly within germinal centers; associated inflammation is variably present. Although the measles

Fig. 6. Lymphoid hyperplasia with numerous associated Warthin-Finkeldey giant cells in a case of measles appendicitis. (A) H&E, original magnification $\times 40$. Multinucleate Warthin-Finkeldey giant cells are seen within germinal centers. (B) H&E, original magnification $\times 400$. (Courtesy of Dr David Owen.)
virus probably does not independently cause true appendicitis, the lymphoid hyperplasia may lead to obstruction, acute inflammation, and even gangrenous appendicitis. Patients often have a concomitant rash, although the GI morphologic findings may precede the viral xanthem, and serologic findings and immunohistochemistry can help confirm the diagnosis.

Acute appendicitis may also develop during the course of infectious mononucleosis as a result of Epstein-Barr virus infection, and changes in the appendiceal lymphoid tissue mimic those occurring in lymph nodes.¹⁸

**SPECIFIC BACTERIAL INFECTIONS CAUSING APPENDICITIS**

Numerous bacterial infections may cause appendicitis, with or without involvement of the surrounding bowel. In many of these cases, the infectious agent is determined only after removal of the appendix and careful examination for organisms, using special stains, microbiologic culture, and/or molecular methods.

**Yersinia Species**

*Yersinia* is one of the most common causes of bacterial enteritis in Western and Northern Europe. It has a worldwide distribution; the incidence of infection is rising within both Europe and the United States, although this may be due to better methods of detection and wider recognition of *Yersinia* as important enteric pathogens. *Yersinia* infection can be transmitted by both food and water, and is associated with meat, dairy products, chocolate, poultry, and produce. *Yersinia* has a preference for cold temperatures, thus there is a natural affinity for refrigerated food, and there is

---

**Fig. 7.** Lymphoid hyperplasia, mucosal ulceration, and epithelioid granulomas in a case of *Y enterocolitica* appendicitis in a child. H&E, original magnification ×20.
speculation that infection is more common in cooler months.19–23 Y enterocolitica and Y pseudotuberculosis are the species that cause human GI disease.19,20,22,24

These fastidious gram-negative coccobacilli have been implicated in numerous GI illnesses, including appendicitis (particularly granulomatous appendicitis) and mesenteric lymphadenitis.19–22,24,25 Fever, pharyngitis, and leukocytosis may be present as well. Symptoms often have been present for weeks to months, leading to misdiagnosis as chronic idiopathic inflammatory bowel disease. Reactive polyarthritis and erythema nodosum are also associated with Yersinia infection. Infants, children, and young adults are most commonly infected. Patients with granulomatous appendicitis caused by Yersinia often present with signs and symptoms indistinguishable from acute nonspecific appendicitis. However, some patients with yersiniosis are initially believed to be suffering from appendicitis, but on exploration are found to have inflammation of the terminal ileum and mesenteric nodes that clinically mimics appendicitis (the pseudoappendicular syndrome).19,22,24–28

Pathologic features

The involved appendix has a thickened, edematous wall with nodular inflammatory masses centered on Peyer patches. Aphthoid and linear ulcers may be seen, and perforation is frequent. Involved lymph nodes may show grossly apparent foci of necrosis. Both suppurative and granulomatous patterns of inflammation are common, and are often mixed. Y enterocolitica typically features epithelioid granulomas, along with hyperplastic Peyer patches and overlying ulceration (Fig. 7).20,29–32 GI infection with Y pseudotuberculosis has been described characteristically as a granulomatous process with central microabscesses (Fig. 8).20,26 However, there is significant overlap between the histologic features of Y enterocolitica and Y pseudotuberculosis infection, and either species may show epithelioid granulomas with prominent lymphoid cuffing (Fig. 9), lymphoid hyperplasia, transmural lymphoid aggregates (Fig. 10), mucosal ulceration, and lymph node involvement.20 The transmural inflammation, fissuring and/or aphthoid ulcers, focal architectural distortion, skip lesions, and granulomas may closely mimic Crohn disease.

