Management of acute appendicitis in adults

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INTRODUCTION

Acute appendicitis is the most common abdominal surgical emergency in the world, with a lifetime risk of 8.6 percent in males and 6.9 percent in females [1]. For over a century, open appendectomy was the only standard treatment for appendicitis. Contemporary management of appendicitis is more sophisticated and nuanced: laparoscopic appendectomy has surpassed open appendectomy in usage, some patients with perforated appendicitis may benefit from initial antibiotic therapy followed by interval appendectomy, and several trials have even suggested that it is feasible to treat uncomplicated appendicitis nonoperatively with antibiotics alone.

The management of appendicitis in **adults** will be reviewed here. Appendicitis in children and pregnant patients is discussed separately:

- (See "Acute appendicitis in children: Management".)
- (See "Acute appendicitis in pregnancy".)

The clinical manifestations and diagnostic evaluation of appendicitis, as well as the techniques of appendectomy in adults, are also discussed elsewhere.

- (See "Acute appendicitis in adults: Clinical manifestations and differential diagnosis".)
- (See "Acute appendicitis in adults: Diagnostic evaluation".)
- (See "Appendectomy".)

NONPERFORATED APPENDICITIS

Nonperforated appendicitis, also referred to as simple appendicitis or uncomplicated appendicitis, refers to acute appendicitis that presents without clinical or radiographic signs of perforation (eg, inflammatory mass, phlegmon, or abscess). Approximately 80 percent of appendicitis are not perforated at presentation [2].

For over 100 years, appendectomy was the only therapy for appendicitis, and it continues to be the dominant treatment for appendicitis around the world [3]. However, there is mounting evidence that, in many respects, antibiotic therapy is not inferior to surgery for nonperforated appendicitis in healthy patients (algorithm 1). (See 'Shared decision making' below.)

Nonoperative management — Nonoperative treatment is a strategy in which patients receive antibiotics with the aim of avoiding surgery. For these patients, appendectomy is reserved for those who do not have a response to antibiotics or have recurrence of appendicitis.

Nonoperative management may offer certain benefits such as expedited recovery and reduced days away from work or other activities. In exchange, patients must be counselled and be willing to accept greater uncertainties of possible disease progression despite antibiotics, disease recurrence, or missed neoplasm (table 1).

Candidates — Nonoperative management is appropriate in patients who have a clinical diagnosis of localized appendicitis without physical findings of diffuse peritonitis or imaging evidence of large abscess, phlegmon, perforation, or tumor [2].

- **Relative contraindications** – Nonoperative management can be instituted in these patients, but the response to antibiotics may be delayed, and for those with appendicolith, the failure and complication rate of nonoperative management is known to be higher. (See 'Expectations' below.)

  - **Appendicolith** – Patients with imaging-identified appendicolith (present in approximately 25 percent of patients) are at increased risk for complications such as abscess and undergo appendectomy more frequently than patients without appendicolith. CODA was the only trial that included patients with appendicoliths [4].

  - **Older patients** – Antibiotic response may be delayed in patients who are 45 years of age or older and in those who have appendicoliths, extraluminal fluid or air, fever, or elevated inflammatory markers and in those who have had symptoms for more than 48 hours, all of which are associated with appendiceal abscess. Such patients were

excluded from some trials. Additionally, older adults are more likely to have an occult appendiceal malignancy [5-9].

- **Contraindications** – Nonoperative management has not been sufficiently studied in these patients, as they have been excluded from the trials.

  - Diffuse peritonitis
  - Hemodynamically instability or severe sepsis
  - Pregnancy [10], immunocompromise, or history of inflammatory bowel disease

Protocols — The nonoperative management of nonperforated appendicitis is not standardized; treatment protocols vary between trials.

- **Antibiotics** – Most trials require initial intravenous antibiotics for one to three days, followed by oral antibiotics for up to a total of 7 to 10 days [11]. The choices of antibiotics are not standardized, but one of the intravenous regimens that we suggest for low-risk community-acquired intra-abdominal infections is likely to provide sufficient coverage (table 2). A long-acting agent such as ceftriaxone, given in combination with metronidazole, can facilitate early discharge [2,12].

  In some cases, patients may be treated only with oral antibiotics. Potential oral regimens (either for initial therapy or as step-down therapy after an initial intravenous regimen) include a fluoroquinolone (eg, ciprofloxacin or levofloxacin) in combination with metronidazole, a third-generation cephalosporin (eg, cefdinir) in combination with metronidazole, or amoxicillin-clavulanate [12]. In the APPAC II trial, 70 percent of patients who received seven-day oral moxifloxacin and 74 percent of patients who received two-day intravenous ertapenem followed by five-day oral levofloxacin and oral metronidazole successfully avoided appendectomy at one year [13]. However, some UpToDate experts avoid moxifloxacin because of concern for resistance in *Bacteroides*. Furthermore, ertapenem is usually reserved for high-, rather than low-risk community-acquired intra-abdominal infections because of its broader spectrum [12].

  Antibiotic selection for community-acquired intra-abdominal infections is discussed in detail elsewhere. (See "Antimicrobial approach to intra-abdominal infections in adults".)

  Whether antibiotics are necessary for nonoperative management of nonperforated appendicitis has also been investigated. In the APPAC III trial (66 patients), 87 percent (95% CI 75-99) of those treated with placebo and 97 percent (95% CI 92-100) of those treated with antibiotics were successfully treated without surgery within 10 days; the difference was not statistically significant (p = 0.142) [14]. In an earlier Korean trial (245 patients), the

initial treatment failure rate was similar (both 7 percent) with or without a four-day course of antibiotics [15]. In both trials, all patients were hospitalized for at least three days. These results are thought provoking, suggesting that perhaps, unlike perforated appendicitis, uncomplicated appendicitis may be of inflammatory rather than infectious etiology. However, more studies of larger populations are required before nonoperative management of appendicitis without antibiotics can be recommended, especially with only a brief observation or outpatient treatment as performed in the CODA trial.

- **Disposition** – After the initiation of antibiotics, pain, fever, leukocytosis, and anorexia typically subside within 24 hours in half of patients with nonperforated appendicitis and most patients in 48 hours [16,17]. As such, patients are typically admitted to the hospital during the first one to three days for close observation in case of clinical deterioration, which requires prompt rescue appendectomy. Response to antibiotics may be delayed in certain patients listed above; longer period of observation and intravenous antibiotics may be warranted in such patients. (See 'Candidates' above.)

  The CODA trial permitted discharge from the emergency department after the patient has received parenteral antibiotics for 24 hours or the bioavailability equivalent of 24 hours [4]. A post-hoc analysis reported that outpatient antibiotic management (discharge <24 hours) was not associated with any greater risk of complications or appendectomy than hospital care (discharge >24 hours) [18]. Outpatients require close follow-up in the clinic or by telemedicine in one to two days to ensure continued clinical improvement.

Expectations — Several randomized trials have compared antibiotics with appendectomy for nonperforated appendicitis [4,19-25]. Many more prospective comparative studies and meta-analyses have been published [11,26-30]. The results are summarized below and in this table (table 1).

- **Initial appendicitis** – Approximately 90 percent of patients treated with antibiotics are able to avoid surgery during the initial admission. The other 10 percent who fail to respond to antibiotics require a rescue appendectomy. However, there is no reliable way of predicting who will or will not respond to antibiotics, except that the presence of an appendicolith was associated with a nearly twofold increased risk of undergoing appendectomy within 30 days of initiating antibiotics to 21 percent [31].

  Most patients treated with antibiotics respond clinically with a reduction in white blood cell count [21], avoidance of peritonitis [19], and general symptom reduction [4,20,22,23]. Compared with those who underwent upfront appendectomy, patients treated with antibiotics have lower or similar pain scores [19-21], require fewer doses of narcotics [21],

and require fewer missed work days for the patient or caregiver [4,20,21]. In one trial, the 30-day general health statuses of those treated with antibiotics were noninferior to those of those who underwent appendectomy [4].

- **Recurrent appendicitis –** Fifteen to 49 percent of patients who choose nonoperative treatment may develop recurrent symptoms, which may lead to additional emergency department visits or hospitalizations typically not required after upfront appendectomy [4,19,32,33]. It is unclear whether the success in avoiding surgery justifies the fear and burden of potential recurrent appendicitis. When appendicitis recurs, surgery is commonly performed and may be preferred in adults who are 40 years of age or older given the possibility of a malignancy. Retreatment with antibiotics is an option in younger patients.

  - **One-year risk** – In the trials that only enrolled patients without appendicolith, approximately 70 percent of those successfully treated with antibiotics during the initial admission were able to avoid surgery during the first year. The other 30 percent eventually require appendectomy for recurrent appendicitis or symptoms of abdominal pain (mean time to appendectomy 4.2 to 7 months [19,21,22]). In the only trial that included patients with appendicoliths, 40 percent required appendectomy at one year [33].

  - **Three- to five-year risk** – Follow-up data beyond the first year are available for the APPAC trial and the CODA trial. In the five-year observational follow-up of 257 patients initially treated with antibiotics for uncomplicated acute appendicitis in the APPAC trial, the cumulative incidence of recurrent appendicitis was 27.3 percent at one, 34.0 percent at two, 35.2 percent at three, 37.1 percent at four, and 39.1 percent at five years [34]. At seven years, 39 percent of those in the antibiotic group required appendectomy (17 percent during initial hospitalization, 83 percent due to recurrent appendicitis) [35]. In the CODA trial, which included patients with appendicolith, 29 percent of patients required appendectomy at 90 days (41 percent with appendicolith versus 25 percent without appendicolith) [4], 40 percent at one year, 46 percent at two years, and 49 percent at three and four years [33].

  - **Long-term risk** – Follow-up data for up to 25 years are now available from the first two randomized trials conducted in Sweden in the 1990s [21,22]. For patients originally assigned to the nonoperative management group, the cumulative risk of appendectomy at 25 years is 40 percent; for those who were discharged without appendectomy at the initial visit, the cumulative risk of subsequent appendectomy is 30 percent [36]. That is to say, the curve flattens after the first few years, or after the

first few years, the risk of needing appendectomy returns to that of the general population.

- **Missed appendiceal neoplasm** – The prevalence of appendiceal neoplasms in patients with nonperforated appendicitis is generally an order of magnitude lower than that of appendiceal neoplasm in those with perforated appendicitis (1 versus 10 percent). However, interval appendectomy is usually performed in the latter but not the former group of patients, leading to possibly missed neoplasms in patients who undergo nonoperative management of nonperforated appendicitis. (See 'Interval appendectomy' below and "Appendectomy", section on 'Appendiceal neoplasms'.)

- **Quality of life** – Patient quality of life was the focus of the COMMA trial (186 patients with uncomplicated appendicitis), which reported a 25 percent recurrence rate at one year in patients initially treated with antibiotics. The quality-of-life scores were better at both 3 and 12 months for patients who underwent appendectomy compared with those who were treated with antibiotics [25].

  In a seven-year observational follow-up of 423 patients in the APPAC trials, however, there was no difference in patient satisfaction after successful antibiotic treatment (no appendectomy) compared with appendectomy; both groups were more satisfied than patients who required both antibiotic therapy and appendectomy [35].

- **Cost** – It is unclear whether antibiotic treatment increases hospital utilization, and therefore cost, both during the initial phase of treatment and for recurrences. A cost analysis of one of the trials (APPAC) associated the antibiotic-first approach with lower five-year cost than the appendectomy approach, albeit within a single highly selected Finnish population [37]. The COMMA trial also reported lower cost for the antibiotic-first approach (EUR €3077 versus €4816) [25].

  Regardless, antibiotic therapy for appendicitis should not be promoted as a cost-saving measure. It has not been sufficiently studied and is not practical in resource-limited settings for a number of reasons (eg, lack of advanced imaging capacity, lack of reliable follow-up, surgeon perception) [38].

Shared decision making — Because nonoperative management of appendicitis is a newer concept compared with appendectomy, for cases appropriate for nonoperative management, some surgeons are engaging patients in a shared decision making (SDM) activity to help them choose between antibiotics and appendectomy based on their unique circumstances, characteristics, and preferences [2,39-42]. A commonly used online tool is linked here.

Appendectomy — The surgical treatment for appendicitis is appendectomy, which can be performed open or laparoscopically [43]. The perioperative logistic issues of appendectomy are discussed here; the techniques are discussed elsewhere. (See "Appendectomy".)

Timing of appendectomy — Patients present with appendicitis at all times of the day. A large randomized trial showed that a short in-hospital delay up to 24 hours before surgery in patients with uncomplicated appendicitis (including those with appendicolith on CT) did not incur an increased risk of perforation or other complications compared with operation within eight hours [44]. Another trial showed that, for appendicitis diagnosed in the evening, delaying appendectomy until the morning is safe [45]. However, data from another meta-analysis associated delaying appendectomy for >48 hours with increased surgical site infections and other complications [46].

Thus, for acute nonperforated appendicitis in a stable patient, we perform appendectomy within 24 hours of presentation; the patients should be admitted to the hospital and receive intravenous hydration, pain control, and intravenous antibiotics while awaiting surgery. The exact timing of surgery should depend on the availability of surgeons and operating room resources. (See 'Patients on antiplatelet or antithrombotic therapy' below.)

Preoperative preparation — Patients with acute appendicitis require adequate hydration with intravenous fluids, correction of electrolyte abnormalities, pain control, and perioperative antibiotics [47].

Prophylactic antibiotics — Prophylactic antibiotics are important for preventing wound infection and intra-abdominal abscess following appendectomy [47]. The flora of the appendix reflects that of the colon and includes gram-negative aerobes and anaerobes.

Patients proceeding directly from the emergency department to the operating room for appendectomy without further delay should receive prophylactic antibiotics within a 60 minute "window" before the initial incision [48,49]. In general, a single preoperative antibiotic dose for surgical wound prophylaxis is adequate. Guidelines established by the Medical Letter and the Surgical Care Improvement Project suggest the following options for appendectomy (table 3) [50,51]:

- Cefoxitin (2 g intravenously [IV])
- Cefotetan (2 g IV)
- Cefazolin (2 g if <120 kg or 3 g if ≥120 kg IV) PLUS metronidazole (500 mg IV)
- In patients allergic to penicillins and cephalosporins, clindamycin PLUS one of the following: ciprofloxacin, levofloxacin, gentamicin, or aztreonam

Postoperative antibiotics are unnecessary [52]. (See "Antimicrobial prophylaxis for prevention of surgical site infection in adults" and "Antimicrobial prophylaxis for prevention of surgical site infection following gastrointestinal surgery in adults", section on 'Gastroduodenal procedures'.)

Patients who present at night and will not undergo appendectomy until the next morning should be admitted to the hospital and started on intravenous antibiotics as soon as possible (often in the emergency department), rather than waiting until just before surgery. In this case, we suggest choosing antibiotics from the list intended for patients with perforated/complicated appendicitis to provide broad-spectrum coverage (see 'Antibiotics for perforated appendicitis' below). Additional prophylactic antibiotics may be required if patients did not receive antibiotics within the 60 minute "window" before incision.

Patients on antiplatelet or antithrombotic therapy — Appendectomy is commonly performed urgently. Although it is generally considered a low-bleeding-risk procedure, the decision to interrupt anticoagulation also depends on the patient's thrombotic risk. In discussion with the clinician prescribing the medication, if the risk of interrupting anticoagulation is considered too high, nonoperative management should be offered. If it is reasonable to temporarily interrupt anticoagulation, and the decision is to proceed with appendectomy, the following timelines are suggested based on the pharmacokinetics of the medications, assuming appendectomy needs to be performed semiurgently.

- Aspirin **or** clopidogrel – Prehospital use of aspirin or clopidogrel should not preclude or delay laparoscopic appendectomy. In a retrospective case-control study of patients undergoing laparoscopic appendectomy, those who were taking aspirin, clopidogrel (Plavix), or both did not have more blood loss or transfusion requirements than matched controls; neither was there any difference in complications, length of hospital stay, readmission, or mortality between the two groups [53].

- **Direct oral anticoagulants** – Patients on one of the direct oral anticoagulants (DOACs), such as dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), or edoxaban (Savaysa), should wait for 24 hours (creatinine clearance >50 mL/min) to 48 hours (creatinine clearance ≤50 mL/min) from the last dose before undergoing appendectomy (table 4). Evidence from the nonoperative management trials suggests that the rate of perforation is not higher as long as they are observed and receive antibiotics. (See "Perioperative management of patients receiving anticoagulants", section on 'DOAC interruptions (overview)' and 'Expectations' above.)

- Warfarin – Patients on warfarin should receive vitamin K (2.5 to 5 mg oral or intravenous), which will reverse the warfarin in one to two days. Appendectomy can then proceed once

the international normalized ratio (INR) value is normalized [54]. (See "Perioperative management of patients receiving anticoagulants", section on 'Urgent/emergency invasive procedure'.)

PERFORATED APPENDICITIS

Patients with perforated appendicitis may appear acutely ill and have significant dehydration and electrolyte abnormalities, particularly if fever and vomiting have been present for a long time. The pain usually localizes to the right lower quadrant if the perforation has been walled off by surrounding intra-abdominal structures, such as the omentum, but can be diffuse if generalized peritonitis ensues. On imaging studies, appendicitis can present with a contained perforation (an inflammatory mass often referred to as a "phlegmon," or an intra-abdominal or pelvic abscess) or, rarely, a free perforation.

Other unusual presentations of appendiceal perforation can occur, such as retroperitoneal abscess formation due to perforation of a retrocecal appendix or liver abscess formation due to hematogenous spread of infection through the portal venous system. An enterocutaneous fistula can result from an intraperitoneal abscess that fistulizes to the skin. Appendiceal perforation can result in a small bowel obstruction, manifested by bilious vomiting and obstipation. High fevers and jaundice can be seen with pylephlebitis (septic portal vein thrombosis) and can be confused with cholangitis.