Special stains are usually not helpful in the diagnosis of Yersinia, because the organisms are small, usually present in low numbers, and are difficult to distinguish from normal nonpathogenic colonic flora. Because Yersinia is a fastidious organism that requires specific culture conditions, and serologic studies show significant cross-

Fig. 8. Ypseudotuberculosis appendicitis, featuring granulomatous inflammation with prominent, irregular microabscesses and mucosal ulceration. H&E, original magnification ×40.
reactivity with other gut pathogens, recognition of the histologic pattern of infection and molecular confirmation by PCR assay is the most reliable method of confirming the diagnosis.19,20,22,29,33

Uncomplicated cases of *Yersinia*-associated appendicitis and the pseudoappendicular syndrome usually resolve spontaneously without antibiotic therapy. Localized

**Fig. 9.** Epithelioid granulomas typical of yersiniosis, with prominent surrounding lymphoid cuffs. (A) H&E, original magnification ×100. The granulomas are often present transmurally. (B) H&E, original magnification ×100.

**Fig. 10.** Transmural lymphoid aggregates in *Yersinia*-associated appendicitis may mimic Crohn disease. H&E, original magnification ×100.
suppurative infections, bacteremic patients, and severe systemic infections may require antibiotics, especially in immunocompromised patients or patients at risk for severe yersiniosis (such as those on desferrioxamine therapy). However, optimal anti-Yersinial therapy has yet to be determined. *Y enterocolitica* is susceptible to many broad-spectrum antibiotics, although there is resistance to ampicillin and first-generation cephalosporins. Fluoroquinolones are the treatment of choice for *Y pseudotuberculosis*.34–37

**Differential diagnosis**
The major differential diagnosis includes other infectious processes, particularly *Mycobacteria*. Acid-fast stains and culture results help distinguish mycobacterial infection from yersiniosis. Sarcoidosis, foreign body reaction to fecal material, and granulomatous inflammation secondary to delayed (interval) appendectomy with antibiotic therapy are also in the differential diagnosis of *Yersinia*-associated granulomatous appendicitis.38–41

Crohn disease and yersiniosis may be difficult to distinguish from one another. Features favoring Crohn disease include fistula formation, cobblestoning of mucosa, presence of creeping fat, and histologic changes of chronicity including crypt distortion, thickening of the muscularis mucosa, and prominent neural hyperplasia. However, some cases are simply indistinguishable on histologic grounds alone.

Although Crohn disease and yersiniosis may be indistinguishable on histologic grounds alone, patients with isolated granulomatous appendicitis develop generalized inflammatory bowel disease less than 10% of the time.29,42,43 In addition, many cases of granulomatous appendicitis previously considered to be either a limited form of Crohn disease or idiopathic are probably caused by infection. Features that suggest an underlying infectious cause include a large number of granulomas, confluent granulomas, and necrosis or central abscess formation.42,43 Ultimately, because either species of *Yersinia* may mimic Crohn disease histologically and clinically, it is important to carefully consider other potential causes of granulomatous appendicitis before rendering a diagnosis of Crohn disease.29,42,43

**Actinomycosis (Actinomyces Israelii)**
This filamentous anaerobic gram-positive bacterium is a normal inhabitant of the oral cavity and upper GI tract that occasionally produces chronic, usually granulomatous appendicitis. Patients frequently present with fever, weight loss, abdominal pain, and, occasionally, a palpable mass that may mimic malignancy.44–47 The correct diagnosis is usually not established preoperatively, but is discovered only once the appendix has been resected for a suspected neoplasm.45

**Pathologic features**
The appendix is the most common intra-abdominal organ involved by actinomycosis, followed by the right colon.44–46 Grossly, appendices are often markedly enlarged, indurated, and adherent to adjacent structures, mimicking malignancy. Mucosal ulceration is variably present. The inflammatory reaction is predominantly neutrophilic.44–46 Palisading histiocytes and giant cells, as well as frank granulomas, often surround the neutrophilic inflammation. Transmural inflammation, lymphoid hyperplasia, and marked fibrosis (Fig. 11) are common histologic features,44–47 along with mucosal ulceration and architectural distortion. Small sinuses may track from the lumen into the wall of the appendix, and there is often marked fibrosis with variable abscess formation.
The organism typically produces actinomycotic (sulfur) granules, consisting of irregular round clusters of bacteria rimmed by eosinophilic, clublike projections of proteinaceous material (Splendore-Hoeppli material) (Fig. 12). Gram stain reveals the filamentous, gram-positive organisms (Fig. 13). Actinomyces may stain with Grocott methenamine silver (GMS) stain and Warthin-Starry stain.

Commensal actinomyces may be present at the lumenal surface of the appendix, and these do not necessarily imply invasive infection, particularly if there is no inflammatory response. A definite diagnosis of invasive actinomycosis (rather than the presence of commensal organisms) is important, given the therapeutic implications discussed later, and requires evidence of the organisms within the wall of the bowel with an associated inflammatory response. This process may require multiple levels of lesional tissue sections.44,48

Combined surgical and medical therapy produces good results in most cases of invasive actinomycosis. After resection and/or drainage of abscesses, long-term antibiotic therapy is necessary, because of both the difficulty of achieving good antibiotic penetration in fibrous tissue, and the propensity of the infection to recur. Actinomyces are sensitive to penicillins, but tetracycline and clindamycin are also effective. Intravenous antibiotics are usually given initially, followed by oral administration.44,45,47

**Differential diagnosis**

Macroscopically, the infiltrative, fibrotic masses produced by actinomycosis can mimic malignancy. The histologic differential primarily includes other infectious processes, particularly *Nocardia*. *Nocardia* are partially acid-fast and do not form the typical sulfur granules of actinomycosis; however, cultures may be required to distinguish these 2 filamentous organisms. Even although actinomyces are GMS positive, they have a more slender morphology than fungi, and do not bud or produce hyphae. Care should be taken not to confuse actinomycosis with other bacteria that form clusters and chains but are not truly filamentous, such as *Pseudomonas* and *Escherichia coli*. Occasionally, the transmural inflammation, fibrosis, and granulomatous inflammation produced by actinomycotic infection may mimic Crohn disease.
Tuberculous Appendicitis

Despite the proximity of the appendix to the ileocecum, tuberculosis of the appendix is rare, and usually secondary to infection elsewhere in the abdomen. Although the ileocecum is involved in more than 40% of cases of abdominal tuberculosis, the appendix is involved in only about 1%. In nonendemic countries, many patients with intestinal and appendiceal tuberculosis are immunocompromised. Mechanisms of involvement include extension from ileocecal or genital tuberculosis, hematogenous spread from a distant focus of infection, and contact with intestinal contents.

Fig. 12. Appendiceal actinomycosis, showing mucosal ulceration with overlying acute inflammation and admixed actinomycotic granules. (A) H&E, original magnification ×100. Actinomycotic granules are often associated with proteinaceous debris at the periphery (Splendore-Hoeppli material) and acute inflammation. (B) H&E, original magnification ×200.

_Tuberculous Appendicitis_

Despite the proximity of the appendix to the ileocecum, tuberculosis of the appendix is rare, and usually secondary to infection elsewhere in the abdomen. Although the ileocecum is involved in more than 40% of cases of abdominal tuberculosis, the appendix is involved in only about 1%. In nonendemic countries, many patients with intestinal and appendiceal tuberculosis are immunocompromised. Mechanisms of involvement include extension from ileocecal or genital tuberculosis, hematogenous spread from a distant focus of infection, and contact with intestinal contents.
containing bacilli. Patients may present with symptoms and signs typical of acute appendicitis, or with milder, chronic symptoms and nonspecific intermittent right iliac fossa pain. A high index of suspicion is required, and appendiceal tuberculosis should be considered in immigrants presenting with the symptoms mentioned earlier who are from regions where tuberculosis is endemic. Patients need several months of antitubercular therapy after appendectomy.

Pathologic features
The appendix is usually grossly inflamed, with mural thickening, and is often adherent to the surrounding bowel with associated lymphadenitis. Histologically, involved appendices show lymphoid hyperplasia with associated caseating granulomas (Fig. 14). Mucosal ulceration may be present as well. Organisms may be rare, and even multiple sets of special stains may fail to reveal acid-fast bacilli; therefore, culture and molecular assays may be invaluable to diagnosis.

Differential diagnosis
The differential diagnosis primarily includes other granulomatous infectious process, and rarely Crohn disease. Showing organisms by histochemical, microbial, or molecular methods, as well as the clinical context, helps to resolve the differential in most cases.

Fig. 13. The filamentous actinomyces are gram-positive on Gram stain. H&E, original magnification ×200.

Fig. 14. Confluent, epithelioid granulomas with giant cells and a surrounding lymphoid infiltrate are seen in tuberculosis. H&E, original magnification ×200.
Atypical mycobacteria (particularly *Mycobacterium avium-intracellulare* [MAI]) only rarely cause appendicitis, and this scenario occurs almost exclusively in immunocompromised patients. The diffuse histiocytic infiltrate typical of GI MAI infection may be seen, and discrete granulomas are variably present. Numerous acid-fast bacilli are usually detectable with appropriate acid-fast stains. Mycobacterial spindle cell pseudotumors have also been reported rarely in patients with AIDS.