Perforation is found in 13 to 20 percent of patients who present with acute appendicitis [55]. The perforation rate is higher among men (18 percent men versus 13 percent women) and older adults [5,55]. Although perforation is a major concern when evaluating a patient with symptoms that have lasted more than 24 hours, the time course of progression of appendicitis to necrosis and perforation varies among patients, and perforation can develop more rapidly and should always be considered. Approximately 20 percent of patients with perforated appendicitis present within 24 hours of the onset of symptoms [56].

The management of perforated appendicitis depends on the condition of the patient (stable versus unstable), the nature of the perforation (contained versus free perforation), and whether an abscess or phlegmon is present on imaging studies (algorithm 2):

Unstable patients or patients with free perforation — A free perforation of the appendix can cause intraperitoneal dissemination of pus and fecal material and generalized peritonitis. These patients are typically quite ill and may be septic or hemodynamically unstable, thus requiring preoperative resuscitation. The diagnosis is not always appreciated before exploration.

For patients who are septic or unstable, and for those who have a free perforation of the appendix or generalized peritonitis, emergency appendectomy is required, as well as drainage and irrigation of the peritoneal cavity. Emergency appendectomy in this setting can be accomplished open or laparoscopically; the choice is determined by surgeon preference with consideration of patient condition and local resources. (See 'Appendectomy for perforated appendicitis' below.)

Since appendectomy for unstable or freely perforated patients is a true surgical emergency and can carry a high risk of bleeding, anticoagulation should be immediately reversed prior to surgery (table 5 and table 6).

Stable patients — Stable patients with perforated appendicitis who have symptoms localized to the right lower quadrant can be treated with immediate appendectomy or initial nonoperative management. Both approaches are safe. A 2017 Cochrane review of two randomized trials concluded that the quality of the evidence was too low to make a recommendation [57]. Thus, the decision ultimately rests with the treating surgeon. We suggest the following initial approach based on imaging findings on presentation (algorithm 2):

- Patients with a small (≤3 cm) appendiceal abscess may undergo immediate appendectomy. Larger (>3 cm) abscesses should be treated with intravenous antibiotics and percutaneous drainage first, although immediate appendectomy is required if the abscess is not amenable to percutaneous drainage.

- Patients with a phlegmon of the right lower quadrant should be assessed for the likelihood that an appendectomy can be safely performed without the need for an ileocecal resection. If appendectomy is feasible and an ileocecal resection is not likely required, immediate appendectomy may be performed. If the contrary is true, the patient should be treated with intravenous antibiotics first.

Patients who fail initial antibiotic therapy clinically or radiographically require rescue appendectomy, whereas those who respond to initial antibiotic therapy can be discharged with oral antibiotics to complete a 7- to 10-day course (in total) and return for follow-up in six to eight weeks. (See 'Initial nonoperative management' below.)

Initial nonoperative management — Stable patients with perforated appendicitis who have symptoms localized to the right lower quadrant (ie, no free perforation or generalized peritonitis) may be treated initially with antibiotics, intravenous fluids, and bowel rest, rather than immediate surgery [16]. These patients will often have a palpable mass on physical examination; a computed tomography (CT) scan may reveal a phlegmon or abscess.

Immediate surgery in patients with a long duration of symptoms and phlegmon or abscess formation has been associated with increased morbidity, due to dense adhesions and inflammation [58]. Under these circumstances, appendectomy often requires extensive dissection and may lead to injury of adjacent structures. Complications such as a postoperative abscess or enterocutaneous fistula may ensue, necessitating an ileocolectomy or cecectomy [59]. Nonoperative management during the initial admission allows the local inflammation to subside; interval appendectomy can be carried out at a lower risk. Fortunately, many of these patients will respond to initial nonoperative management since the appendiceal process has already been "walled off."

A 2010 meta-analysis of 17 nonrandomized studies showed that, compared with immediate surgery, the initial nonoperative management of perforated appendicitis with abscess or phlegmon is associated with fewer complications and a similar length of stay and duration of antibiotics [60]. Although a small randomized trial published after the meta-analysis showed immediate laparoscopic appendectomy to be feasible for perforated appendicitis with abscess (median duration of symptom seven days) and resulted in fewer readmissions and fewer additional interventions than nonoperative management, substantial portions of patients who underwent immediate surgery required bowel resection (10 percent), required conversion to open surgery (10 percent), or had incomplete appendectomy (13 percent) [58].

Initial nonoperative management includes intravenous antibiotics and fluids as well as bowel rest; any accessible abscess should be drained percutaneously under image guidance. Patients should be closely monitored in the hospital during this time. Treatment failure, as evidenced by bowel obstruction, sepsis, or persistent pain, fever, or leukocytosis, requires immediate rescue appendectomy. If fever, tenderness, and leukocytosis improve, diet can be slowly advanced, usually within three to five days. Patients are discharged home when clinical parameters have normalized and return for a follow-up in six to eight weeks. (See 'Interval appendectomy' below.)

Antibiotics for perforated appendicitis — In patients with perforated appendicitis, the antibiotic regimen should consist of empiric broad-spectrum therapy with activity against gram-negative rods and anaerobic organisms pending culture results. The choice of agents is based on patient and disease factors and is discussed in detail separately (see "Antimicrobial approach to intra-abdominal infections in adults", section on 'Approach to empiric antibiotic selection'):

- Most perforated appendices or appendiceal abscesses fall into the category of mild-to-moderate community-acquired intra-abdominal infections without risk factors for antibiotic resistance or treatment failure (table 7). Coverage of streptococci,

nonresistant Enterobacteriaceae, and (in most cases) anaerobes is generally sufficient (table 2).

- In cases of perforated appendicitis that are severe, or in patients at high risk for adverse outcomes or resistance (table 7), broader empirical coverage is warranted. We generally include an agent with gram-negative activity broad enough to cover *Pseudomonas aeruginosa* and Enterobacteriaceae that are resistant to nonpseudomonal cephalosporins in addition to coverage against enteric streptococci and (in most cases) anaerobes (table 8).

- Although rare for appendicitis, in patients with health-care-associated infections, the likelihood of drug resistance is high. Thus, to achieve empiric coverage of likely pathogens, in addition to coverage against streptococci and anaerobes, regimens should at least include agents with expanded spectra of activity against gram-negative bacilli (including *P. aeruginosa* and Enterobacteriaceae that are resistant to nonpseudomonal third-generation cephalosporins and fluoroquinolones). We also usually use an empiric regimen that has antienterococcal activity for patients with health-care-associated intra-abdominal infection, particularly those with postoperative infection, those who have previously received cephalosporins or other antimicrobial agents selecting for *Enterococcus* species, immunocompromised patients, and those with valvular heart disease or prosthetic intravascular materials (table 9).

Regardless of the initial empiric regimen, the therapeutic regimen should be revisited once culture and susceptibility results are available. Recovery of more than one organism should suggest polymicrobial infection including anaerobes, even if no anaerobes are isolated in culture. In such circumstances, anaerobic coverage should be continued.

The duration of antibiotic treatment differs depending on whether definitive therapy (appendectomy) is performed. In patients with perforated appendicitis who undergo appendectomy during the same admission, antibiotics should generally be continued for two to four days after surgery, as supported by the following studies:

- In the STOPIT trial, patients with an intra-abdominal infection (including 73/518 patients with appendicitis) were randomly assigned to four versus eight days of antibiotics after source control [61]. The two groups had similar numbers of infectious complications and mortalities (composite rate 21.8 versus 22.3 percent).

- In the APPIC trial, about 1000 patients with complex appendicitis (defined as necrosis, perforation, or abscess formation) were randomly assigned to either two or five days of intravenous antibiotics after appendectomy [62]. The composite rate of infectious

complications and mortality was similar between the two groups (10 percent two day versus 8 percent five day), although the two-day group had a higher rate of emergency room visits (15 versus 8 percent). It should be noted that 95 percent of the appendectomies were laparoscopic, and in the subgroup analysis of the 50 patients who underwent open appendectomy (half of which converted from laparoscopy), the infection rate was much higher in the two-day group (27 versus 4 percent).

- In another trial of 104 patients with complicated appendicitis (defined as gangrenous or perforated) who received 24 hours of intravenous or oral amoxicillin-clavulanate, the 30-day complication rate was not different (15 percent in both groups) [63]. However, the study population was dominated by those with gangrenous appendicitis (75 percent), yet 67 percent of organ/space infections occurred in those with perforated appendicitis. This calls into question whether 24 hours of postoperative antibiotics is sufficient for perforated appendicitis. Larger trials with more perforated patients are required.

The duration of antibiotics for patients with perforated appendicitis who do not undergo appendectomy during the same admission varies depending on whether percutaneous drainage is performed, as well as the patient's clinical response to treatment. Those who respond to initial antibiotic therapy can be discharged with oral antibiotics to complete a seven- to ten-day course in total.

Percutaneous abscess drainage — If imaging studies demonstrate an intra-abdominal or pelvic abscess, CT- or ultrasound-guided drainage can often be performed percutaneously or transrectally [64]. Studies suggest that percutaneous drainage of appendiceal abscesses results in fewer complications and shorter overall length of stay than surgical drainage [16,65,66]. It also allows inflammation to subside before appendectomy, thereby negating the need for a more extended bowel resection (eg, ileocecectomy) in some cases.

Appendectomy for perforated appendicitis — Appendectomy during the same admission may be required to treat perforated appendicitis in one of three clinical scenarios (algorithm 2):

- Emergency appendectomy is required for patients with free perforation of the appendicitis, with diffuse peritonitis, or who are septic or hemodynamically unstable as a result of perforated appendicitis. (See 'Unstable patients or patients with free perforation' above.)

- Rescue appendectomy is required for patients with perforated appendicitis who fail to respond to nonoperative management with intravenous antibiotics with or without percutaneous drainage, regardless of initial imaging findings. (See 'Stable patients' above.)

- Upfront appendectomy may be performed for perforated appendicitis associated with a small but well-contained abscess or a larger abscess not accessible to percutaneous drainage. It may also be performed in the presence of a right lower quadrant phlegmon if the surgeon judges the risk of requiring an ileocecal resection is low. (See 'Stable patients' above.)

Operative techniques are similar to those used for nonperforated appendicitis, with a few variances to accommodate the perforation. (See "Appendectomy", section on 'Technical variances for perforation'.)

Interval appendectomy — Using the initial nonoperative approach outlined above, more than 80 percent of patients who present with a "walled-off" appendiceal process (ie, contained perforation) can be spared an appendectomy during the initial admission [67].

After successful nonoperative management of perforated appendicitis, patients should be seen in six to eight weeks, at which time those over 40 who have not undergone routine colonoscopic screening should be offered a colonoscopy. The risk of such patients harboring a cecal or appendiceal neoplasm can be high [8]. (See 'Older adults' below.)

We also suggest interval appendectomy for all patients with perforated appendicitis managed nonoperatively primarily to exclude an appendiceal neoplasm [68].

- The prevalence of appendiceal neoplasm is an order of magnitude higher in interval appendectomy specimens (10 to 29 percent [8,69,70]) than in routine appendectomy specimens (0.9 to 1.4 percent [5,70,71]), especially in adults over 40 [69,72].

- In a 2019 Finnish trial, 60 adult patients with periappendicular abscesses managed nonoperatively underwent either interval appendectomy or follow-up with magnetic resonance imaging (MRI). After an interim analysis, the trial was terminated early and interval appendectomy was recommended to all patients. In the end, the overall incidence of neoplasms was 12 out of 60 (20 percent) and 12 out of 41 (29 percent) in patients older than 40 years of age. Five of the 12 tumors were low-grade appendiceal mucinous neoplasms (LAMNs), three were serrated adenomas, two were adenocarcinomas, one was a carcinoid tumor, and one was pseudomyxoma peritonei [72]. (See "Appendiceal mucinous lesions".)

Although pursuing interval appendectomy also has the added benefit of preventing recurrent appendicitis, which occurs in 5 to 38 percent of patients [32,58,71,73], this is not the most compelling reason for routine interval appendectomy, as some argue that the incidence of

recurrent symptoms following successful conservative management of perforated appendicitis is too low to justify routine surgery in asymptomatic patients [74,75].

SPECIAL PATIENT POPULATIONS

Older adults — One in every 2000 adults over age 65 will develop appendicitis annually, making appendicitis an important cause of abdominal pain in this age group [76]. Older adults tend to have a diminished inflammatory response, resulting in fewer cases of leukocytosis [77] and less remarkable findings on history and physical examination [78]. For these reasons, older patients often delay seeking medical care, and, as a result, they have a considerably higher rate of perforation at the time of presentation [77,79,80]. Older patients may have comorbid cardiac, pulmonary, and renal conditions with resulting morbidity and mortality from perforation. In one series, the mortality from perforated appendicitis in patients over age 80 was 21 percent [81]. Older patients can also have a redundant sigmoid colon that can cause right-sided pain from sigmoid diseases. Accordingly, CT scanning can improve diagnostic accuracy in this population [82].

Laparoscopic appendectomy can be used successfully in the older adult population and results in shorter hospitalization for older patients with both perforated and nonperforated appendicitis [83,84].

- In a database study of over 21,000 patients undergoing appendectomy between 2016 and 2017, 9.5 percent were geriatric patients [77]. Compared with younger patients undergoing laparoscopic appendectomy, geriatric patients had a higher rate of conversion to open surgery (4.2 versus 1.5 percent), a higher percentage of tumor and/or malignancy on final pathology (2 versus 0.8 percent), and both an increased risk of intraoperative perforation and/or abscess and postoperative intra-abdominal abscess, but they had a similar risk for mortality.

- In a large retrospective cohort study of 30 day morbidity after laparoscopic appendectomy, the predicted probability of postoperative complications was 9.8 percent at age 65, 11.9 percent at age 75, and 14.5 percent at age 85 in the nonveteran cohort, and the risk was 7.5 percent at age 65, 8.3 percent at age 75, and 9.1 percent at age 85 among veterans [85].

Because colonic neoplasms are more common in older patients and can mimic appendicitis, patients over 40 who are managed nonoperatively for perforated appendicitis should undergo

colonic screening with colonoscopy, CT, or both [8], in additional to undergoing an interval appendectomy. (See 'Interval appendectomy' above.)

In addition, in a review of the Surveillance, Epidemiology, and End Results (SEER) database (2000 to 2014), 28.6 percent of appendiceal cancer patients over the age of 65 were initially misdiagnosed as having inflammatory appendicitis [86]. Thus, nonoperative management for appendicitis should be offered to older adults cautiously, and only with follow-up imaging and interval appendectomy as part of the treatment plan. (See 'Candidates' above.)

Immunocompromised patients — Immunocompromised patients are increasingly common in surgical practice and include organ transplant recipients and those receiving immunosuppressive therapy for autoimmune diseases, cancer, and acquired immunodeficiency syndrome (AIDS). Although certain causes of abdominal pain are specific to the immunocompromised state, appendicitis remains a concern [87,88]. (See "Surgical issues in HIV infection".)

The immunocompromised are susceptible to infection, and their immune response is blunted due to immunosuppressive medication or disease. As a result, they may not exhibit the typical signs and symptoms of appendicitis and may have only mild tenderness on examination. In addition, laboratory and radiological tests may not show the expected level of inflammation. An expanded differential diagnosis includes but is not limited to opportunistic (mycobacterial) and viral (cytomegalovirus) infections, fungal infections, secondary malignancies (lymphoma and Kaposi's sarcoma), and typhlitis. Because of the broad differential diagnoses, there is often a delay in reaching the diagnosis and presentation to surgical evaluation, which can increase the risk of perforation [87,89].

CT is particularly useful in this patient population as it may not only diagnose appendicitis but may exclude or diagnose other potential causes for the patient's symptoms. If appendicitis is strongly suspected, operation should not be delayed, as there is no specific contraindication to operation in immunocompromised patients, and nonoperative management is not well studied in this population. (See 'Candidates' above.)

Children — Appendicitis in children is discussed in detail separately. (See "Acute appendicitis in children: Diagnostic imaging" and "Acute appendicitis in children: Clinical manifestations and diagnosis" and "Acute appendicitis in children: Management".)

Pregnancy — Pregnancy poses unique challenges in the diagnosis and treatment of appendicitis. Acute appendicitis in pregnancy is discussed in detail separately. (See "Acute appendicitis in pregnancy".)

OUTCOMES

Mortality — The mortality associated with appendicitis is low but can vary by geographic locations. In developed countries, the mortality rate is between 0.09 and 0.24 percent. In resource-limited countries, the mortality rate is higher, between 1 and 4 percent [90].

In a worldwide observational study of 4282 consecutive patients from 44 countries treated for acute appendicitis in 2016 (95 percent surgically), the overall mortality rate was 0.28 percent [3]. In univariate analyses, predictors of mortality included age >80 years, immunosuppression, severe cardiovascular disease, Charlson comorbidity score >5, previous episodes of suspected appendicitis, previous antimicrobial therapy, World Society of Emergency Surgery (WSES) appendicitis grade 3C to 4, and a pathologic report of perforation. At multivariate analysis, however, only Charlson comorbidity score >5 (odds ratio [OR] 52.45, $p<0.05$) and WSES grade 3C (OR 11.77, $p<0.05$) and 4 (OR 11.32, $p<0.05$) were confirmed as independent variables that were predictors of mortality.

Morbidity — For nonperforated appendicitis, the overall risk of antibiotic therapy is not greater than that of upfront appendectomy, and complications that occur with appendectomies performed after trying antibiotics first are not more common than those of upfront appendectomies [4,24]. Specifically, delaying surgery while taking antibiotics does not increase the risk of perforation, which is a big patient concern and impediment to nonoperative management [4].

The most common complication of appendectomy is surgical site infection, most of which occur in patients with perforated as opposed to nonperforated appendicitis. (See "Appendectomy", section on 'Complications'.)