**Campylobacter Species**

*Campylobacter* species, particularly *Campylobacter jejuni*, have been isolated from resected appendices using molecular, microbiological, immunohistochemical, and electron microscopic methods. Grossly, appendices are often normal. Histologic findings are similar to those of early nonspecific acute suppurative appendicitis, although inflammatory changes may be limited to the mucosa (without transmural inflammation or periappendicitis) in some cases. Most patients do not require postappendectomy antibiotic therapy.

**Clostridium Difficile**

Appendiceal involvement by *Clostridium difficile* is usually associated with more widespread colonic involvement by pseudomembranous colitis. The *Clostridium difficile* toxin assay is helpful in confirming the diagnosis, and patients require antimicrobial therapy, usually oral vancomycin or flagyl.

**Pathologic features**

Grossly, appendices may contain pseudomembranes similar to those seen in the colon, or may have nonspecific suppurative inflammation. Histologic changes are also similar to those seen in the colon, and include volcano or mushroom mucosal lesions (Fig. 15) with intercrypt necrosis and ballooned crypts, giving rise to the laminated pseudomembrane composed of fibrin, mucin, and neutrophils. The ballooned glands are filled with neutrophils and mucin, and the superficial epithelial cells are often lost.

Other bacterial infections that may cause appendicitis are listed in Table 1. *Salmonella* species (both typhoid and nontyphoid) are rarely isolated from acutely inflamed appendices; clinical presentation and histologic findings are identical to acute

---

**Fig. 15.** *Clostridium difficile* infection of the appendix. Note the attenuated, exploding crypts giving rise to an inflammatory pseudomembrane composed of mucin, neutrophils, and fibrinous debris. H&E, original magnification ×100.
nonspecific appendicitis. Patients often remain febrile postoperatively, and Salmonella infection requires antibiotic treatment following appendectomy. Appendicitis has been reported rarely associated with dysentery caused by Shigella.

Bacterial Infection and Acute Nonspecific Appendicitis

Although the appendix is the most commonly resected and examined intra-abdominal organ in surgical pathology practice, the pathogenesis of acute nonspecific appendicitis (the most common diagnosis made in this organ) and its association with specific bacterial causes remain enigmatic. Historically, obstruction of the appendiceal lumen, with subsequent secondary infection, has been the most popular theory regarding the pathogenesis of acute nonspecific appendicitis. Proponents of this theory argue that obstruction, either by fecalith, lymphoid hyperplasia, or adhesions, leads to an increase in intraluminal pressure, which in turn causes vascular compromise, mucosal ischemia, mucosal ulceration, and ultimately infection by luminal microorganisms. However, evidence of obstruction can be shown in only a minority of resected appendices, and some investigators have argued that obstruction is the result, rather than the cause, of appendiceal inflammation. Other purported risk factors that may lead to bacterial superinfection include mucosal ulceration from viral infection, and low-fiber diets with slowing of intestinal transit time and retention of stool in the appendix. No single theory can explain all cases of acute nonspecific appendicitis, and it is likely that multiple causes, varying with the individual patient, may lead to invasion of the appendiceal wall by intraluminal bacteria and associated mucosal ulceration.

The possible role of gut bacteria in both the development and the sequelae of acute appendicitis has also been a subject of discussion. Bacteriologic studies, usually historically performed using microbiologic culture techniques, reveal a wide variety of anaerobic and aerobic bacteria. When correlated with histologic findings, it seems that aerobic infection predominates in early appendicitis, with a shift toward a mixture of aerobes and anaerobes later in the course of disease. Bacteroides species are the most common isolate, particularly Bacteroides fragilis, and their role in the pathogenesis of acute appendicitis has been hotly debated. Some studies have found a higher incidence of Bacteroides fragilis in inflamed appendices when compared with normal, whereas others have found no difference. Studies examining the immunologic response to commonly isolated bacteria have shown a greater serologic antibody response to Bacteroides species than to other isolated organisms in gangrenous and perforated appendices, but this may reflect a greater extent of organ destruction and tissue immune response rather than a true pathogenetic role. In addition, other workers showed similar serologic results when patients with noninflamed appendices were studied. The possible contributions that any of these organisms might make to the pathogenesis of acute appendicitis remain unclear, but it is important to be aware of the mixture of anaerobic and aerobic bacteria that can exist within an inflamed appendix. If antibiotic therapy is necessary for either wound infections or peritonitis secondary to perforation, the antimicrobials selected should cover the variety of organisms that may be present.