Recurrent or stump appendicitis — Recurrent appendicitis can occur in 15 to 49 percent of patients who are managed nonoperatively, depending on the study and the length of follow-up. Interval appendectomy eliminates the risk of recurrent appendicitis but is usually reserved for patients who had perforated appendicitis because of a much higher incidence of appendiceal neoplasm. (See 'Expectations' above and 'Interval appendectomy' above.)

Stump appendicitis is a form of recurrent appendicitis that is related to incomplete appendectomy that leaves an excessively long stump after open or laparoscopic surgery, more commonly for perforated appendicitis. To minimize stump appendicitis, the appendix should be transected no further than 0.5 cm from its junction with the cecum and removed as a whole. In case stump appendicitis occurs, stump resection can be performed open or laparoscopically. A

perforated appendiceal stump, however, typically requires a more extensive bowel resection to control [91].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Appendicitis in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Appendicitis in adults (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Nonperforated appendicitis** – For healthy adult patients with nonperforated appendicitis, nonoperative management with antibiotics and appendectomy are both safe treatment options for the initial presentation (algorithm 1). (See 'Nonperforated appendicitis' above.)

  - **Nonoperative management** – Nonoperative management may offer certain benefits such as expedited recovery and reduced days away from work or other activities. In exchange, patients must be counselled and be willing to accept greater uncertainties of possible disease progression despite antibiotics, disease recurrence, or missed neoplasm (table 1). (See 'Nonoperative management' above.)

- **Appendectomy** – If the decision is for surgery, we perform appendectomy within 24 hours of presentation. Both open and laparoscopic appendectomy are appropriate for all patients; the choice is by patient factors and surgeon preference. (See 'Appendectomy' above and "Appendectomy", section on 'Surgical approaches'.)

- **Perforated appendicitis** – The management of perforated appendicitis depends on the acuity of clinical presentation (algorithm 2). (See 'Perforated appendicitis' above.)

  - **Unstable patients** – Patients with perforated appendicitis causing hemodynamic instability, sepsis, free perforation, or generalized peritonitis require emergency appendectomy, irrigation and drainage of the peritoneal cavity, and sometimes bowel resection. Both open and laparoscopic approaches are appropriate, depending on surgeon experience, patient condition, and local resources. (See 'Unstable patients or patients with free perforation' above.)

  - **Stable patients** – For most stable patients with perforated appendicitis and symptoms localized to the right lower quadrant, we suggest initial nonoperative management rather than immediate appendectomy (algorithm 2) (**Grade 2C**). (See 'Stable patients' above.)

    Initial nonoperative management consists of intravenous antibiotics and, if an abscess is present, percutaneous drainage. The choice of antibiotics depends on whether the disease is mild to moderate (table 2) or severe (table 8), or if the patient has been recently hospitalized (table 9). Patients who fail to respond to antibiotics require rescue appendectomy.

    Patients who respond to initial antibiotic therapy should undergo interval appendectomy after six to eight weeks to exclude an appendiceal neoplasm; the prevalence of neoplasm in patients with complicated appendicitis is reported to be 10 to 30 percent. (See 'Interval appendectomy' above.)

    Immediate appendectomy is reasonable for patients who present with a small (≤3 cm) appendiceal abscess or if the abscess is not amenable to percutaneous drainage. Immediate appendectomy may also be performed in the presence of a phlegmon if the surgeon judges the risk of requiring an ileocecal resection to be low. (See 'Appendectomy for perforated appendicitis' above.)

- **Older adult and immunocompromised patients** – Appendicitis often presents late and is more likely to perforate in the older adult and immunocompromised patient populations due to a blunted inflammatory response. Nonoperative management of nonperforated

appendicitis is not well studied in either population; therefore, appendectomy may be offered without delay. The incidence of appendiceal and colonic neoplasm is also higher in the older adult population, which calls for colonoscopy and interval appendectomy whenever indicated. (See 'Special patient populations' above.)

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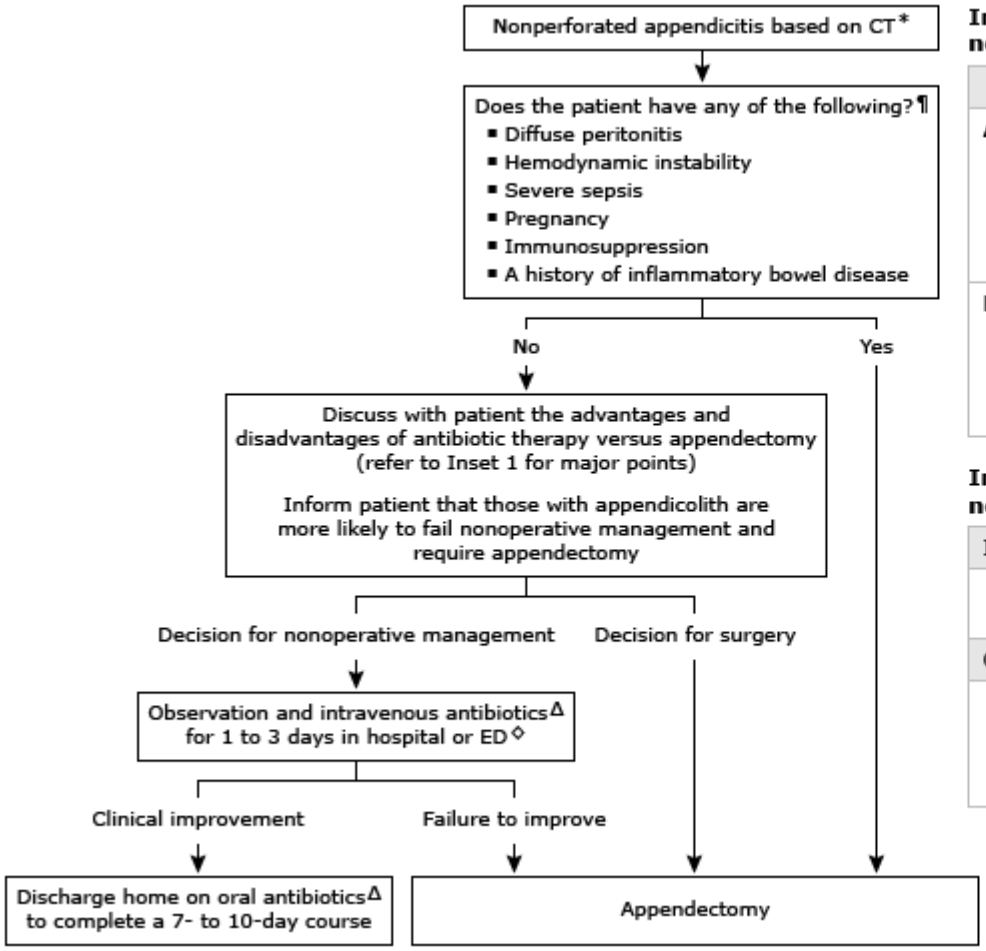
Topic 1383 Version 80.0

GRAPHICS

Management of nonperforated appendicitis in adults



Inset 1: Comparison of antibiotic nonperforated appendicitis

	Antibiotics
Advantages	▪ Avoid surgery and ▪ Shorter duration c compared with su ▪ Not associated wit risk of appendix r compared with su
Disadvantages	▪ 10 to 20% failure ▪ 30 to 40% recurre ▪ 40 to 50% recurre ▪ Small risk of miss (mostly in older p

Inset 2: Sample antibiotic choice nonperforated appendicitis¥

Intravenous antibiotics (for 1 to 3 da
▪ Ceftriaxone 2 grams once daily PLUS ▪ Levofloxacin 750 mg once daily PLUS
Oral antibiotics (to complete 7 to 10
▪ Cefdinir 300 mg twice daily ▪ Ciprofloxacin 500 mg twice daily or le metronidazole 500 mg every 8 hours ▪ Amoxicillin-clavulanate 875 mg twice

CT: computed tomography; ED: emergency department.

* Nonperforated appendicitis, also referred to as simple appendicitis or uncomplicated appendicitis, refers to acute appendicitis that presents without CT signs of perforation (eg, inflammatory mass, phlegmon, or abscess).

¶ Nonoperative management has not been sufficiently studied in these patients, as they have been excluded from the trials.

Δ Antibiotic choices are not standardized. Refer to Inset 2 for sample choices. Refer to UpToDate content on the management of appendicitis for other appropriate antibiotic regimens.

◇ Antibiotic response may be delayed in patients who are 45 years of age or older; in those who have appendicoliths, extraluminal fluid or air, fever, or elevated inflammatory markers; and in those who have had symptoms for more than 48 hours, all of which are associated with appendiceal abscess. A longer period of observation and intravenous antibiotics may be required for these patients.

§ The lower percentage has been reported by trials excluding patients with appendicolith; the higher percentage has been reported by trials including patients with appendicolith.

¥ These are sample choices for low- to moderate-risk community-acquired infections. For the full complement of suitable regimens, refer to the appropriate UpToDate content on management of appendicitis. Doses shown are for patients with normal kidney function; some agents require adjustment for kidney impairment; refer to drug monograph(s) included within UpToDate.

‡ Amoxicillin-clavulanate is a reasonable option if the community rate of *Escherichia coli* resistance to the agent is not >10%.

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Graphic 138820 Version 4.0

Comparison of antibiotics versus appendectomy for nonperforated appendiciti

	Antibiotics	Appendectomy
Advantages	▪ Avoid surgery and anesthesia ▪ Shorter duration of disability compared with surgery ▪ Not associated with an increased risk of appendix rupturing compared with surgery	▪ Appendicitis almost never recurs after appendectomy ▪ Lower incidence of subsequent hospitalization than nonoperative management
Disadvantages	▪ 10 to 20% failure rate at 30 days* ▪ 30 to 40% recurrence rate at 1 year* ▪ 40 to 50% recurrence rate at 5 years* ▪ Small risk of missed neoplasm (mostly in older patients)	▪ Requires surgery and anesthesia ▪ Longer duration of disability required to recover from surgery

* The lower percentage has been reported by trials excluding patients with appendicolith; the higher percentage has been reported by trials including patients with appendicolith.

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Graphic 138819 Version 1.0

Empiric antibiotic regimens for low-risk community-acquired intra-abdominal infections in adults

	Dose
Single-agent regimen	
Piperacillin-tazobactam*	3.375 g IV every 6 hours
Combination regimen with metronidazole*	
One of the following:	
Cefazolin	1 to 2 g IV every 8 hours
or	
Cefuroxime	1.5 g IV every 8 hours
or	
Ceftriaxone	2 g IV once daily
or	
Cefotaxime	2 g IV every 8 hours
or	
Ciprofloxacin	400 mg IV every 12 hours or 500 mg PO every 12 hours
or	
Levofloxacin	750 mg IV or PO once daily
Plus:	
Metronidazole¶	500 mg IV or PO every 8 hours

For empiric therapy of low-risk community-acquired intra-abdominal infections, we cover streptococci, Enterobacteriaceae, and anaerobes. Low-risk community-acquired intra-abdominal infections are those that are of mild to moderate severity (including perforated appendix or appendiceal abscess) in the absence of risk factors for antibiotic resistance or treatment failure. Such risk factors include recent travel to areas of the world with high rates of antibiotics-resistant organisms, known colonization with such organisms, advanced age, immunocompromising conditions, or other major medical comorbidities. Refer to other UpToDate content on the antimicrobial treatment of intra-abdominal infections for further discussion of these risk factors.

The antibiotic doses listed are for adult patients with normal renal function. The duration of antibiotic therapy depends on the specific infection and whether the presumptive source of infection has been controlled; refer to other UpToDate content for details.

IV: intravenously; PO: orally.

* When piperacillin-tazobactam or one of the combination regimens in the table cannot be used, ertapenem (1 g IV once daily) is a reasonable alternative.

¶ For most uncomplicated biliary infections of mild to moderate severity, the addition of metronidazole is not necessary.

Graphic 106948 Version 13.0

Antimicrobial prophylaxis for gastrointestinal surgery in adults

Nature of operation	Common pathogens	Recommended antimicrobials	Usual adult dose*	Redose interval[¶]
Gastroduodenal surgery				
Procedures involving entry into lumen of gastrointestinal tract	Enteric gram-negative bacilli, gram-positive cocci	Cefazolin[Δ]	<120 kg: 2 g IV ≥120 kg: 3 g IV	4 hours
Procedures not involving entry into lumen of gastrointestinal tract (selective vagotomy, antireflux)	Enteric gram-negative bacilli, gram-positive cocci	High risk[◇] only: cefazolin[Δ]	<120 kg: 2 g IV ≥120 kg: 3 g IV	4 hours
Biliary tract surgery (including pancreatic procedures)				
Open procedure or laparoscopic procedure (high risk)[§]	Enteric gram-negative bacilli, enterococci, clostridia	Cefazolin[Δ¥] (preferred)	<120 kg: 2 g IV ≥120 kg: 3 g IV	4 hours
		OR cefotetan	2 g IV	6 hours
Laparoscopic procedure (low risk)	N/A	None	None	None
Appendectomy[‡]				
	Enteric gram-negative bacilli, anaerobes, enterococci	Cefazolin[Δ] PLUS metronidazole (preferred)	*For cefazolin:* <120 kg: 2 g IV ≥120 kg: 3 g IV *For metronidazole:* 500 mg IV	*For cefazolin:* 4 hours *For metronidazole:* N/A
		OR cefotetan[Δ]	2 g IV	6 hours
Small intestine surgery				
Nonobstructed	Enteric gram-negative bacilli, gram-positive cocci	Cefazolin[Δ]	<120 kg: 2 g IV ≥120 kg: 3 g IV	4 hours

Obstructed	Enteric gram-negative bacilli, anaerobes, enterococci	Cefazolin[Δ] PLUS metronidazole (preferred)	*For cefazolin:* <120 kg: 2 g IV ≥120 kg: 3 g IV *For metronidazole:* 500 mg IV	*For cefazolin:* 4 hours *For metronidazole:* N/A
		OR cefotetan[Δ]	2 g IV	6 hours
Hernia repair				
	Aerobic gram-positive organisms	Cefazolin[Δ]	<120 kg: 2 g IV ≥120 kg: 3 g IV	4 hours
Colorectal surgery[†]				
	Enteric gram-negative bacilli, anaerobes, enterococci	Parenteral:		
		Cefazolin[Δ] PLUS metronidazole (preferred)	*For cefazolin:* <120 kg: 2 g IV ≥120 kg: 3 g IV *For metronidazole:* 500 mg IV	*For cefazolin:* 4 hours *For metronidazole:* N/A
		OR cefotetan[Δ]	2 g IV	6 hours
		Oral (used in conjunction with mechanical bowel preparation):		
		Neomycin PLUS erythromycin base or metronidazole	**	**

IV: intravenous.

* Parenteral prophylactic antimicrobials can be given as a single IV dose begun within 60 minutes before the procedure. If vancomycin or a fluoroquinolone is used, the infusion should be started within 60 to 120 minutes before the initial incision to have adequate tissue levels at the time of incision and to minimize the possibility of an infusion reaction close to the time of induction of anesthesia.

¶ For prolonged procedures (>3 hours) or those with major blood loss or in patients with extensive burns, additional intraoperative doses should be given at intervals one to two times the half-life of the drug.

Δ For patients allergic to penicillins and cephalosporins, clindamycin (900 mg) or vancomycin (15 mg/kg IV; not to exceed 2 g) with either gentamicin (5 mg/kg IV), ciprofloxacin (400 mg IV), levofloxacin (500 mg IV), or aztreonam (2 g IV) is a reasonable alternative. Metronidazole (500 mg IV) plus an aminoglycoside or fluoroquinolone is also an acceptable alternative regimen, although metronidazole plus aztreonam should not be used, since this regimen does not have aerobic gram-positive activity.

◇ Severe obesity, gastrointestinal (GI) obstruction, decreased gastric acidity or GI motility, gastric bleeding, malignancy or perforation, or immunosuppression.

§ Factors that indicate high risk may include age >70 years, pregnancy, acute cholecystitis, nonfunctioning gallbladder, obstructive jaundice, common bile duct stones, immunosuppression.

¥ Cefotetan, cefoxitin, and ampicillin-sulbactam are reasonable alternatives.

‡ For a ruptured viscus, therapy is often continued for approximately 5 days.

† Use of ertapenem or other carbapenems not recommended due to concerns of resistance.

** In addition to mechanical bowel preparation, the following oral antibiotic regimen is administered: neomycin (1 g) plus erythromycin base (1 g) OR neomycin (1 g) plus metronidazole (1 g). The oral regimen should be given as 3 doses over approximately 10 hours the afternoon and evening before the operation. Issues related to mechanical bowel preparation are discussed further separately; refer to the UpToDate topic on overview of colon resection.