Fungal Infections Causing Appendicitis

Fungal infection of the appendix is rare. Mucormycosis has been reported to cause inflammatory masses of the right lower quadrant involving the appendix, ileum, and cecum in patients undergoing chemotherapy. Histoplasmosis may involve the
appendix as part of generalized infection of the GI tract, usually in immunocompromised patients (Fig. 16). Patients usually require antifungal therapy following resection.

PARASITIC INFECTIONS CAUSING APPENDICITIS

Many parasites can be found in the lumen of the appendix, including pinworms (most commonly), *Ascaris* (roundworms), *Giardia*, and *Entamoeba histolytica*. Clinicians should be alerted when parasites are found in the appendix that could affect other parts of the GI tract.

**Enterobius Vermicularis (Pinworms)**

Pinworms are one of the most common human parasites. These nematodes have a worldwide distribution, but are more common in cold or temperate climates and in developed countries. Prevalence is highest among children ages 5 to 10 years, and it has been reported that pinworm infections of the GI tract affect 4% to 28% of children around the globe. These infections are common in the United States and Northwestern Europe. The infective egg resides in dust and soil, and transmission is believed to be via the fecal-oral route. Pinworms are known as *Oxyuris vermicularis* in the older literature.

The worms live and reproduce in the ileum, cecum, proximal colon, and appendix, and the female migrates to the anus to deposit eggs and die. The perianal eggs and worms produce the characteristic symptoms of pruritis ani, which often leads to perianal scratching and insomnia. Many infections are asymptomatic.

---

Fig. 16. Numerous silver-stained *Histoplasma* are seen within macrophages in this appendix. H&E/methenamine silver, original magnification \( \times 400 \).
The causal role of *Enterobius* in appendicitis remains controversial. Although pinworms are detected in approximately 0.6% to 13% of resected appendices, they are usually not invasive, and their ability to cause mucosal damage has been a subject of intense debate.\(^76–79\) The relationship between pinworm infection and the symptoms of acute appendicitis also remains unclear. Some authorities believe that the lack of inflammation surrounding invasive pinworms indicates that the organism invades only after the appendix has been removed to escape the decrease in oxygen tension.\(^76\) However, invasion has been documented occasionally, with associated mucosal ulceration and inflammation, and it has been suggested that if additional sections were submitted from appendices containing lumenal pinworms, more cases of invasive enterobiasis would be found. In addition, both worms and ova may obstruct the appendiceal lumen and cause inflammation similar to that caused by fecaliths.\(^48,76–79\)

**Pathologic findings**

In the appendix, the mucosa usually seems normal, and pinworms are most often found in the appendiceal lumen (Fig. 17). Even invasive pinworms incite little, or no, inflammatory reaction, but rarely an inflammatory infiltrate composed of neutrophils and eosinophils may occur,\(^76–79\) along with hemorrhage and ulceration. Granulomas, sometimes with necrosis, may develop rarely as a reaction to degenerating worms or eggs.

The worms are 2 to 5 mm long, white or ivory, and pointed at both ends; the posterior end is curved. They may be seen with the naked eye. Morphologically, pinworms have prominent lateral alae with easily visible internal organs (Fig. 18); eggs are ovoid with one flat side, and a bilayered refractile shell.

![Fig. 17. Multiple pinworms are present in the lumen of a resected appendix. H&E, original magnification ×100.](image-url)
Differential diagnosis
The morphologic features of the worm, described earlier, are characteristic of enterobiasis. As discussed earlier, it may be difficult to distinguish between primary Enterobius infection and the presence of worms complicating or existing within the context of preexisting acute appendicitis.