Data from:

1. *Antimicrobial prophylaxis for surgery. Med Lett Drugs Ther 2016; 58:63.*
2. *Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infec (Larchmt) 2013; 14:73.*

Graphic 65369 Version 37.0

Perioperative management of oral direct thrombin inhibitors and factor Xa inhibitors

Anticoagulant	Kidney function and dose	Interval between last dose and procedure NOTE: No anticoagulant is administered the day of the procedure		Resumption after procedure	
		High bleeding risk	Low bleeding risk	High bleeding risk	Low bleeding risk
Dabigatran	CrCl >50 mL/minute Dose 150 mg twice daily	Give last dose 3 days before procedure (ie, skip 4 doses on the 2 days before the procedure)	Give last dose 2 days before procedure (ie, skip 2 doses on the day before the procedure)	Resume 48 to 72 hours after surgery (ie, postoperative day 2 to 3)	Resume 24 hours after surgery (ie, postoperative day 1)
	CrCl 30 to 50 mL/minute Dose 150 mg twice daily	Give last dose 5 days before procedure (ie, skip 8 doses on the 4 days before the procedure)	Give last dose 3 days before procedure (ie, skip 4 doses on the 2 days before the procedure)		
Rivaroxaban	CrCl >50 mL/minute Dose 20 mg once daily	Give last dose 3 days before procedure (ie, skip 2 doses on the 2 days before the procedure)	Give last dose 2 days before procedure (ie, skip 1 dose on the day before the procedure)		
	CrCl 30 to 50 mL/minute Dose 15 mg once daily				
Apixaban	CrCl >50 mL/minute Dose 5 mg twice daily	Give last dose 3 days before procedure (ie, skip 4 doses on the 2 days before the procedure)	Give last dose 2 days before procedure (ie, skip 2 doses on the day before the procedure)		
	CrCl ≤50 mL/minute				

	Dose 2.5 mg twice daily				
Edoxaban	CrCl 51 to 95 mL/minute Dose 60 mg once daily	Give the last dose 3 days before the procedure (ie, skip 2 doses on the 2 days before the procedure)	Give the last dose 2 days before the procedure (ie, skip 2 dose on the day before the procedure)		
	CrCl ≤50 mL/minute* Dose 30 mg once daily				

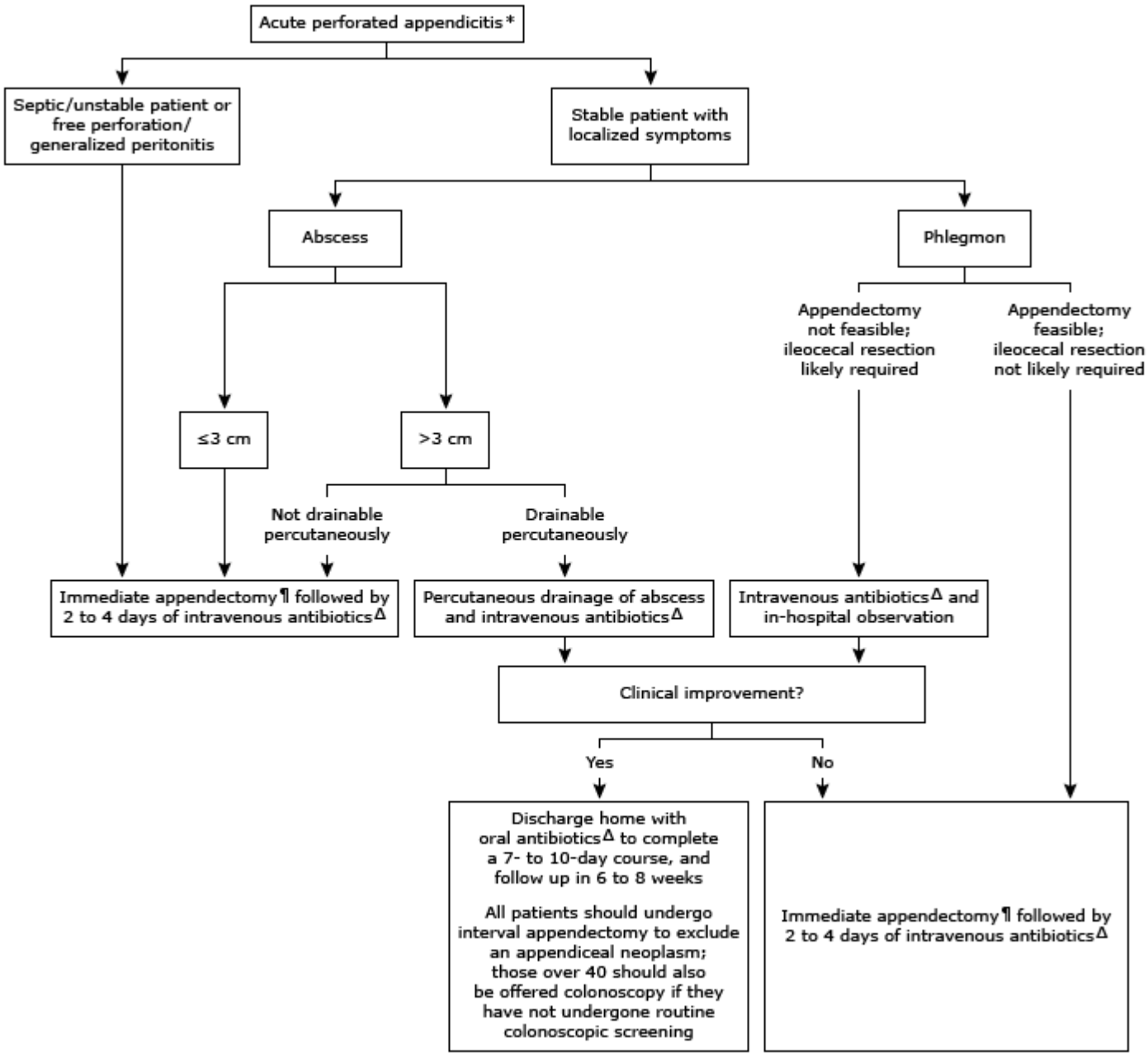
Bleeding risk is determined primarily by the type of surgery; patient comorbidities may also play a role. In patients undergoing neuraxial anesthesia or a very high bleeding risk procedure, a longer period of interruption may be warranted. In many low bleeding risk procedures, the anticoagulant does not need to be interrupted. Bridging anticoagulation may be appropriate preoperatively in patients with a very high thromboembolic risk who require more prolonged interruption of the anticoagulant (eg, for renal insufficiency) and/or postoperatively in patients who are unable to resume the anticoagulant (eg, unable to take oral medication due to intestinal ileus). Refer to the UpToDate topics on perioperative management of patients receiving anticoagulants for further details.

CrCl: creatinine clearance.

* Product information varies in different countries regarding a lower limit of CrCl below which the drug should not be used. As an example, product information in the United States specifies avoiding use with CrCl <15 mL/minute.

Graphic 93260 Version 12.0

Management of acute perforated appendicitis in adults



* Perforated appendicitis, also referred to as complicated appendicitis, is characterized by a palpable mass in the right lower quadrant on physical examination or by a phlegmon (inflammatory mass) or abscess on imaging studies. Refer to the separate UpToDate algorithm for the management of nonperforated appendicitis in adults.

¶ Immediate appendectomy, as opposed to interval appendectomy, should be performed within 12 hours of the decision to operate, except in the case of an unstable/septic patient or the presence of free perforation or generalized perforation, where surgery should be performed as soon as possible.

Δ The choice of antibiotics varies by clinical situations and is constantly evolving. Refer to related topics in UpToDate for information on antibiotic selection.

Graphic 115333 Version 5.0

Direct oral anticoagulant reversal agents for life-threatening bleeding (imminent risk of death from bleeding)

Anticoagulant	Reversal agent (all are given intravenously)
Dabigatran (Pradaxa; oral thrombin inhibitor)	▪ Idarucizumab (Praxbind). Dose: 5 grams*
Oral factor Xa inhibitors: ▪ Apixaban (Eliquis) ▪ Edoxaban (Lixiana, Savaysa) ▪ Rivaroxaban (Xarelto)	▪ Andexanet alfa (AndexXa). Dosing for the initial bolus and subsequent infusion depend on the dose level of the factor Xa inhibitor and the interval since it was last taken. **or** ▪ 4-factor PCC (Kcentra, Beriplex P/N, Octaplex). Dosing can be done with a fixed dose of 2000 units **or** a weight-based dose of 25 to 50 units per kg.

Reversal agents carry a risk of life-threatening thrombosis and should only be used under the direction of a specialist with expertise in their use and/or in a patient at imminent risk of death from bleeding. In general, a single dose is given; dosing may be repeated in rare situations in which the oral anticoagulant persists for longer in the circulation, such as severe kidney dysfunction.

Andexanet dosing is as follows:

- If the patient took rivaroxaban >10 mg, apixaban >5 mg, or dose unknown within the previous 8 hours: Andexanet 800 mg bolus at 30 mg/minute followed by 960 mg infusion at 8 mg/minute for up to 120 minutes.
  or
- If the patient took rivaroxaban ≤10 mg or apixaban ≤5 mg, or if ≥8 hours have elapsed since the last dose of a factor Xa inhibitor: Andexanet 400 mg bolus at 30 mg/minute followed by 480 mg infusion at 4 mg/minute for up to 120 minutes.

Refer to UpToDate topics on treatment of bleeding in patients receiving a DOAC or perioperative management of patients receiving a DOAC for additional information on administration, risks, and alternative therapies.

DOAC: direct oral anticoagulant; FEIBA: factor eight inhibitor bypassing activity; PCC: prothrombin complex concentrate.

* If idarucizumab is unavailable, an activated PCC (FEIBA, 50 to 80 units per kg intravenously) may be a reasonable alternative.

Graphic 112299 Version 10.0

Emergency reversal of anticoagulation from warfarin for life-threatening hemorrhage in adults: Suggested approaches based upon available resources

A. If 4-factor prothrombin complex concentrate (4F PCC) is available (preferred approach):

1. Give 4F PCC* 1500 to 2000 units¶ IV over 10 minutes. Check INR 15 minutes after completion of the infusion. If INR is not ≤1.5, give additional 4F PCC (refer to topic or drug reference for details).
2. Give vitamin K 10 mg IV over 10 to 20 minutes.

B. If 3-factor prothrombin complex concentrate (3F PCC) is available but 4F PCC is not available:

1. Give 3F PCC* 1500 to 2000 units¶ IV over 10 minutes. Check INR 15 minutes after completion of the infusion. If INR is not ≤1.5, give additional 3F PCC (refer to topic or drug reference for details).
2. Give Factor VIIa 20 mcg/kg IV **or** give FFP 2 units IV by rapid infusion. Factor VIIa may be preferred if volume overload is a concern.
3. Give vitamin K 10 mg IV over 10 to 20 minutes.

C. If neither 3F PCC nor 4F PCC is available:

1. Give FFP 2 units IV by rapid infusion. Check INR 15 minutes after completion of infusion. If INR ≥1.5, administer 2 additional units of FFP IV rapid infusion. Repeat process until INR ≤1.5. May wish to administer loop diuretic between FFP infusions if volume overload is a concern.
2. Give vitamin K 10 mg IV over 10 to 20 minutes.

These products and doses are for use in life-threatening bleeding only. Evidence of life-threatening bleeding and over-anticoagulation with a vitamin K antagonist (eg, warfarin) are required. Anaphylaxis and transfusion reactions can occur.

It may be reasonable to thaw 4 units of FFP while awaiting the PT/INR. The transfusion service may substitute other plasma products for FFP (eg, Plasma Frozen Within 24 Hours After Phlebotomy [PF24]); these products are considered clinically interchangeable. PCC will reverse anticoagulation within minutes of administration; FFP administration can take hours due to the volume required; vitamin K effect takes 12 to 24 hours, but administration of vitamin K is needed to counteract the long half-life of warfarin. Subsequent monitoring of the PT/INR is needed to guide further therapy. Refer to topics on warfarin reversal in individual situations for further management.

3F PCC: PCC containing factors II, IX, and X and only trace factor VII; 4F PCC: PCC containing coagulation factors II, VII, IX, X, protein S and protein C; FEIBA: factor eight inhibitor bypassing agent; FFP: fresh frozen plasma; INR: international normalized ratio; PCC: unactivated prothrombin complex concentrate; PT: prothrombin time.

* Before use, check product label to confirm factor types (3 versus 4 factor) and concentration. Activated complexes and single-factor IX products (ie, FEIBA, AlphaNine, Mononine, Immunine, BeneFix) are **not**

used for warfarin reversal.

¶ PCC doses shown are those suggested for initial treatment of emergency conditions. Subsequent treatment is based on INR and patient weight if available. Refer to topic and drug reference included with UpToDate for INR-based dosing.

Graphic 89478 Version 12.0

Risk factors that warrant broad empiric antimicrobial coverage for intra-abdominal infections

Factors associated with mortality
Age >70 years
Medical comorbidity (eg, renal or liver disease, presence of malignancy, chronic malnutrition)
Immunocompromising condition (eg, poorly controlled diabetes mellitus, chronic high-dose corticosteroid use, use of other immunosuppressive agents, neutropenia, advanced HIV infection, B or T leukocyte deficiency)
High severity of illness (ie, sepsis)
Extensive peritoneal involvement or diffuse peritonitis
Delay in initial intervention (source control) >24 hours
Inability to achieve adequate debridement or drainage control
Factors associated with infection with antibiotic-resistant bacteria
Health care-acquired infection
Travel to areas with higher rates of antibiotic-resistant organisms* within the few weeks prior to infection onset or if antibiotics were received during travel
Known colonization with antibiotic-resistant organisms

* High rates of antibiotic resistance have been reported from southeast Asia, east Asia, the Middle East, and Africa.

References:

1. *Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010; 50:133.*
2. *Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. Clin Microbiol Rev 2013; 26:744.*

Graphic 105865 Version 3.0

Empiric antibiotic regimens for high-risk community-acquired intra-abdominal infections in adults

	Dose
Single-agent regimen	
Imipenem-cilastatin	500 mg IV every 6 hours
Meropenem	1 g IV every 8 hours
Doripenem	500 mg IV every 8 hours
Piperacillin-tazobactam	4.5 g IV every 6 hours
Combination regimen with metronidazole	
ONE of the following:	
Cefepime	2 g IV every 8 hours
OR	
Ceftazidime	2 g IV every 8 hours
PLUS:	
Metronidazole	500 mg IV or orally every 8 hours

High-risk community-acquired intra-abdominal infections are those that are severe or in patients at high risk for adverse outcomes or antimicrobial resistance. These include patients with recent travel to areas of the world with high rates of antibiotics-resistant organisms, known colonization with such organisms, advanced age, immunocompromising conditions, or other major medical comorbidities. Refer to the UpToDate topic on the antimicrobial treatment of intra-abdominal infections for further discussion of these risk factors.

For empiric therapy of high-risk community-acquired intra-abdominal infections, we cover streptococci, Enterobacteriaceae resistant to third-generation cephalosporins, *Pseudomonas aeruginosa*, and anaerobes. Empiric antifungal therapy is usually not warranted but is reasonable for critically ill patients with an upper gastrointestinal source.

Local rates of resistance should inform antibiotic selection (ie, agents for which there is >10% resistance among Enterobacteriaceae should be avoided). If the patient is at risk for infection with an extended-spectrum beta-lactamase (ESBL)-producing organism (eg, known colonization or prior infection with an ESBL-producing organism), a carbapenem should be chosen. When beta-lactams or carbapenems are chosen for patients who are critically ill or are at high risk of infection with drug-resistant pathogens, we favor a prolonged infusion dosing strategy. Refer to other UpToDate content on prolonged infusions of beta-lactam antibiotics.

The combination of vancomycin, aztreonam, and metronidazole is an alternative for those who cannot use other beta-lactams or carbapenems (eg, because of severe reactions).

The antibiotic doses listed are for adult patients with normal renal function. The duration of antibiotic therapy depends on the specific infection and whether the presumptive source of infection has been controlled; refer to other UpToDate content for details.

IV: intravenous.

Graphic 106949 Version 12.0

Empiric antibiotic regimens for health care-associated intra-abdominal infections in adults

	Dose
Single-agent regimen	
Imipenem-cilastatin	500 mg IV every 6 hours
Meropenem	1 g IV every 8 hours
Doripenem	500 mg IV every 8 hours
Piperacillin-tazobactam	4.5 g IV every 6 hours
Combination regimen	
ONE of the following:	
Cefepime	2 g IV every 8 hours
OR	
Ceftazidime	2 g IV every 8 hours
PLUS:	
Metronidazole	500 mg IV or orally every 8 hours
PLUS ONE of the following (in some cases*):	
Ampicillin	2 g IV every 4 hours
OR	
Vancomycin	15 to 20 mg/kg IV every 8 to 12 hours

For empiric therapy of health care-associated intra-abdominal infections, we cover streptococci, enterococci, Enterobacteriaceae that are resistant to third-generation cephalosporins and fluoroquinolones, *Pseudomonas aeruginosa*, and anaerobes. We include coverage against methicillin-resistant *Staphylococcus aureus* (MRSA) with vancomycin in those who are known to be colonized, those with prior treatment failure, and those with significant prior antibiotic exposure. Empiric antifungal coverage is appropriate for patients at risk for infection with *Candida* spp, including those with upper gastrointestinal perforations, recurrent bowel perforations, surgically treated pancreatitis, heavy colonization with *Candida* spp, and/or yeast identified on Gram stain of samples from infected peritoneal fluid or tissue. Refer to other UpToDate content on treatment of invasive candidiasis.

If the patient is at risk for infection with an extended-spectrum beta-lactamase (ESBL)-producing organism (eg, known colonization or prior infection with an ESBL-producing organism), a carbapenem should be chosen. For patients who are known to be colonized with highly resistant gram-negative bacteria, the addition of an aminoglycoside, polymyxin, or novel beta-lactam combination (ceftolozane-tazobactam or ceftazidime-avibactam) to an empiric regimen may be warranted. In such cases, consultation with an expert in infectious diseases is advised.

When beta-lactams or carbapenems are chosen for patients who are critically ill or are at high risk of infection with drug-resistant pathogens, we favor a prolonged infusion dosing strategy. Refer to other UpToDate content on prolonged infusions of beta-lactam antibiotics.

The combination of vancomycin, aztreonam, and metronidazole is an alternative for those who cannot use other beta-lactams or carbapenems (eg, because of severe reactions).

The antibiotic doses listed are for adult patients with normal kidney function. The duration of antibiotic therapy depends on the specific infection and whether the presumptive source of infection has been controlled; refer to other UpToDate content for details.

IV: intravenous.

* We add ampicillin or vancomycin to a cephalosporin-based regimen to provide enterococcal coverage, particularly in those with postoperative infection, prior use of antibiotics that select for *Enterococcus*, immunocompromising condition, valvular heart disease, or prosthetic intravascular materials. Coverage against vancomycin-resistant enterococci (VRE) is generally not recommended, although it is reasonable in patients who have a history of VRE colonization or in liver transplant recipients who have an infection of hepatobiliary source.

Graphic 106950 Version 12.0

Contributor Disclosures

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