Strongyloides stercoralis is a nematode with a worldwide distribution. It is endemic in tropical climates; in the United States, it is endemic in the southeast, urban areas with large immigrant populations, and mental institutions.\textsuperscript{80–84} Strongyloides stercoralis is contracted from soil containing the organism, and infection occurs primarily in adults, many of whom are hospitalized, suffer from chronic illnesses, or are immunocompromised. Corticosteroids and human T-lymphotropic virus 1 viral infection are also associated with strongyloidiasis. Patients with AIDS do not seem to be unusually susceptible. *Strongyloides stercoralis* is a rare cause of appendicitis, and the diagnosis of strongyloidiasis is almost always made postsurgically.\textsuperscript{84}

Patients may have symptoms that are clinically indistinguishable from acute nonspecific appendicitis.\textsuperscript{80–82} Some patients have a more protracted course of nonspecific chronic abdominal pain.\textsuperscript{84} GI manifestations may be accompanied by mesenteric adenopathy, rash, urticaria, pruritis, mild anemia, peripheral eosinophilia and leukocytosis, and concomitant pulmonary symptoms.\textsuperscript{83}

Pathologic features
Affected appendices typically show a marked transmural eosinophilic and neutrophilic infiltrate. Granulomas are occasionally present as well. Larvae may be found within granulomas.\textsuperscript{80,82,83} Both adult worms and larvae may be found in the crypts (Figs. 19 and 20), but they may be difficult to detect. Worms typically have sharply pointed tails that may be curved. In severe infections, larvae may be seen transmurally, and in lymphatics and small vessels. Examination of stool may be an invaluable aid to diagnosis.
Fig. 19. *Strongyloides* are seen in the crypts of an appendix; note also that there are pinworms in the overlying debris. H&E, original magnification ×100. (*Courtesy of Dr Dennis Baroni-Cruz.*)

Fig. 20. High-power view of *Strongyloides* in the appendiceal crypts. The surrounding inflammatory infiltrate contains numerous eosinophils. H&E, original magnification ×400. (*Courtesy of Dr Dennis Baroni-Cruz.*)
**Differential diagnosis**

The presence of larvae with sharply pointed, sometimes curved tails within the glands of the GI mucosa is essentially diagnostic of strongyloidiasis. Ancillary diagnostic tests include stool examination for larvae, worms, or eggs, and serologic tests.

**Schistosomiasis**

Schistosomes, most commonly *Schistosoma haematobium*, only rarely cause appendicitis even in nations where schistosomiasis is endemic. Patients usually present with signs and symptoms typical of acute appendicitis, although some present with inflammatory masses. Patients may require antischistosomal therapy in addition to appendectomy.

**Pathologic features**

Histologically, appendices may show transmural inflammation rich in eosinophils, with a granulomatous reaction to ova. Older granulomas may be fibrotic and hyalinized, with numerous calcified eggs (Fig. 21). Similar to earlier discussion, arguments regarding the pathogenicity of *Enterobius* in the appendix have also occurred pertaining to schistosomes. However, it has been shown at least in some cases that schistosomes do cause acute appendicitis, either by inducing granulomatous inflammation, or by producing such marked fibrosis that lumenal obstruction leads to signs and symptoms of acute appendicitis.

**Entamoeba Histolytica**

*Entamoeba histolytica* are occasionally found in the appendix, usually in the lumen without accompanying inflammation, and rarely with associated acute appendicitis.

---

*Fig. 21.* Schistosome eggs in the wall of the appendix, with surrounding marked fibrosis and calcification of eggs. H&E, original magnification ×40. (*Courtesy of Dr Joseph Misdraji.*)
These cases are usually associated with heavy infection of the right colon, and patients may require antiparasitic therapy in addition to surgery.

When amoebae are found in the appendix, pathogenic *Entamoeba histolytica* must be distinguished from nonpathogenic amoeba such as *Entamoeba coli*, and from macrophages. Amebic trophozoites have distinct cell membranes with foamy cytoplasm, round and eccentrically located nuclei with peripheral margination of chromatin, and a central karyosome. The presence of ingested red blood cells is essentially pathognomonic of *Entamoeba histolytica*, and helps to distinguish it from other amoebae (see later discussion) (Fig. 22). Distinction of trophozoites from macrophages within inflammatory exudates may be difficult, particularly in poorly fixed tissue sections. Amoebae are trichrome and periodic acid-Schiff positive; in addition, their nuclei are usually more rounded, smaller, paler, and have a more open nuclear chromatin pattern than those of macrophages. Macrophages stain with CD68, α1-antitrypsin, and chymotrypsin, whereas amoebae do not. Useful diagnostic tests for *Entamoeba histolytica* include stool examination for cysts and trophozoites, stool culture, serologic tests, and PCR assays, although the latter are not widely available.

Other parasites that may affect the appendix (summarized in Table 1) include *Trichuris* species (whipworms) and *Ascaris lumbricoides* (roundworms). Rarely, coccidians such as *Cryptosporidium* have been found in the appendix, primarily in immunocompromised patients.

REFERENCES


